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REVIEW ARTICLE

Zinc for Acute Diarrhea and Amoxicillin for Pneumonia, Do They Work?

Delivered at the AIIMS, IJP Excellence Award for the year 2013 on 7th September 2014

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Abstract Acute diarrhea and pneumonia are the two largest killers of under-five children in the world. Zinc, used in management of acute diarrhea and Amoxicillin, used in community acquired pneumonia, feature in the list of 13 Life Saving Commodities for Women's and Children Health by the UN Commission. Zinc has caught wide scientific attention for the conceptual promise it has to offer for prevention, control and treatment of acute diarrhea. This presentation focuses on author's research on the mechanisms by which zinc might contribute to the pathogenesis of acute diarrhea and the degree of success achieved in diarrhea control and treatment by zinc supplementation including its impact on mortality. However, emerging evidence in terms of controlled studies in humans beckons a more complete understanding of the mechanistic basis for zinc supplementation. Current evidence indicates that studies specifically addressing the variability in response to zinc supplementation need to be undertaken to better comprehend these mechanisms. Similarly, the author presented her research that examined the role of oral amoxicillin in community management of severe pneumonia in children and the need to assess its universal efficacy in all children with severe pneumonia.

Keywords Community based challenges · Research in diarrhea and pneumonia management · Quality of care · Infants and children

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Introduction

This article is based on author's oration at the IJP Excellence Research Award 2014, on 7th September 2014 at the AIIMS, New Delhi. She briefly traced her journey and modest efforts to contribute meaningfully to child health research and in particular to research in acute diarrhea and pneumonia in children. India still struggles with problems like malnutrition, infectious diseases, poverty, food insecurity, poor hygiene and sanitation that result in high morbidity and mortality in infants. Research and new developments should drive improvements in quality of care for children. The author fervently hopes that this article helps to understand how research can be reviewed and applied for clinical and programmatic decisions for better health outcomes in children.

Zinc for Acute Diarrhea

Diarrhea continues to be a persistent threat to health in the developing countries. Annually 10.8 million children die before their fifth birthday; of whom 70 % die during infancy [1]. Much of the success achieved in the control of diarrheal morbidity and mortality has been conventionally attributed to two therapeutic interventions: the oral rehydration solution (ORS) and zinc supplementation [2, 3]. Zinc has been used because of its compelling biological role in etiopathogenesis of diarrhea that offers therapeutic and prophylactic benefits. Zinc plays a substantive and significant role in immunity. Zinc is a signalling molecule in several immune cells like monocytes, dendritic cells and macrophages and it plays an important role in cell-mediated immune functions and oxidative stress. It is an anti-inflammatory agent and improves general immune function by its direct effect on the stimulation of thymus, naïve

T cell production, clonal expansion, Th1/Th2 cell differentiation and Th1 T cell stimulation. Interestingly, differential immune effects of zinc have been noted on pathogen specific immune responses. For example, a zinc upregulated Th1 response is more protective against invasive diarrheal pathogens such as Salmonella spp. and Shigella spp. Zinc can modify expression of genes encoding several zinc-dependent enzymes like metalloproteases and uroguanylin. In cases of zinc deficiency, the activity of these enzymes is decreased. Moreover, zinc may also modulate the cytokine gene expression especially of interleukin-8 and tumor necrosis factor–α. These latter influences of zinc further contribute to its actions on the immune system. Lastly, contradictory to these anti-diarrhea mechanisms of action, zinc reduces the intestinal absorption of other important trace elements like iron and copper. The latter, combined with a reduced activity of the erythrocytic superoxide dismutase can have detrimental effect on diarrheal outcomes. Nevertheless, the net biological effect of zinc on diarrhea is considered to be favorable, therefore the effect of zinc supplementation for prevention and treatment of diarrhea continues to be evaluated since three and half decades [4].

The author and team reviewed the preventive effect of zinc for reducing the incidence of diarrhea [5]. They included 37 studies (220,805 subjects for reports having one or more of the following five outcomes- Incidence of diarrhea, prevalence of diarrhea, incidence of persistent diarrhea, incidence of dysentery and incidence of mortality). For the incidence of diarrhea, they included 38 comparisons from 37 studies (a comparison of 69,934 children in zinc and 75,028 in comparison group). They found that zinc supplementation has a modest 9 % beneficial association (prediction interval was 0.9 with 95 % CI 0.73–1.13) and heterogeneity was 66 %. The cumulative meta-analysis of the chronologically ordered studies showed that there was a trend for monotonically decreasing benefit of zinc with the chronological rank of the studies. Significant benefit of zinc was observed in the first two quartiles of publication year but not in the third and fourth ones, suggesting that more recent evidence points towards diminished preventive benefit ascribable to zinc supplementation. No publication bias was observed. They examined the reasons for heterogeneity. Age explained 6.3 % of heterogeneity using meta-regression. Restricted meta-analysis showed that as age increased by each month, the beneficial association of zinc supplementation increased by 0.31 %. They also observed that the studies from Asia showed a significant reduction in diarrheal incidence but with large heterogeneity between study groups. In contrast, studies from America, Africa, Oceania did not demonstrate a significant benefit of zinc. The effect of zinc on prevalence of diarrhea was evaluated from 15 studies that enrolled 3501 and 3033 children respectively in zinc and comparison groups. There was a 19 % reduction in acute diarrhea prevalence (RR 0.8, 95 % CI 0.75–0.88), however, there was significant heterogeneity of 89.5 %. For the incidence of persistent diarrhea, 11 studies which enrolled 31,106 and 36,899 participants in zinc and comparison group respectively showed a non-significant association on the reduction of risk by 11 %. The reduction of incidence of dysentery was estimated from 7 studies including 33,391 and 39,446 children in zinc and comparison group, respectively. There was a non-significant reduction of 11 % and heterogeneity of 38 %. The effect of zinc on mortality was assessed from 12 studies enrolling 111,790 and 118,140 children in zinc and comparison group, respectively. Although there was 10 % reduction in risk of mortality with 48 % heterogeneity, it did not achieve statistical significance. Finally a recent meta-analysis by Mayo-Wilson et al. reported reduction in incidence of all-cause diarrhea (RR 0.87, 95 % CI 0.85–0.89), but there was evidence of reporting bias and 88 % heterogeneity. The effect on mortality was small and non-significant (0.95, 95 % CI 0.86–1.05). Although this systematic review also reported a decrease in hemoglobin and increase in vomiting in zinc supplemented group, they concluded that the overall modest and insignificant effect on mortality, and, a 13 % reduction in incidence of diarrhea using preventive zinc supplementation outweighed potential harms in areas with high risk of zinc deficiency [6].

The author also reviewed the therapeutic effect of zinc supplementation for acute and persistent diarrhea. Their meta-analysis included 19 trials, with 26 comparisons representing 8957 children. The results support a statistically significant effect of zinc supplementation on reduction in mean diarrheal duration by 19.7 % (95 % CI 11.9 %–27.4 %). The extent of heterogeneity across studies was statistically significant (I^2 86.5 %, p 0.001). For this outcome, the subgroup meta-analyses showed that the country of origin could not explain the heterogeneity, however age and study setting were associated with a differential reduction in the mean diarrheal duration. The author observed that in the five study groups from two studies that recruited infants only, the standardized mean difference (SMD) was 0.06 whereas, when the analysis was restricted to the studies that included other age groups also, the SMD was −0.32, a difference that was highly statistically significant (unpaired Student's t test p-value for difference in SMDs=0.006). The hospital-based studies were more likely to show improvement as compared to studies conducted in community settings (SMD −0.33 *vs.* −0.13, respectively and unpaired Student's t test p value=0.049). Studies using zinc gluconate, and those using vitamin A as a co-intervention showed a significant reduction in diarrheal duration and were homogeneous. Rates of vomiting after zinc administration were assessed from 10 trials and 14 comparisons representing 6779 children. In a quantitative synthesis of these results, the authors observed that the risk of vomiting

was significantly increased after zinc administration [(19.2 % in the zinc supplemented group and 9.2 % in the zinc withheld group) summary OR 2.13, 95 % CI 1.37–3.31]. However, this zinc effect was significantly heterogeneously distributed across the trials (I^2 81.2 %, $p<0.001$) [7]. The author also explored the effect of causative organisms. Seven trials have reported the array of causative organisms for diarrhea and in the present review the author observed that the effect of zinc on mean diarrheal duration was significant in trials not reporting *Escherichia coli* and rotavirus as the causes (SMD −0.14, 95 % CI −0.21 – −0.07; data not shown) [8]. The author also used data on 801 children with acute diarrhea recruited in a randomized, double blind controlled trial of zinc and copper supplementation conducted by her, to understand the impact of zinc and diarrheal etiology. Using pre-specified subgroup analyses, multidimensionality reduction analyses, tests of heterogeneity, and stepwise logistic regression for tests of interactions, they found that the influence of zinc on the risk of diarrhea for more than 3 d depended on the isolated organism—beneficial in Klebsiella, neutral in *Escherichia coli* and parasitic infections, and detrimental in rotavirus co-infections. Although they found similar results for the outcome of high stool volume, the results did not reach statistical significance. These findings suggest that the current strategy of zinc supplementation in all cases of acute diarrheas in children may need appropriate fine tuning to optimize the therapeutic benefit based on the causative organism, but further studies need to confirm and extend these findings. Zinc supplementation had a clear benefit in reducing the incidence of persistent diarrhea by approximately 25 %. It improved the recovery from persistent diarrhea by 24 % and reduced the proportion of children with persistent diarrhea extending beyond 3 d after zinc supplementation by 30 % and of mean duration of persistent diarrhea by 21.5 %–29.3 %. However it was associated with significantly high risk of vomiting. The most recent Cochrane review of therapeutic effect of zinc supplementation for acute diarrhea concluded that zinc supplementation shortened duration of diarrhea by 10 h (MD −10.44 h, 95 % CI −21.13 to 0.25; 2175 children, six trials, low quality evidence), and reduced the number of children whose diarrhea lasted until day seven (RR 0.73, 95%CI 0.61 to 0.88; 3865 children, six trials, moderate quality evidence). The effect was greater in children with signs of moderate malnutrition (reduction of duration by 27 h, three trials, high quality evidence). In children aged less than 6 mo, zinc supplementation did reduce the duration of diarrhea (5.23 h, 95 % CI −4.00 to 14.45; 1334 children, two trials, low quality evidence), but alarmingly increased the proportion of children whose diarrhea persisted until day seven (RR 1.24, 95 % CI 0.99 to 1.54; 1074 children, one trial, moderate quality evidence). No trials reported serious adverse events, but zinc supplementation during acute diarrhea caused vomiting in both age groups (RR 1.59, 95 % 1.27 to 1.99; 5189 children, 10 trials, high quality evidence). They also concluded lack of sufficient evidence to conclude whether therapeutic zinc supplementation reduces death or hospitalization (very low quality evidence) [9]. Therefore research is needed to understand reasons for heterogeneity in effect measures and the populations where zinc is likely to be most beneficial so that most effective strategies to deliver zinc to this population can be identified.

Role of Oral Amoxicillin in Community Management of Severe Pneumonia

Injectable penicillin and hospitalization was the recommended treatment for World Health Organization (WHO)-defined severe pneumonia (fast breathing, lower chest in-drawing and absence of danger signs) based on the 2005 WHO guidance for management of pneumonia in children [10]. Potential benefits of oral treatment include decrease in possibility of need for referral, hospitalization, needle-borne infections, costs to family and the hospital. So there was a need to evaluate the efficacy of oral amoxicillin for management severe community acquired pneumonia (CAP). This is especially important to prevent morbidity and mortality when families delay treatment and decline to take their children to the hospital, preferring home management or treatment by healers. Therefore the aim was to determine whether oral amoxicillin and parenteral penicillin were equivalent in the treatment of severe pneumonia in children aged 3–59 mo. APPIS (amoxicillin penicillin pneumonia international study), a multicentric, randomised, open-label equivalency study was undertaken at tertiary-care centres in eight developing countries in Africa, Asia, and South America. Children aged 3–59 mo with severe pneumonia were admitted for 48 h and randomly allocated to receive either oral amoxicillin (n=857) or parenteral penicillin (n=845) for 48 h [11]. A review of this study and four others that were subsequently published reported non-inferiority of oral amoxicillin as compared to standard parenteral treatment for WHO-defined severe CAP in 3–59 mo old children [12]. The four trials that were included in this review were the NOSHOTS at seven sites in Pakistan, comparing hospitalization with parenteral ampicillin to home treatment with oral amoxicillin [13]; two cluster-randomized trial in Haripur and Matiari districts of Pakistan where oral amoxicillin was compared to standard treatment of first dose of trimethoprim/sulfamethoxazole and referral for parenteral therapy [14, 15]; ISPOT - a mutlicentric open trial of oral amoxicillin at hospital compared to oral amoxicillin at home for CAP severe pneumonia. Based on the above evidence, WHO revised and simplified the management guideline for CAP in children aged 3–59 mo [16].

Children with fast breathing with chest-indrawing that were previously classified as “severe pneumonia” are now classified as “pneumonia with chest indrawing” and can be

managed with oral amoxicillin at least 40 mg/kg/dose twice daily (80 mg/kg/d) for 5 d. Those that were previously classified as very severe disease are now classified as severe pneumonia that require hospitalization and parenteral therapy. It is expected that this simplified management will facilitate early identification and management of cases in the community and reduce mortality. The studies that contributed to revision of the recommendations have few limitations. The studies were not blinded, included large numbers of children with chest indrawing who had wheeze and excluded sick children with radiological consolidation, those with co-morbidities, moderate to severe malnutrition and recent history of measles. The recent recommendations have two caveats. Firstly, children at high risk for treatment failure such as those with malnutrition, measles and other co-morbidities such as congenital heart diseases, cerebral palsy *etc* may not present with danger signs such as hypoxia, lethargy, failure to feed, convulsions or cyanosis that categorize them as severe pneumonia based on the recent recommendations. However these children are at high risk for mortality and may respond inadequately to oral amoxicillin. It is also likely that large number of children who may receive amoxicillin for fast breathing with or without chest indrawing could have viral pneumonia, bronchiolitis or asthma, and frequent use of amoxicillin in such patients could lead to widespread antimicrobial resistance [17].

In conclusion, despite compelling evidence for use of zinc supplementation to reduce duration of acute diarrhea in children, there is significant variability in its effectiveness to prevent and treat diarrhea with no reduction in diarrhea related mortality. Therefore further research is needed to understand the reasons and the population that is most likely to be benefited. Similarly oral amoxicillin may not be universally beneficial for all patients of CAP with chest in-drawing. Therefore ongoing programmatic evaluation of its effectiveness in reducing mortality, the populations where it is most likely to be effective and its impact on anti-microbial resistance is needed.

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