International Child Health Review Collaboration

What is the evidence that copper supplementation for children with severe malnutrition is 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 is the evidence that copper supplementation for children with severe malnutrition is beneficial?*

The **WHO Pocketbook of Hospital Care for Children** recommends that all severely malnourished children should receive 0.3 mg Cu/kg/day. (Pocketbook chapter 7.4.6, page 183)

Introduction:

Today, approximately 800 million people are living in areas of significant food insecurity. Malnutrition affects all age groups although certain populations are more vulnerable than others. Children, especially those less than 5 years old, are among the most susceptible. It is clear that malnutrition plays a major role in half of the 10-11 million annual child deaths in the developing world, and continues to be a cause and consequence of disease and disability in the children who survive [1]. Several adjuvant treatments have been proposed in the nutritional rehabilitation of children with severe malnutrition. This review intends to answer the question: What is the evidence that copper supplementation for children with severe malnutrition is beneficial?

Methodology

The first clinical search strategy employed for this review was as follows: copper AND malnutrition. Using the clinical filters for both "clinical trials" and "human", 17 articles were found. The same search strategy restricted to "review" articles identified 114 articles. No articles were found when "practice guideline" or "meta-analysis" filters were applied to this search strategy.

A second search strategy was employed utilizing the following search terms: copper AND (protein-energy malnutrition OR kwashiorkor OR marasmus). Seventy-nine, 42, and 78 articles were found, respectively.
All abstracts were read. If there was any doubt as to the relevance of the article, the complete article was sourced.

A single randomized controlled trial (type 1b) was found and is appraised in this review.

Results

In a randomized, blinded, controlled study involving a small number of infants receiving treatment for marasmus, Castillo-Durán et al investigated the effect of copper supplementation (80 micrograms per kilogram per day) on plasma copper and ceruloplasmin levels, growth indicators, and the frequency and severity of intercurrent infections [2]. Of note, the effect of copper supplementation between intervention (13 patients) and control (14 patients) groups may have been tempered by three infants in the placebo group who crossed over and received supplementation because of markedly low plasma copper levels.

Both groups had similar energy intakes; copper levels were elevated in the supplemented group at 30 and 60 days. Weight-for-age and weight-for-length were not significantly different between supplemented and control groups, neither were the number of upper respiratory infections, febrile

days, and febrile episodes per child per month. There was however a significant difference in the incidence of lower respiratory infections between the two groups: seven children in the placebo group had clinical evidence of severe LRI versus one child in the supplemented group ($p<0.025$).

Discussion

Serum copper levels have been found to be low in children with severe malnutrition [3].Milk-based diets commonly utilized in the nutritional rehabilitation of these children may not provide a sufficient quantity of copper replacement. Copper is necessary for proper function of superoxide dismutase (SOD), a cytosolic enzyme that infers a cellular protective effect against free oxygen radicals produced during anaerobic metabolism2. Low SOD activity may occur in patients with copper deficiency and therefore result in a relative immune deficiency.

Summary

Copper supplementation may be beneficial for children with severe malnutrition. However, only a single randomized clinical trial has investigated this possibility, by measuring the effects of copper in a population of marasmic infants. This study suggested that copper supplementation resulted in a decreased incidence of lower respiratory tract infections (Grade B evidence). Further larger scale studies would be needed to confirm these findings or identify other beneficial effects of copper supplementation in severely malnourished children.

References

1. What do we mean by malnutrition? (Accessed August 15, 2005, at http://www.who.int/nut/nutrition2.htm).
2. Castillo-Duran C, Fisberg M, Valenzuela A, Egana JI, Uauy R. Controlled trial of copper supplementation during the recovery from marasmus. Am J Clin Nutr. 1983 Jun;37(6):898-903
3. Singla PN, Chand P, Kumar A, Kachhawaha JS. Serum, zinc and copper levels in children with protein energy malnutrition. Indian J Pediatr. 1996 Mar-Apr;63(2):199-203.

Table 1: Summary of studies comparing s/c adrenaline (epinephrine) with inhaled salbutamol.

Study	Subjects	No. of subjects	Intervention	Main outcome measures	Main results	Ref
Sharma A et al	Children 6-14 years	50	Sc epinephrine versus nebulized salbutamol	Increase in PEFR (%)	Mean increase in PEFR (%) similar in both groups epinephrine 27.7 + 0.7 vs salbutamol 28.8 + 0.06, p >0.05	4
Anantharaman V.	Children and adults 15-40 years	71	Sc adrenaline, nebulised salbutamol and intravenous aminophylline	Respiratory rate, Peak Expiratory Flow Rate (PEFR) and Patient's Subjective Assessment Scale (PSAS)	PEFR and PSAS were similar in subjects who received adrenaline and salbutamol; both were better than those who received aminopylline	5
Kornberg AE et al	Children 3-12 years	43	Sc adrenaline (long-acting) plus albuterol versus only albuterol*	Clinical score, peak expiratory flow rate and respiratory rate.	All three comparable in both groups	6
Becker AB et al	Children	40	Sc adrenaline versus nebulized salbutamol	Clinical score, respiratory rate, PaO2, PaCO2, FVC, FEV1, FEV1/FVC, and FEF25-75%.	All clinical and spirometry parameters comparable in both groups. PaO2 remained unchanged after salbutamol but increased significantly after epinephrine.	7
Ferres Mataro J et al	Children	100	Sc epinephrine versus inhaled salbutamol (4 puffs and 7 puffs delivered by metered dose inhaler)[†]	Clinical score at 0, 30 and 60 minutes	No statistical differences were observed between the three groups	8

[†]Salbutamol was delivered by metered dose inhaler

* Albuterol = Salbutamol