ROLE OF ZINC AS AN ADJUNCT IN THE TREATMENT OF
CHILDHOOD DIARRHEA

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DECLARATION

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis, when deposited in the University Library.

Signed

Archana Patel
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SYNOPSIS

ROLE OF ZINC AS AN ADJUNCT IN THE TREATMENT OF CHILDHOOD DIARRHEA

Introduction: Diarrhea causes an estimated 1.8 million child deaths in the developing countries each year, 35% of which are due to acute diarrhea. Zinc and copper stores in the body are known to be depleted during acute diarrhea. However the results of many published trials do not show consistent effects of zinc in reducing the duration of childhood diarrhea.

Objective: The objectives were to evaluate the efficacy of zinc and copper supplementation, when given with standard treatment to children with acute watery or bloody diarrhea as measured by the duration of diarrhea, and morbidity and growth over 12 weeks of subsequent follow-up. We also assessed factors that modulated its effect on diarrhea, its cost effectiveness within the trial and finally investigated the impact of zinc by an updated meta-analysis that included this study.

Methods: We conducted a double blind randomized placebo controlled clinical trial in the Department of Pediatrics at Indira Gandhi Government Medical College, Nagpur, India. Eight hundred and eight children aged 6 – 59 months with acute diarrhea (acute watery or bloody diarrhea i.e. > 3 unformed stools in the last 24 hours for less than 72 hours) were selected and individually randomized to receive a 14 day course of placebo (Pl), zinc (Zn) only, and zinc and copper (Zn+Cu) together with standard treatment for acute diarrhea. We also investigated the aetiology of diarrhea, serum zinc and copper at enrolment and after 14 days, and morbidity and growth for 12 weeks after enrolment. Baseline characteristics that predict risk of prolongation of diarrhea were also assessed.
Finally we searched medical databases for published reviews and meta-analyses on the use of zinc supplementation for the prevention and treatment of childhood diarrhea. Additional randomized clinical trials (RCTs) published following the meta-analyses were also sought. The reviews and published RCTs were qualitatively mapped, followed by updated random-effects meta-analyses, subgroup meta-analyses and meta-regression to quantify and characterize the role of zinc supplementation with diarrhea-related outcomes. Lastly we estimated the cost of treating diarrhea with supplements and its cost-effectiveness.

**Main outcome measures:** They were the duration of diarrhea (in hours) from onset, the total stool weight in grams during hospitalization, the amount of ORS and the amount of intravenous fluids used, percentage change in zinc and copper at day 14 after discharge as compared to baseline in each patient, the rate of complications in hospital, and the episodes of any or severe dehydration in hospital. After discharge the following outcomes were measured: incidence of diarrhea, its prevalence, prevalence of acute lower respiratory infections (ALRI), fever, sick days, haemoglobin, serum ferritin and anthropometry. Costs incurred in each study group were also measured to estimate the incremental cost-effectiveness ratio (ICER).

**Results:** The mean duration of diarrhea from enrolment and the mean stool weight during hospital stay were 63.7 hours and 940 grams, respectively, and there were no significant differences in the adjusted means across treatment groups. Similarly the adjusted means of the amount of ORS or IV fluids used, the proportion of participants with diarrhea >7 days from onset, and the severity of diarrhea indicated by >3 episodes of some dehydration or any episode of severe dehydration after enrolment, did not differ across the three groups. There was no reduction in subsequent risk of diarrhea or ALRI and no improvement in growth in the supplemented groups. The predictors of
prolonged diarrhea were younger age, fever, dehydration, dysentery, weight for age Z score <-2 and those who received medications at enrolment. The influence of zinc on the risk of diarrhea for more than 3 days also depended on the isolated organism – beneficial in *Klebsiella*, neutral in *Escherichia coli* and parasitic infections but detrimental in rotavirus co-infections. The results of the meta-analyses showed that zinc supplementation reduced the mean duration of diarrhea by 4-5 hours a day but had no effect on stool frequency or stool output, and increased the risk of vomiting. The subgroup meta-analyses and meta-regression showed that age, stunting, breast-feeding and baseline zinc levels could not explain the heterogeneity associated with differential reduction in the mean diarrheal duration. The ICER showed that the both cost and duration of diarrhea was more in the supplemented groups.

**Conclusions:** The expected beneficial effects of zinc supplementation for acute diarrhea were not observed. Therapeutic Zn or Zn and Cu supplementation may not have a universal beneficial impact on the duration of acute diarrhea in children. Understanding the predictors of zinc efficacy, including the role of diarrheal disease aetiology on the response to zinc, would help to identify the populations most likely to benefit from supplementation. To improve the programmatic use of zinc, further evaluations of the zinc salts used, the dose, the frequency and duration of supplementation, and its acceptability are required. The significant heterogeneity of responses to zinc suggests the need to revisit the strategy of universal zinc supplementation in the treatment children with acute diarrhea in developing countries.