Micronutrients for the Prevention and Treatment of Diarrhea in Children in Low- and Middle-Income Countries

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Published online: 27 March 2014
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Abstract Diarrhea is one of the leading causes of childhood morbidity and mortality. This review synthesizes the most recent evidence on micronutrients interventions for the prevention and treatment of diarrhea in children in low- and middle-income countries. Systematic reviews and high-quality trials were searched in the Cochrane Library, MEDLINE, and the e-Library of Evidence for Nutrition Actions (eLENA) in January 2014. Evidence supports a benefit of zinc supplementation for prevention and treatment of diarrhea, although this is limited to children over 6 months of age and in countries with moderate to high levels of zinc deficiency. Evidence supports the use of vitamin A supplementation for reducing all-cause mortality as well as diarrhea-related mortality, the substantial heterogeneity of findings in different studies remains unexplained. Multiple micronutrient powders have recently been associated with an increased risk of diarrhea and dysentery, which calls for careful monitoring in future studies as well as in ongoing programs.

Keywords Diarrhea · Children · Zinc · Vitamin A · Multiple micronutrient powders · Review · Tropical medicine · GI infections · Bacterial infection · Bacterial tropical medicine

Introduction

According to recent global estimates, in 2010 there were 1.731 billion episodes of diarrhea in children younger than

5 years. Among these, 36 million children had a severe episode of diarrhea and 700,000 children died [1].

The global burden of diarrhea is highest in Southeast Asia and Africa, with 15 countries – Afghanistan, Angola, Burkina Faso, China, Democratic Republic of the Congo, Ethiopia, India, Indonesia, Kenya, Mali, Niger, Nigeria, Pakistan, Tanzania, and Uganda – accounting for approximately half (53 %) of total episodes and 74 % of the total diarrhea mortality in children [1].

Although overall morbidity and mortality from childhood diarrhea is decreasing, only a minority of countries experienced the recent rates of decline for diarrhea needed to achieve target four of the Millennium Development Goals [2]. It is estimated that only about one-third of episodes of severe diarrhea are preventable by vaccination (i.e., through rotavirus and cholera vaccines) [1, 3]. Other interventions to prevent and treat diarrhea include breastfeeding support, improving water provision and use, sanitation and hygiene, oral rehydration solutions, and community case management [3]. This article reviews the role of micronutrients in preventing and treating infantile diarrhea in the developing world.

Methods

This paper is an umbrella review synthesizing the most recent evidence on micronutrient interventions for the prevention and treatment of diarrhea in children in low- and middle-income countries. Evidence searched included Cochrane systematic reviews and other high-quality systematic reviews, complemented with reports of the more recent high-quality randomized controlled trials. Three electronic databases were searched in January 2014 to retrieve relevant studies: the Cochrane Library, MEDLINE, and the e-Library of Evidence for Nutrition Actions (eLENA). Studies reporting on diarrhea in children younger than 5 years of age were selected for

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inclusion. The relevant current WHO recommendations are also presented.

Results

Zinc

It is estimated that nearly 20 % of children worldwide are at risk of zinc deficiency, in particular in Sub-Saharan Africa and South Asia [3, 4]. Zinc requirement is higher during childhood due to rapid growth. Zinc cannot be stored in the body, and its excretion is increased during episodes of diarrhea. Zinc intake occurs with foods, but only “expensive foods” such as meat and fish guarantee high content of easily absorbable zinc. All of these factors contribute to the high prevalence of zinc deficiency in small children in low- and middle-income countries. Adequate zinc intake is essential for immune system functioning and skin and mucosal resistance to infection, as well as overall growth and development [4]. Although the primary mechanisms through which zinc can be of benefit for preventing and treating diarrhea are not yet fully elucidated, at least three different mechanisms have been proposed: a) direct effect on ion channels (i.e., zinc acts as a potassium channel blocker of adenosine 3-5-cyclic monophosphate-mediated chlorine secretion), b) stimulation of the immune reaction (i.e., zinc promotes the production of antibodies and circulating lymphocytes against intestinal pathogens), and c) mucosal effect (i.e., zinc may help to restore the integrity of the gut mucosa) [5–7].

Since 2004, WHO/UNICEF have been recommending zinc supplementation for children with diarrhea [8, 9•]. The recommended dose is 20 mg/day (10 mg for infants under 6 months of age) for 10–14 days.

A recently updated Cochrane review of 24 randomized controlled trials on more than 9,000 children showed that in countries with moderate to high risk of zinc deficiency, zinc supplementation reduced the duration of diarrhea in children aged 6 months and older [10•]. Zinc supplementation shortened the duration of diarrhea by around 10 hours (mean difference [MD] 10.44 hours, 95 % CI, 21.13–0.25; 2,175 children, 6 trials) and reduced the number of children whose diarrhea persisted until day 7 (risk ratio [RR] 0.73, 95 % CI, 0.61–0.88; 3,865 children, 6 trials). In children with moderate malnutrition, the effect of zinc appears to be greater, reducing the duration of diarrhea by around 27 hours (MD 26.98 hours, 95 % CI 14.62–39.34; 336 children, 3 trials). Zinc supplementation also shortened the duration of persistent diarrhea by around 16 hours (MD 15.84 hours, 95 % CI, 25.43–6.24; 529 children, 5 trials). No benefit was observed in children aged less than 6 months, who may have sufficient zinc reserves with adequate breastfeeding. These studies were not designed to assess the effect of zinc on death or hospitalization, and there was no direct evidence from randomized controlled trials

on these two outcomes. The main adverse effect of zinc supplementation was vomiting (RR 1.59, CI 95 %, 1.27–1.99; 5,189 children, 10 trials), which may be due to the metallic zinc aftertaste [10•].

The most recent systematic review on zinc supplementation for prevention of diarrhea included 37 studies on a total population of 220,805 children [11•]. As with previously published data [12–15], this review showed benefit of zinc, reduced incidence of diarrhea by 9 % (RR 0.91, 95 % CI, 0.88–0.94, 32 studies) and prevalence of diarrhea by 19 % (RR 0.01, CI 95 %, 0.75–0.88, 15 studies). However, high heterogeneity of effect was noted across studies. Factors significantly associated with greater effect of zinc or lesser heterogeneity across studies were age of over 12 months, setting (Asia or lower-middle-income countries), type of zinc supplement (zinc gluconate), and period during which the study was conducted (with most recent trials showing a lower effect of zinc).

The review [11•] also showed that zinc supplement had no significant effect on reducing all-cause mortality in children aged less than 5 years (RR 0.90, 95 % CI, 0.78–1.04, 12 studies), thus contradicting previous meta-analyses [14]. It is possible that zinc supplementation may have a more pronounced effect on diarrhea-related mortality, which may have been masked when considering all-cause mortality, or that zinc has a more pronounced effect in select groups of children, such as those with higher risk of zinc deficiency [16]. Further studies are needed to explore this hypothesis.

Vitamin A

It is estimated that vitamin A deficiency affects approximately 190 million preschool-age children, mostly from Africa and Southeast Asia [17, 18•, 19•]. Vitamin A requirement is higher during childhood due to rapid growth. Vitamin A deficiency is due to inadequate intake with foods and it is favored by infectious diseases. The combination of poor diet and infection perpetuates a vicious circle that particularly affects young children and pregnant or lactating mothers. Vitamin A is required for normal functioning of the visual system, maintenance of cell function for growth, epithelial integrity, red blood cell production, immunity, and reproduction [20•, 21•]. Severe vitamin A deficiency can cause night blindness and may increase the risk of illness and death from childhood infections, including measles and diarrhea [17, 18•, 19•, 20•, 21•].

WHO guidelines for vitamin A supplementation in children were recently revised. In settings where vitamin A deficiency is a public health problem, current guidelines recommend high-dose vitamin A supplementation every 4 to 6 months for infants and children 6–59 months of age, including HIV-positive children, as a public health intervention to reduce child morbidity and mortality [18•]. Vitamin A is not recommended for children younger than 6 months; mothers

are encouraged to exclusively breastfeed infants for the first 6 months to achieve optimal growth, health, and development [19•, 20•].

A Cochrane review of 43 trials and a total 215,633 children evaluated the effectiveness of vitamin A supplementation in the prevention of morbidity and mortality in children 6–59 months of age [21••]. Vitamin A reduced the overall risk of death by 24 % (RR 0.76, 95 % CI, 0.69–0.83, 17 trials). Diarrhea-related mortality was reduced by 28 % (RR 0.72, 95 % CI, 0.57–0.91, 7 trials) and the occurrence of new episodes of diarrhea by 15 % (RR 0.85, 95 % CI, 0.82–0.87, 13 trials). Vitamin A administration was not associated with any immediate serious adverse effects with the exception of more vomiting within the first 48 hours (RR 2.75, 95 % CI, 1.81–4.19, 3 trials). It was not possible to perform subgroup analyses for dose and frequency of supplementation, as the analyses were underpowered and any effects would have been attributed to chance.

The DEVTA trial [22••], which was published after the above-cited Cochrane review, challenged the previous results. This study was the largest drug trial ever undertaken, with 2 million preschool children in India consuming four tons of vitamin A over five years. The effect of vitamin A on mortality in DEVTA was not significant (RR 0.96, 95 % CI, 0.89–1.03). When the results from DEVTA are pooled with the other studies reporting on mortality, the resulting effect size of vitamin A supplementation on mortality is reduced from 24 % to 12 % (RR 0.89, 95 % CI, 0.84–0.95). Although DEVTA enrolled 10 times the number of children included in the other studies, the weight of the study in the pooled analysis is reduced by the cluster effect [23].

Taken together, these findings suggest that the magnitude of the effect of vitamin A may differ depending upon characteristics of the setting and of population. Other factors such as the efficiency of the delivery platform may also influence the effectiveness of micronutrient supplementations.

Another four Cochrane reviews contributed in summarizing the evidence on vitamin A supplementation in children with different characteristics.

Irlam et al. [24•] synthesized the evidence on vitamin A supplementation in HIV-infected children. A meta-analysis of three existing trials suggested that vitamin A reduces the overall risk of death in HIV-positive children (RR 0.55, 95 % CI, 0.37–0.82, 287 children), while effects on diarrhea morbidity were heterogeneous among trials.

Both Haider et al. [25] and Gogia et al. [26] reported on vitamin A supplementation in newborns. Although the two reviews had slightly different criteria of inclusion and results, overall, there was no convincing evidence that vitamin A supplementation in children under the age of 6 months results in a reduction in infant mortality or morbidity in low- and middle-income countries. Several randomized double-blind placebo-controlled trials are currently ongoing to assess the

efficacy of vitamin A supplementation in children less than 6 months of age.

Darlow et al. [27] evaluated vitamin A supplementation in very low-birth-weight infants, but diarrheal was not included among the outcomes assessed.

Multiple Micronutrient Powders (MNP)

Micronutrient powders (MNP), also called “sprinkles,” are single-dose packets of powder containing iron, vitamin A, zinc, and other vitamins and minerals that can be sprinkled onto any semisolid food, at or away from home, to increase the content of essential micronutrients in the diet.

WHO recommends the use of MNP containing at least iron, vitamin A, and zinc for home fortification of foods as an option to improve iron status and reduce anemia in infants and children 6–23 months of age [28••]. In malaria-endemic areas, the iron provision should be implemented in conjunction with measures to prevent, diagnose, and treat malaria [28••].

A Cochrane review on MNP [29••] included 8 trials and a total of 3,748 children. Home fortification with MMP reduced anemia by 31 % (RR 0.69, 95 % CI, 0.60–0.78; 6 trials, 1,447 participants) and iron deficiency by 51 % (RR 0.49, 95 % CI, 0.35–0.67; 4 trials, 586 participants), but no benefit on other outcomes was demonstrated. Few studies reported on diarrhea, and results were conflicting.

A subsequent review [30••] identified an additional 7 studies and essentially confirmed the previous findings. MMP significantly reduced the prevalence of anemia by 34 %, iron-deficiency anemia by 59 %, and retinol deficiency by 21 %. No significant benefit was observed for other outcomes (i.e., serum zinc, zinc deficiency, linear growth), for which there were few contributing studies.

In a recent large trial on MNP supplement in children in Pakistan [30••], while the expected decrease in iron-deficiency anemia was noted, there was strong evidence of increased proportion of days with diarrhea ($p=0.001$) and increased incidence of bloody diarrhea ($p=0.003$). Two previous systematic reviews had suggested that iron supplementation in children may be associated with an increase in diarrhea episodes [31, 32] as well as malaria episodes [32]. It is still unclear whether the observed increased risk of diarrhea was due to increased risk of malaria or to other pathogens [30••]. It is also not clear whether the association of different micronutrients, such as iron and zinc, compared to iron alone, increases or decreases the risk of diarrhea in the supplemented children [33]. It is imperative that future trials on MNP report more specifically on diarrhea and malaria outcomes. At the present time, WHO recommends that in malaria-endemic areas, MNP should be implemented together with measures to prevent, diagnose, and treat malaria [28••]. According to recent findings [30••], when using MNP, attention should also

be given to measures to record, prevent, diagnose, and treat diarrhea.

Conclusions

Overall, evidence supports a benefit of zinc supplementation for treatment and prevention of diarrhea. However, this is limited to children over 6 months of age and in countries with moderate to high levels of zinc deficiency. Evidence supports the use of vitamin A supplementation for reducing all-cause mortality as well as diarrhea-related mortality. However, substantial heterogeneity of findings in different studies remains unexplained, and reasons for such findings should be explored in future studies. Multiple micronutrients powders have been recently associated with an increased risk of diarrhea and dysentery. This calls for the careful monitoring of diarrheal diseases in MNP-supplemented children, both in future studies as well as in ongoing programs.

Compliance with Ethics Guidelines

Conflict of Interest Marzia Lazzarini declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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