Original Article

DOI: 10.7860/JCDR/2023/61222.18130

Paediatrics Section

Oral Zinc as an Adjunct in the Treatment of Enteric Fever: A Randomised Double-blinded Controlled Trial

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ABSTRACT

Introduction: Enteric fever is an important tropical disease which takes an average of five days for defervescence even with effective antibiotic therapy. Zinc has been successfully used as an adjuvant in diarrhoeal disease. If addition of oral zinc can lead to reduction in time to defervescence, it will be a useful adjuvant in the therapy of enteric fever.

Aim: To determine the effect of oral zinc supplementation, along with standard antibiotic therapy, for early defervescence among children with enteric fever.

Materials and Methods: This double-blinded, randomised controlled trial was conducted in the Department of Paediatrics, ESICMC and PGIMSR, Chennai, Tamil Nadu, India from November 2014 to August 2016. A total of 58 children aged <12 years with enteric fever were included and were randomised to receive 40 mg elemental zinc per day (n=29) or placebo (n=29) for one week. All children received intravenous ceftriaxone (75 mg/kg every 12 hours) until five days after defervescence. The main outcome measures studied were time taken for defervescence of fever and resolution of toxaemia. Kaplan-Meier survival analysis was used to compare differences in the time to resolution of toxaemia and defervescence of fever between the two groups and the log rank test was used to test for significance.

Results: The mean age of the children of the two groups was 6.48±3.15 years and 7.55±2.59 years, respectively. The mean time for fever defervescence was shorter among the zinc supplemented children than among the children in the control group (2 vs 3 days, p-value=0.043). Resolution of toxaemia was noted earlier in the zinc group than in the control group (75% vs 43%, p-value=0.054).

Conclusion: Zinc when used as an adjunct along with standard antibiotic therapy in children with enteric fever, resulted in earlier defervescence of fever.

Keywords: Early defervescence, Placebo, Toxaemia, Tropical disease

INTRODUCTION

Enteric fever is a systemic infection caused predominantly by *Salmonella* enteric serotype typhi and paratyphi (A, B, and C) which leads to significant morbidity and mortality [1]. Children in South-central and Southeast Asia experience the greatest burden of this disease [1]. The economic burden due to prolonged hospital stay and loss of wages for the parents is an important consideration. Over the past few decades, micronutrients are gaining prominence in the field of preventive and therapeutic medicine, especially infections. One such important micronutrient is zinc [2]. Zinc is necessary for maintaining the integrity of the immune system, starting from the barrier of the skin [2,3]. Immunologically, zinc is necessary for the normal development of immune cells and affects the function of almost all cells namely neutrophils, macrophages and lymphocytes [4,5]. Brown KH et al., estimated that over half of the world's population may be affected by zinc deficiency [2]. Its beneficial effects have been definitively established in diarrhoea [6,7]. It has also been used as an adjunct in bacterial sepsis and found to reduce treatment failure when used along with antibiotics. This has been attributed to its immunomodulatory effect and antioxidant properties [6]. A few studies have shown its effectiveness in the treatment of other gram negative infections like shigellosis and cholera [8-10].

Enteric fever is also an infection spread by the feco-oral route similar to the infections such as acute gastroenteritis or shigellosis and zinc supplementation may favourably impact the treatment. To the best of our knowledge, there is no study, evaluating the role of zinc as an adjunct in the treatment of enteric fever. Hence, the present study was conducted to determine the effect of oral zinc supplementation, when used as an adjunct with standard antibiotic therapy, for early defervescence in children with enteric fever.

MATERIALS AND METHODS

This randomised, double- blinded, controlled trial was conducted at the Depaertment of Paediatrics, ESICMC & PGIMSR, Chennai, Tamil Nadu, India from November 2014 to August 2016. The study was approved by the Institute Ethics Committee (IEC) (Approval no. 11/27/10/2014).

Inclusion criteria: Paediatric patients, aged <12 years with enteric fever, admitted in paediatric ward, were included after informed written consent was obtained from the caregiver.

Diagnosis of enteric fever was made in patients with fever and blood culture showing growth of *Salmonella* typhi or paratyphi or Widal suggestive of enteric fever (O antigen titre >1:160, or a four-fold rise in titre of blood Widal in two weeks) [11].

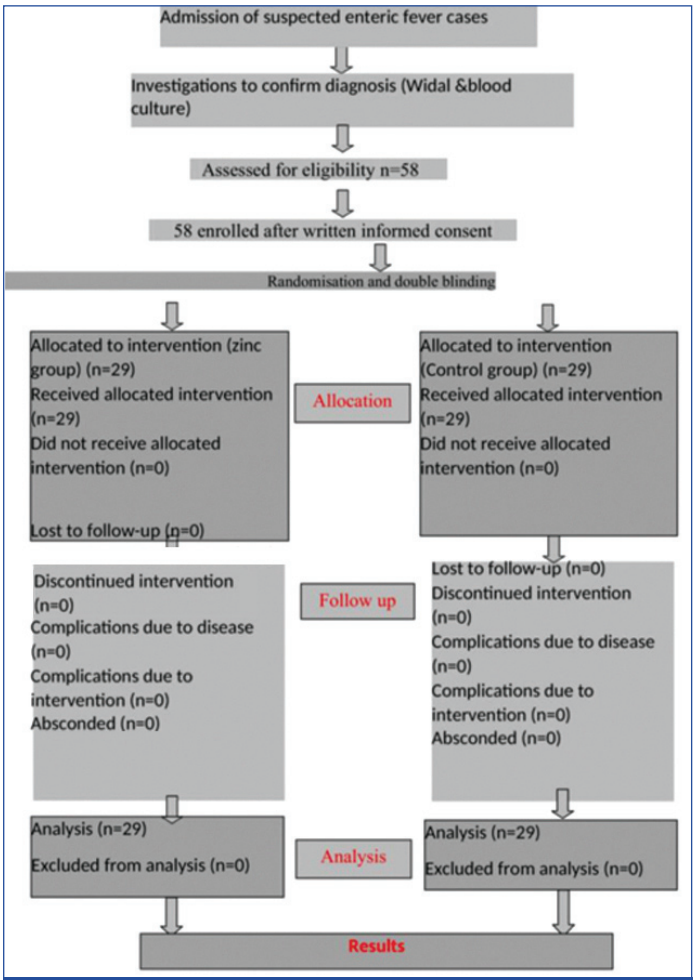
Exclusion criteria: Children with enteric fever with septic shock requiring inotropes, or perforation and those with no response to i.v. ceftriaxone even after 10 days of therapy were excluded from the study.

Sample size: As there are no previous studies of zinc use in enteric fever, authors attempted to estimate a 25% reduction in the time taken for defervescence of fever between the intervention and control groups for a 95% confidence level and 80% power. The sample size was calculated using the formula,

$$N=2\times SD^2/d^2$$

Where, N- sample size, SD- standard deviation of time taken for defervescence of fever (1 day), d- required reduction in time taken for defervescence (25%). The sample size thus arrived was 32 for

each group. In the present study, a total 58 children with enteric fever were enrolled and randomised to 29 children in each group. Method of randomisation used was simple randomisation and allocation concealment was done by using sealed envelopes [Table/Fig-1]. The key investigator and participants were blinded in the present study.



[Table/Fig-1]: Algorithm of the study.

Data collection: Data of all the study participants, including demographic and anthropmometric details such as age, gender, weight, height, clinical findings, investigations, treatment details, and response to treatment were documented in a prestructured study proforma. Children were classified as normal, Severe Acute Malnutrition (SAM), Moderate Acute Malnutrition (MAM) or thinness based on the World Health Organisation (WHO) charts [12].

Intervention: Both groups were treated with Inj. ceftriaxone 75 mg/kg/day in two divided doses intravenously until five days after defervescence of fever or for a total of 10 days, whichever was earlier. Intervention group was given tablet zinc sulphate 40 mg (children >6 months) or 20 mg (children <6 months) once daily as powdered sachets without label and the other group was given placebo (powdered calcium tablets) without label for seven days. The above dose of zinc was chosen based on the study by Sachdev HP et al., [7]. Oral zinc and placebo were both administered as powders in sachets and they were similar in colour, smell and taste.

The primary outcome observed was the time taken for defervescence of fever and resolution of toxaemia in both groups. Secondary outcome was the duration of hospital stay after start of intervention in both groups. Monitoring for side-effects was done meticulously. Upon completion of intravenous therapy and defervescence of fever, the child was discharged on oral antibiotics to complete a 14-day course. The principal investigator monitored all the patients through the entire course of the study.

STATISTICAL ANALYSIS

The statistical software used was Statistical Package for the Social Sciences (SPSS) version 15.0. Student's t-test was used to find the significance of study parameters on continuous scale between two groups. Chi-square/Fisher-exact test was used to find the significance of study parameters on categorical scale between two or more groups. Kaplan-Meier survival analysis was used to compare differences in the time to resolution of toxaemia and defervescence of fever between the two groups and the log-rank test for significance. A p-value <0.05 was considered significant.

RESULTS

A total of 58 enteric fever cases were found eligible for recruitment and were enrolled in this study. They were randomised into two arms of 29 each. Analysis was done for all these patients as there were no drop outs.

Of 58 patients, 43 (74.1%) of the study population was normally nourished, 12 (20.7%) were malnourished and 3 (5.2%) were obese. There was no significant difference in the nutritional status in the patients of the two groups. History of prior treatment with antibiotics was observed in 16 (55%) of cases in the zinc group and 21 (72.4%) patients in the placebo group. Only one child in the placebo group and none in the zinc group were given prior vaccine for typhoid fever.

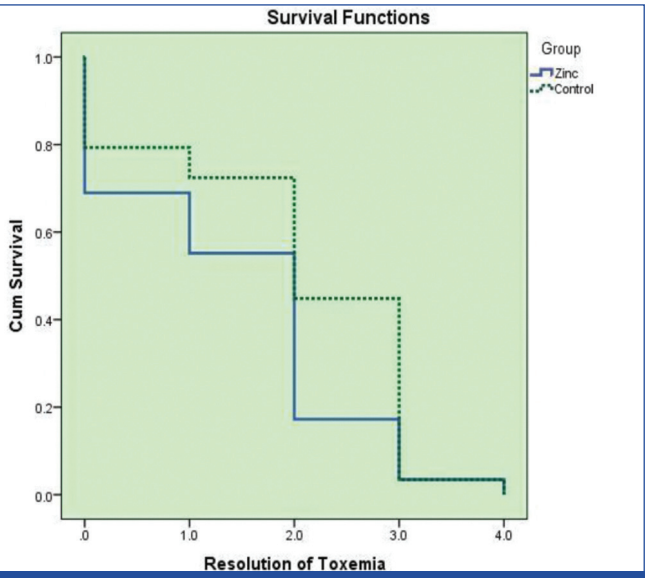
A total of 41 (70.7%) of the study population grew enteric bacilli in blood culture i.e., 19 (46.3%) of children in the zinc group and 22 (53.7%) in the placebo group. Blood Widal was positive in 24 (41.4%) of children in the study population; 13 (44.8%) in the zinc group and 11 (37.9%) in the placebo group. Blood culture and Widal positivity were comparable in both the groups (p-value=0.387 and 0.594, respectively) [Table/Fig-2].

Characteristics	Zinc group (n=29)	Placebo group (n=29)	p-value
Age (years)	6.48±3.15	7.55±2.59	0.163
Sex (Male+Female)	(15+14)	(15+14)	1.000
Weight (kg)	18.21±5.71	19.76±5.36	0.291
Height (cm)	111.93±15.76	117.62±13.42	0.144
Nutritional status			
1. Normal nutritional status	22 (75.9%)	21 (72.4%)	0.153
2. Malnutrition (MAM/SAM/Thinness)	6 (20.7%)	6 (20.7%)	1
3. Obesity	1 (3.4%)	2 (6.9%)	0.057
Features of zinc deficiency- dermatitis	None	None	
History of prior treatment with antibiotics	16 (55%)	21 (72.4%)	0.131
Duration of fever at admission (days)	7.48±3.66	6.72±3.47	0.422
Widal positive	13 (44.8%)	11 (37.9%)	0.594
Culture positive	19 (65.5%)	22 (75.9%)	0.387
Time taken for diagnosis from onset of fever (days)	9.76±2.87	9.17±3.23	0.468
Time taken for diagnosis from admission (days)	2.24±1.57	2.45±1.30	0.587
Number of children with toxaemia	20 (69%)	23 (79.3%)	0.368
Duration of therapy (days)	7.76±1.15	8.28±1.67	0.175

[Table/Fig-2]: Baseline characteristics of the study population.
Student t-test was used to find the significance of study parameters on continuous scale between two groups
Chi-square/Fisher-Exact test was used to find the significance of study parameters on categorical scale between two or more groups
Kaplan-Meier survival analysis was used to compare differences in the time to resolution of toxaemia and defervescence of fever between the two groups
Log-rank test to test for significance. (Significance p</=0.05)

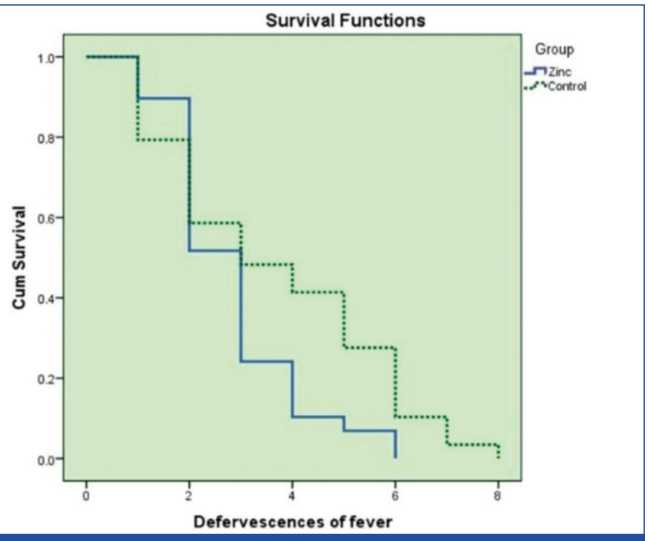
Twenty children in the zinc group (69%) and 23 (79.3%) in the placebo group had toxaemia. The mean toxaemia resolution time after intervention in the zinc group was 1.45±1.18 days and in the placebo group was 2.00±1.22 days, half a day earlier (13 hours) for

the zinc group than for placebo (p=0.054). The Kaplan Meier survival curve showed early resolution of toxaemia (improvement in appetite and general well-being) in both groups [Table/Fig-3].



[Table/Fig-3]: Probability of having toxaemia by day of intervention.
X-axis: Resolution of toxaemia (days), Y-axis: Proportion of patients (Cumulative survival)
Kaplan-Meier survival curve in intention to treat analysis, showing higher recovery from toxaemia in zinc supplemented group

The mean fever resolution time in zinc group was 2.83±1.31 days and in the placebo group it was 3.69±2.21 days. Mean time for defervescence of fever was about one day (21 hours) earlier for the zinc group than for the placebo group. The median time until recovery too was shorter among the zinc supplemented children than among the children in the control group (2 vs 3 days, p-value=0.043). The Kaplan Meier survival curve showed early defervescence in the Zinc supplemented group [Table/Fig-4].



[Table/Fig-4]: Probability of having fever by day of intervention.
X-axis: Defervescence of fever (days), Y-axis: Proportion of patients (Cumulative survival)
Kaplan-Meier survival curve in intention to treat analysis, showing earlier recovery from fever in zinc supplemented group compared with placebo group

The mean duration of hospital stay in the zinc group was 10.31±2.21 days and in the placebo group was 11.17±2.32 days. Children in the placebo arm stayed a day longer in hospital (21 hours) as compared to the intervention group. This difference was not statistically significant (p-value=0.152). There were no adverse effects in either group due to the treatment.

DISCUSSION

The management of enteric fever is plagued by several problems like difficulty in diagnosis, multidrug resistance and a long time to defervescence even with successful antibiotic therapy. Any intervention that can reduce the time to defervescence would be desirable. Hence, the authors decided to explore the possibility of zinc as an adjunct in the therapy of enteric fever. In the present study, resolution of toxaemia was faster and hospital stay was also shorter in the group treated with zinc fever, however the significance of these findings could not be established (p-value >0.05).

The time taken for resolution of fever was significantly lesser by 21 hours (p-value=0.043) in the group treated with zinc and standard antibiotics as against the one treated with antibiotics and placebo alone. This was the most important outcome of the present study as it illustrates the efficacy of zinc as a simple yet useful adjunct in the treatment of enteric fever. Though published literature for zinc in enteric fever is lacking, role of zinc in reducing the duration of acute gastroenteritis has been proved in several studies and has been the basis of zinc administration in diarrhoeal diseases [6,7]. Zinc as an adjunct for enteric fever seems even more promising than in shigellosis; Rahman MJ et al., found increased levels of Shigellocidal antibodies but definite evidence for clinical effect was lacking [8]. Another important aspect of this intervention is its absolute safety. The present study has, for the first time, indicated that zinc supplementation may have benefits over and above antibiotic use in children with enteric fever.

In tropical countries, malnutrition and consequent zinc deficiency is common and this may play a crucial role in the morbidity caused by infectious diseases [9,10]. However, most of the study population (76%), were normally nourished and did not have any overt features of zinc deficiency. Though the exact mechanism by which zinc helps in the defervescence is unknown, some hypothesis may be postulated. The beneficial effect may be due to the effective stimulation of the immune cells as zinc has an important role in immunomodulation as described earlier. Also, zinc deficiency may be induced by infections and stress as an acute phase response as evidenced by several studies and correction of this deficit is likely to prove beneficial for recovery [13-15].

Limitation(s)

There were some important limitations of present study. The sample size of the present study was small. Also, baseline zinc levels could not be performed in the patients to find an underlying zinc deficiency, due to logistical constraints.

CONCLUSION(S)

Oral zinc was found to be a useful adjunct in the treatment of enteric fever along with standard antibiotics as it reduced the duration of fever by atleast one day. This reduction is significant considering that enteric fever takes a long time to defervesce even with appropriate antibiotic therapy leading to prolonged hospital stay, parental anxiety and increased direct and indirect costs of therapy to both the family and the healthcare system. Larger studies are needed to confirm these findings. Considering the absolute safety of zinc, it may be used effectively as an adjunct to standard antibiotic therapy in enteric fever.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Nov 08, 2022
- Manual Googling: Feb 04, 2023
- iThenticate Software: Mar 11, 2023 (16%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Nov 06, 2022**
Date of Peer Review: **Dec 28, 2022**
Date of Acceptance: **Mar 18, 2023**
Date of Publishing: **Jun 01, 2023**