What is the evidence that zinc supplementation is beneficial in the treatment of severe malnutrition?

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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 zinc supplementation is beneficial in the treatment of severe malnutrition?*

The WHO Pocketbook of Hospital Care for Children recommends zinc supplementation, 2mg/kg/day, for at least 2 weeks as part of the rehabilitation protocol. (Pocketbook chapter 7, page 183).

INTRODUCTION

Zinc is an essential micronutrient whose deficiency has been linked to impairment of the nutritional rehabilitation following severe malnutrition in children.

The biological role of zinc is extensive. Over 300 catalytically active zinc metalloenzymes from all the major enzyme classes [1] and more than 2000 zinc dependant transcription factors have been recognised. [2] Zinc has a regulatory role in gene expression, apoptosis and synaptic signalling. [3] It has, as such, an important role in immunological function, where rapid cell turnover is crucial. [4,5]

Importantly, zinc does not have any functional tissue reserves that can be released in deficient states like iron or vitamin A and thus, dietary zinc is crucial to meet the body's daily demand. [3]

Zinc deficiency is common in children of developing countries. Low protein diets contain low levels of zinc; protein value is a close correlate of zinc content. [6] Further, staple based diets have high phyate levels which reduces the bioavailability of zinc. [7]

Current World Health Organisation (WHO) guidelines advise the use of zinc supplementation, 2mg/kg/day, for at least 2 weeks as part of the rehabilitation protocol. [8]

In moderately malnourished or normal children in developing countries, zinc supplementation has previously been shown to significantly increase the rate of linear growth. A meta-analysis of 33 RCTs gave an effect size of 0.309 (95% CI: 0.178, 0.439) for change in weight and for change in height of 0.350 (95% CI: 0.189, 0.511) and found non-significant effects for weight-for-height (WFH). The lack of response measured by WFH suggests that linear growth lean mass gain rather than fat-mass weight gain occurs with supplementation. [9]

The incidence and prevalence of diarrhoea and pneumonia in normal or moderately malnourished children in developing countries has also been conclusively demonstrated. A pooled odds ratio from 7 RCTs for incidence of diarrhoea was was 0.82 (95%CI:0.72, 0.93) and for prevalence 0.75 (95% CI:0.63, 0.88). From 4 RCTs, pooled odds ratio for the incidence of pneumonia was 0.59 (95% CI:0.41, 0.83). The authors identified the correction of a pre-existing zinc deficiency as the likely mechanism of action. [10]

This review intends to answer the question: What is the evidence that zinc supplementation is beneficial in the treatment of severe malnutrition in children under 5?

METHODS

The following search strategy was employed: [09/06/06]

Pubmed: Zinc[title] AND supplement* AND (maln* OR kwashiorkor)
This returned 80 articles of which 26 were relevant. » Run Search

The bibliographic citations from each of the articles used in the review were inspected for further relevant articles. This yielded one further study. [12]

Twenty-seven articles were identified by the literature search. Abstracts of all articles were reviewed to ascertain relevance. Where abstracts were not available complete articles were sourced. Inclusion criteria were then applied.

Criteria for "severe malnutrition" followed the WHO classification of: bilateral oedema, or <-3SD of NCHS reference for weight-for-height (<70). [8] Additionally, studies that met Gomez's classification [11] of <60% weight-for-age were included. There was considerable variation in the inclusion criteria classifications adopted by the studies and therefore Gomez's or equivalent weight-for-age based classifications were accepted.

One review, two studies that did not concern children, and thirteen studies that failed to meet inclusion criteria for "severe malnutrition" were excluded.

In total eleven trials fit the inclusion criteria and were included in this review [12-22], of which two were based on data from a single study. [13,14]

Table 1: Characteristics of included studies

Year	Author	Country	Level	IP/ OP	Inclusion criteria	*n*	Mean age	Random?	Alloc conc?	Blinding?
1978	Golden	Jamaica	1b	IP	Wellcome	10	15.3 ± 7.0	Yes	Yes	Double-blind Placebo
1981	Golden	Jamaica	2b	IP	Wellcome	34	12.5 ±0.9m	No	No	No
1988	Khanum	Bangladesh	2b	IP	Waterlow: Severe	60	29 m	No: Alternate allocation	No	No
1988	Simmer	Bangladesh	2b	IP	McLaren scoring WFH<70%	25	38.9 ± 4.6m	No: Alternate allocation	No	No
1988	Gatheru	Kenya	2b	IP	Wellcome All had: Kwashiorkor	82	1-3 y	No: Alternate allocation	No	No
1992	Golden	Jamaica	2b	IP	Wellcome All had: Marasmus	11	15.3 ± 4 m	No	No	No
1993	Helmalatha	India	1b	IP	Gomez Grade 3 (No infection)	33	27: 2-5y 6: 1-2 y	Yes	Unclear	Double-blind Placebo
1996	Chevalier	Bolivia	3b	IP	Waterlow: Severe	64	18.8 ± 7 m	No	No	No
1997	Vasudevan	India	1b	OP	IAP Grade 3/4	72	8-24 m	Yes	Unclear	Double-blind Placebo
1998	Doherty	Bangladesh	1b	IP/ OP	Wellcome	141	15.6 ± 8.8m	Yes	Yes	Double-blind Placebo
2002	Doherty	AS ABOVE								

Year	Author	Interventions	Follow up	% FU	Outcomes	Result S	Result C	Units	P values
1978	Golden	1% Zinc sulphate ointment applied to one arm	48 hr	100	Delayed hypersensitivity reaction	Greater on arms applied with zinc			P <0.01
1981	Golden	Cow's milk or soy formula 4.52 v 3.47 mg/l Zn	3 wks	100	Rate of weight gain	17	12	g/kg/d	p <0.02
1988	Khanum	10mg/kg/day of Zn as ZnSO4 from 15th day to 36 days	5 wks	100	Rate of weight gain at 36d WFH at 28 d WFA at 28 d	462 ± 232 95 ± 6.6 68.1 ± 8.7	374 ± 268 86 ± 6.6 59.7 ± 9.7	g/week % expected % expected	NS p < 0.001 p < 0.001
1988	Simmer	50mg/day of Zn as ZnSO4 or 10mg/kg/day if <5kg	2 wks	92	Rate of weight gain	8.83 ± 5.40	5.09 ± 5.37	g/kg/d	
1988	Gatheru	5mg/kg/day of Zn as ZnSO4	until discharge mean 17d	70.7	Total weight gain Time to lose oedema Duration of diarrhoea Time to healing: skin lesion Duration of anorexia	531 ± 277 6.3 ± 4.6 3.62 ± 2.78 7.9 ± 3.1 6.0 ± 3.16	338 ± 235 8.1 ± 4.4 10.8 ± 3.4 11.1 ± 2.1 10.3 ± 5.01	g days d d d	p < 0.05 p <0.05 p <0.001 p <0.03 p <0.05
1992	Golden	Added to food:(weight of food) Med: Add 4.97mg (/kg) High: Add 10.0 mg (/kg)	6 weeks	100	Rate of weight gain N net absorption as% N intake N retention as % of N intake	**H** 11.67 ± 2.44 **H** 86.7 ± 0.7 **H** 45.4 ± 4.5	**L** 10.10 ± 0.44 **L** 79.8 ± 2.8 **L** 37.0 ± 4.8	g/kg/d NNA%NI NR%NI	NS p <0.001 NS
1993	Helma-latha	40mg/d of Zn as ZnSO4 for 21 days	1 month	100	Rate of weight gain	23.1 ± 19.8	22.3 ± 25.4	g/kg/d	NS
1996	Chevalier	2mg/kg/day of Zn as elemental Zn	9 weeks	100	WFH at 9 weeks HFA at 9 weeks WFA at 9 weeks Left Thymic Lobule area 9 wks	-0.6 ± 0.9 -3.0 ± 1.2 -2.3 ± 1.0 453.0 ± 17.3	-0.6 ± 1.0 -3.2 ± 1.0 -2.4 ± 1.1 387.7 ± 25	Z score Z score Z score mm2	NS NS NS p < 0.05
1997	Vasude-van	6.6mg/day of Zn as ZnSO4 for 3 months	3 months	86.1	Rate of weight gain	1.4	0.98	g/kg/d	NS
1998	Doherty	1: 1.5mg Zn/kg 15 days 2: 6.0mg Zn/kg 15 days 3: 6.0mg Zn/kg 30 days Given as elemental Zn	3 months discharged at 15 days	88.7	change in WFH over 90d change in HFA over 90d change in WFA over 90d Mortality	**H** 1.62 ± 0.86 **H** 0.49 ± 0.27 **H** 1.45 ± 0.66 **H** 9 **M** 8	**L** 1.54 ± 0.93 **L** 0.44 ± 0.32 **L** 1.35 ± 0.69 **L** 2	Z score Z score Z score Deaths	NS NS NS p < 0.03

Key to table 1:

Level= Oxford Centre for Evidence Based Medicine Level of Evidence
Alloc Conc= Adequate Allocation Concealment?
%FU= % Follow up
WFA= Weight for age, WFH= Weight for height, HFA= Height for age
IP/OP: In patient or outpatient
S= Number in supplement group at completion
C= Number in control group at completion
All results in talbe are given as Mean± Standard deviation

RESULTS

There were five randomised controlled trials (RCTs) (level 1b evidence*), of which two were based on the same trial. There were five low quality RCTs (level 2b), which failed to apply either adequate blinding or randomisation and one case historically matched control study, which failed to get ethical approval for the creation of a true control group. (level 3b).

Of the eleven studies, most were relatively small, ranging from 11 to 141 participants. Eight were in-patient studies while the latest three were community-based studies. Three studies were from Jamaica, four from Bangladesh, two from India, one from Bolivia and one from Kenya. Seven used zinc sulphate; one added zinc acetate to a cow's milk based diet; one used two diets based on either soy or cow's milk based, with different proportions of zinc; one did not describe the form given and one used zinc sulphate ointment applied on the arm. Doses ranged from 1.5 to 10mg/kg/d. The length of intervention and follow up varied from 2 weeks to 3 months.

Weight gain and growth

In terms of outcomes, the main outcome assessed was weight gain and was evaluated by nine studies. This was measured by six studies as rate of weight gain, by one as total weight gain, by one as change in weight-for-age and by one as end weight-for-age in supplemented and control groups.

Five measured non-significant increases. [12,13,18,19,22] Four gave significant increases. [15,17,20,21]

Four of the five non-significant studies were RCTs (level 1b evidence) [13,18,19,22] and one was a case historically matched control study (level 3b). [12] Although these studies failed to reach statistical significance, all gave numerically increased measures of growth for zinc.

All of the four studies that gave statistically significant increases were low quality RCTs (level 2b). [15,17,20,21] P values varied between <0.02 and <0.05.

One randomised controlled trial [14] (level 1b study), examined IGF-1, its binding proteins and six markers of bone and collagen turnover. Three different doses of zinc produced no discernable effects in any of these markers. This may be because 1.5mg/kg/d provided for 15 days in the lowest-dose group was sufficient to produce an effect, particularly compared with the WHO recommendation of 2mg/kg/d.

A small low quality RCT (level 2b) [18] (n=11) measured the nitrogen (N) absorption and retention as a percentage of N intake. Supplementation increased absorption. Intestinal N absorption thus appeared to be limited by zinc deficiency. Due to the small sample size these findings need larger-scale verification.

Immune function

One RCT (level 1b) [16], measured the cutaneous hypersensitivity reaction after injecting Candida antigen intradermally after either zinc sulphate or placebo ointment was applied one on each arm so that infants acted as their own controls. They found that reactions were greater on the zinc arms, suggesting local increased zinc concentration improved the cell-mediated immune response. These results cannot be generalised to the effect of systemic supplementation.

A low quality RCT (level 2b) [15] measured the time taken for healing of skin lesions. They found reduced time in the supplemented group over controls (7.9 ± 3.1 versus 11.1 ± 2.1 days, P<0.03). They also found significantly reduced time for time to lose oedema, duration of diarrhoea, and duration of anorexia. The authors proposed that effects on diarrhoea were due to the necessity of zinc for the restoration of intestinal mucosa. Mechanisms for reducing anorexia were unclear. Effect on oedema was derived from increased albumin synthesis from the repletion of zinc.

The case historically matched control study (level 3b) [12] measured the size of the thymus by examining the left thymic lobule area using a mediastinal echographic camera on a longitudinal plane. They found a significantly increased thymus size at the study end-point of 9 weeks (453.0 ± 17.3 versus 387.7 ± 25.0mm2, P < 0.05). At 5 weeks, an even greater effect was observed (P < 0.001). They also noted decreased levels of immature lymphocytes (T6 or CD1) while mature lymphocytes (T3 or CD3) were stable. They concluded that zinc supplementation at physiological doses (2mg/kg/d) reduced immune recovery time and acted as an immune stimulating factor.

Mortality

One RCT (level 1b) [13] found that mortality was increased on higher dose zinc regimens. The high dose regimen received 6mg/kg/d for 30 days, the medium 6mg/kg/d for 15 days and the low dose 1.5mg/kg/d for 15 days. The risk of death (Yates-corrected chi square value) was 4.52 (P=0.03) for high and medium versus low dose regimens, (95% confidence intervals: 1.09, 18.8). Most of the deaths were sepsis related. The authors acknowledged that this could be a chance finding. This relationship with mortality was not borne by any other study. Two of the other eight studies that used oral zinc compounds used a dose greater than Doherty's "high dose" group and found no association with mortality.

DISCUSSION

All studies that measured weight gain favoured the use of zinc numerically, if not statistically significantly. When ranked according to methodological quality, it was immediately apparent that the greatest determinant of effect size was the quality of study. Lower quality studies that did not use blinding or adequate allocation concealment gave the greatest, significant effect sizes. This indicates the presence of ascertainment bias.

The most recent RCT (level 1b) [13], however, used three study groups, with the lowest dose group getting 1.5mg/kg/d for 15 days: there was no zero control group. Even this low dose may have been sufficient to produce substantial growth effects and thus the true effect of zinc supplementation may be larger.

All three studies that measured immune function suggested that zinc supplementation has a positive effect, experimentally and clinically.

Finally, the findings of the RCT (level 1b) [13], of increased mortality on high-dose zinc supplementation, advises caution in the use of high-dose supplementation of the level of 10mg/kg/d.

SUMMARY

In children under 5, recovering from severe malnutrition:

- Zinc supplementation increases the rate of weight gain during nutritional rehabilitation (Grade B recommendation), improves immune function and reduces the incidence of infection (Grade B recommendation).
- Currently available evidence lacks individual statistical power and is too heterogeneous to permit meta-analysis.
- For effect of zinc supplementation on weight gain, trends are evident towards a positive effect in higher quality studies and a significant effect is shown in low quality studies.
- Three studies of various quality observing different measures of immune function consistently found a significant effect of supplementation.
- Findings from one study advise against the use of high-dose zinc supplementation (above the recommended 2mg/kg/d). The WHO advises a dose of 2mg/kg/day.
- On the basis of current evidence it would be unethical to pursue futher trials of zinc supplementation with a no-zinc control group.

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