

The effect of zinc supplementation on HIV-1 replication in HIV-1-infected children.

CITATION

Bobat R, Coovadia H, Stephen C, Naidoo KL, McKerrow N, Black RE, Moss WJ *Safety and efficacy of zinc supplementation for children with HIV-1 infection in South Africa: a randomised double-blind placebo-controlled trial. The Lancet* 2005 Nov; 366 (9500):1862-7

RESEARCH QUESTION

What is the effect of zinc supplementation on plasma HIV-1 viral load and infectious disease morbidity in HIV-1-infected children?

THE STUDY DESIGN

Randomised, double-blind, placebo-controlled equivalence trial

An equivalence trial is conducted to show the therapeutic equivalence between two treatments. In this case it was done to show that the plasma HIV-1 viral load is not altered by the use of either zinc or placebo.

STUDY SETTING

Outpatient clinic at Grey's Hospital, Pietermaritzburg, South Africa
Written informed consent from parent or guardian. Ethics approval obtained

PARTICIPANTS

105 children enrolled over a 10 month period from March 2003 – December 2003. Follow-up completed in September 2004. Two withdrew and seven were found not to be HIV-infected, thus 96 children were block randomised by age group to either the intervention of zinc or placebo.

Included: Children aged between 6 and 60 months who are HIV-1 infected. Children who received a single dose of nevirapine were included.

Excluded: Children who are HIV-negative. Children receiving anti-retroviral treatment.

INTERVENTIONS

10mg of elemental zinc as sulphate or placebo every day for 6 months.

All children received cotrimoxazole and most received multivitamin supplements consisting of vitamins A (3000 IU), B₁ (1.5mg), B₂ (1.2mg), C (50mg), D (400 IU), and nicotinamide (10mg) per 5ml. Children were seen every two weeks for first month, monthly for five months, and a final visit nine months after zinc supplementation or placebo was started. Final visit was three months after stopping study drug.

OUTCOMES

Primary: Plasma HIV-1 viral load and infectious disease morbidity.

RISK OF BIAS (Risk Scale: Low – Moderate – High)

SELECTION BIAS: Low - Moderate

Children were block-randomised in three age strata, 6-23, 24-42 and 42-60 months. Randomisation list computer generated at WHO in a fixed block size of eight. Investigator at Grey's hospital assigned children to treatment groups. No mention of allocation concealment. Baseline characteristics including log₁₀ HIV-1 viral load and percentage of CD4+ T lymphocytes at baseline were similar. Not reported how many received single nevirapine or whether the number was balanced between the two intervention arms.

PERFORMANCE BIAS: Moderate

Double-blind Placebo controlled trial. Clinicians were not blinded. Not mentioned whether the intervention and placebo was identical. Compliance assessed at each follow-up by inspection of number of tablets remaining in packet and examination of log books completed by parent or guardian.

DETECTION BIAS: Low

Investigators not aware of assignment. Parents completed a questionnaire at each visit regarding any recent illness of child. Concentrations of HIV-1 RNA and CD4+ T lymphocyte cell counts were measured 1 month before randomisation, at randomisation and at 3, 6 and 9 months after the start of supplementation.

ATTRITION BIAS: Low

In the statistical analysis, a primary analysis was performed per protocol. No intention-to-treat analysis was done. Loss to follow up very low.

	Zinc	Placebo
Started	46	50
Completed study	44 (96%)	41 (82%)
Loss to follow-up	2 (4%)	9 (18%)

In the zinc group one patient (2%) was lost due to death by 6 months and another one due to death at 9 months. In the placebo group there were two deaths by three months, four deaths and 2 withdrawals by six months and one death by nine months. A study clinical officer or paediatrician surveyed the neighbouring clinics and hospitals to identify study children who went for care at another facility. Hospital records were reviewed and verbal autopsies done for children who died.

STUDY FINDINGS

Study findings are not reported separately for each of the age strata per intervention group.

The mean log₁₀ HIV-1 viral load and mean CD4+ T lymphocyte counts for each of the visits are reported in Table 2 on page 1865

Mean (SD) log ₁₀ HIV-1 viral load (unadjusted)			
	Placebo group	Zinc group	Difference (95% CI)
Baseline	5.4 (0.67)	5.2 (0.56)	0.22 (-0.06 to 0.5)
3 months	5.4 (0.66)	5.3 (0.64)	0.12 (-0.15 to 0.39)
6 months	5.4 (0.61)	5.4 (0.66)	0.0002 (-0.27 to 0.27)
9 months	5.5 (0.77)	5.4 (0.61)	0.05 (-0.24 to 0.35)
Mean of 3, 6, and 9 months	5.4 (0.59)	5.4 (0.57)	0.03 (-0.23 to 0.28)

Log₁₀ HIV-1 viral loads were compared across treatment groups at each follow-up visit adjusting for age, baseline log₁₀ HIV-1 viral load, baseline percentage of CD4+ T lymphocytes using linear regression. (Table 3, page 1865). Mean percentage of CD4+T lymphocytes did not change over time and were similar between the two study groups.

Infectious disease morbidity					
	Zinc group		Placebo group		P*
	Scheduled Visits (n=360)	All visits (n=407)	Scheduled Visits (n=370)	All visits (n=447)	
Watery diarrhoea	24 (6.7%)	30(7.4%)	39 (10.5%)	65 (14.5%)	0.001
Pneumonia	39 (10.8%)	57 (14%)	47(12.7%)	83 (18.6%)	0.07
URI	141 (39.2%)	164(40.3%)	165 (44.6%)	202(45.2%)	0.15
Ear infection	39 (10.8%)	46 (11.3%)	52 (14.1%)	65 (14.5%)	0.16

The percentage of scheduled and illness visits when children were diagnosed with diarrhoea was lower in the zinc group than in the placebo group. P-value is based on logistic regression comparing rate of events during all visits across treatment groups. The number of visits at which pneumonia, upper respiratory infection or ear infection was diagnosed was also lower in the zinc group than in the placebo group, but the difference was not significant. Two deaths occurred in the zinc group and seven in the placebo group.

ADVERSE EVENTS

No death or other serious adverse event was attributed to the zinc supplementation.

COMMENTS

The plasma HIV-1 viral loads were not increased or the number of CD4+ T lymphocytes decreased in the zinc group. The proportion of clinic visits where watery diarrhoea was diagnosed was also reduced with zinc supplementation and also associated with increased weight gain. However, they did not get the required sample size of 64 per treatment arm as per the calculation. They had fewer children per arm as well as loss to follow-up. This means that the power of the study was lowered such that it led to insufficient power to detect any difference which might exist. One also need to keep in mind that for equivalence trials the failure to detect a difference does not imply equivalence. The sample size should be larger than for comparative trials. In addition, when considering the risk of bias, no firm conclusions can be drawn and larger studies are needed to look at zinc supplementation in children across age-groups, differing degrees of clinical disease and malnutrition be done.

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Date: 24 January 2006