

What micronutrient supplements in persistent diarrhoea have been shown to be beneficial?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at: http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What micronutrient supplements in persistent diarrhoea have been shown to be beneficial?*

The **WHO Pocketbook of Hospital Care for Children** recommends that affected children receive nutritional rehabilitation including supplementary multivitamins and minerals for two weeks as part of their treatment. These should provide as broad a range of vitamins and minerals as possible, including at least two recommended daily allowances (RDAs) of folate, vitamin A, zinc, magnesium and copper (Pocketbook, 5.3.1, pg 122f).

Introduction:

Diarrhoeal disease remains a major cause of childhood mortality and is responsible for an estimated 3 million childhood deaths worldwide every year. (1, 2) Persistent diarrhoea, defined as the passage of >3 stools per day for, is the cause of 30-50% of all diarrhoea related deaths and a substantial proportion of diarrhoea related morbidity. (1, 2)

Persistent diarrhoea is closely linked to nutritional status. (1, 2) It often occurs in children who are undernourished and has significant nutritional consequences. (2). Therefore, addressing nutritional issues is an important part of case management of children with persistent diarrhoea.

Methodology

Cochrane data-base: No Cochrane reviews for this subject were found.

Pubmed: Terms used: "micronutrients" OR "vitamins" AND "persistent" OR "chronic" diarrhoea. Using clinical filters for "therapy" and "specific" 12 articles were found. All abstracts were read. 3 relevant double-blind randomised control trials (evidence type 1b) were selected for further analysis. Two randomised controlled trials were excluded because of methodological flaws (non-blinded).

Using the "sensitive" filter, a single type A systematic review on the effect zinc supplementation in persistent diarrhoea was also found. This reviewed all relevant published and unpublished randomised control trials (5 trials in total) at the time of publication (2000).

Results

Effect of zinc supplementation in persistent diarrhoea

Duration of episode

Effect analysis showed that the mean duration of diarrhoea was lower in the zinc-supplemented groups in all studies. (1) The summary estimate of the effect size for reduction in duration was 29% (95% CI: 6%, 53%). (1)

Severity of episode

Individual trials had variable results with regards to severity of diarrhoeal episodes in treatment groups. (1, 4, 5, 6).

One trial in India reported a 21% lower **stool frequency** (P=0.08) and a, hospital-based study in Bangladesh demonstrated a 39% reduction in

stool output in the zinc-supplemented group ($p < 0.02$). (1, 6) However, several studies failed to demonstrate any difference in episode severity with zinc supplementation (5, 7).

In pooled analysis a 42% reduction in **treatment failures** or **death** (OR=0.58 95% CI: 0.37, 0.40) was reported in zinc supplemented groups. (1) There was heterogeneity for this outcome (chi-square=8.6, $P=0.04$) which was attributed to a single study in Pakistan. (1) After exclusion of this study there was no significant heterogeneity (chi-squared=3.2, $P=0.2$). (1)

Growth

The only study that that assessed long-term (6 month) anthropometric measures, found no effect of supplementation on growth (4).

Co-morbidities

Only one study assessed the affect of micronutrient supplementation on development of co-morbid disease in children being treated for persistent diarrhoea. (4) It found a trend towards decreased co-morbidities (fever, lower respiratory tract infection), although this was only statistically significant ($P=0.05$) for a reduction in cough. (4)

Effect of other micronutrients in persistent diarrhoea

Only two studies specifically addressed the effects of other micronutrients in persistent diarrhoea. (4, 6) One study compared effects of zinc alone as well as zinc plus a multivitamin with placebo. (4) In this study the combination of zinc with other micronutrients resulted in higher diarrhoeal morbidity than either zinc alone or placebo. (4) While these adverse effects could not be conclusively attributed to any specific micronutrient, it was speculated, given previous studies showing similar results, that results may have been related to the use of iron in the supplement.(4)

Another study compared zinc, zinc and Vitamin A and Vitamin A alone versus placebo in treatment of persistent diarrhoea. (6) This found no benefit in the addition of Vitamin A to zinc but did not report adverse events from Vitamin A supplementation. (6)

Summary

Adjuvant zinc supplementation in persistent diarrhoea is well supported by research which demonstrates significant reductions in duration and severity of diarrhoea with supplementation. There is also evidence for a significant decrease in treatment failure and even mortality as a result of this intervention.

Evidence for benefit of supplementation of other micronutrients in persistent diarrhoea is less clear. In trials cited above, no benefits were noted with Vitamin A supplementation and use of a multivitamin containing iron was associated with increased morbidity in one study.

This area requires further research to ensure that adverse micronutrient combinations are avoided and that potential benefits of other micronutrients are fully utilised in case management of children with persistent diarrhoea.

References

1. Bhutta ZA, Bird SM et al. Therapeutic affects of oral zinc in acute and persistent diarrhoea in children in developing countries: pooled analysis of randomized controlled trials. *Am J Clin Nutr.* 2000 Dec; 72(6):1516-22.
2. Bhutta ZA, Gishan F et al. Persistent and chronic diarrhoea and malabsorption: Working Group report of the second World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr.* 2004 Jun; 39 Suppl 2:S711-6
3. http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm
4. Penny ME, Marin RM et al. Randomized controlled trial of the effect of daily supplementation with zinc or multiple micronutrients on the morbidity, growth, and micronutrient status of young Peruvian children. *Am J Clin Nutr.* 2004 Mar; 79(3):457-65.
5. Penny ME, Peerson JM. Randomized, community-based trial of the effect of zinc supplementation, with and without other micronutrients, on the duration of persistent childhood diarrhoea in Lima, Peru. *J Pediatr.* 1999 Aug; 135(2 Pt 1):208-17.
6. Khatun UH, Malek MA et al. A randomized controlled clinical trial of zinc, vitamin A or both in undernourished children with persistent diarrhoea in Bangladesh. *Acta Paediatr.* 2001 Apr; 90(4):376-80.
7. Roy SK, Tomkins AM et al. Impact of zinc supplementation on persistent diarrhoea in malnourished Bangladeshi children. *Acta Paediatr* 1998; 87:1235-9

