Malnourished children morbidity following vitamin A supplementation or deworming in Democratic Republic of Congo

by

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Abstract

A randomized controlled trial was conducted in the Eastern part of the Democratic Republic of Congo to assess the impact of high-dose vitamin A supplementation or regular deworming on morbidity of 358 vitamin A deficient and moderately malnourished pre-school age children, discharged from hospital. The children in the treatment groups received either vitamin A (200,000 IU, 100,000 IU for children under 12 months) every 6 months, or mebendazole (500mg) every 3 months whereas the children in the control group received no supplementation. At enrolment,

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anthropometric and clinical data were gathered, faeces were collected and serum retinol concentrations were measured. Morbidity data were collected fortnightly during the first 3 months of follow-up by using a weekly recall method. The three groups had similar socio-demographic indicators, age-sex composition, nutritional status and serum retinol concentrations at baseline. Deficient serum retinol (<0.35mol/L) was found in 23.2% of the study sample. Median percent time ill for diarrhoea, cough, cough and fever and fever were not significantly different in the three groups and prevalence odds ratios for cough, diarrhoea and fever were not significant. High-dose vitamin A supplementation or deworming did not reduce prevalence of common morbidity in this population of children recovering from malnutrition and with biological signs of vitamin A deficiency.

Key words

Democratic Republic of Congo, malnutrition, morbidity, pre-school children, vitamin A deficiency, vitamin A supplementation, deworming

Introduction

Clinically evident vitamin A deficiency which annually affects an estimated 14 million people in the world, represents only about one-tenth of those who are at risk of compromised health from subclinical deficiency. An association between subclinical vitamin A deficiency and an increased rate of infections has been reported in observational studies (1, 2).

Several studies have tried to find out whether vitamin A supplementation in young children can reduce mortality and morbidity. A meta-analysis of these trials (3) has shown average reduction in all-cause mortality of 23% with vitamin A supplementation of children aged 6 months to 6 years. However, the very clear effect of vitamin A supplementation on mortality has not been accompanied by a reduced incidence or prevalence of morbidity. Most of the trials mentioned in the meta-analysis were conducted in populations with evidence of clinical signs of deficiency. Few data are available among populations with biochemical evidence of vitamin A depletion but without associated evidence of clinical manifestations of deficiency. Recently published trials in Ghana (4) and Brazil (5) concerned population closest to this situation.

In both studies, vitamin A supplemented groups showed a reduction in the incidence of severe diarrhoea whereas in Brazil no change was observed in the incidence of acute respiratory infections compared with the control groups.

Parasitic infections, especially with Ascaris lumbricoides is common in Democratic Republic of Congo (DRC) and may interfere with vitamin A absorption (6, 7, 8). In some studies, deworming resulted in improving both vitamin A absorption (6, 8) and serum retinol concentrations (9). However, a recent study in Indonesia found that treatment with mebendazole failed to improve vitamin A stores (10)

In the South-Kivu Province of DRC, Protein Energy Malnutrition (PEM) is endemic. Pre-school children mortality rate is high in outpatients (45 per 1000 per year) (11) and in hospitalized children, most of whom suffering from severe PEM (12). Vitamin A deficiency co-exists in this region with PEM and is characterized by a high prevalence of severe biochemical depletion and a low prevalence of clinical signs (13).

Deworming and vitamin A supplementation could reveal efficient strategies to improve vitamin A status of deficient populations. The lack of consistency in available findings and the scarcity of data among populations with biochemical evidence of vitamin A depletion but without associated evidence of clinical manifestations of deficiency led us to conduct a randomized, controlled trial of the effects of a six monthly high-dose vitamin A supplement and a three monthly deworming on morbidity of pre-school children in the South-Kivu Province of DRC.

Methods

Study design and sample. A randomized controlled trial was conducted between April 1991 and May 1993 in Eastern DRC. 358 children aged 0 to 72 months discharged consecutively from the Lwiro paediatric hospital were included in the trial and followed up for one year. The study took place in the health district of Katana, province of South Kivu. This mountainous province is located along the borders with Burundi and Rwanda. The highlands have a mean altitude of approximately 1500 m. The climate is temperate and the year divided into 2 raining seasons (March to June and October to January). The population settled in the region, most of whom are farmers, live in a poor rural environment characterized by subsistance economy, rapid demographic expansion and

rudimentary sanitation. The food supply is constantly poor in energy and periodically low in protein, depending on the seasons. Protein shortage is at its most acute by the end of the dry season and at the beginning of the rainy season, i.e. from October to end of December. The diet is also very poor in lipids (14). All forms of protein energy malnutrition are frequently encountered and prevail essentially among young children but also among lactating women (15).

The Children's hospital at Lwiro is considered in the health district of Katana as the reference hospital for malnutrition. It admits close to 600 children each year, the majority of whom suffer from severe PEM, notably kwashiorkor (16). There was no vitamin A supplementation program within the study area. The study protocol was approved by the local Ethical Authorities and parental or legal guardian consent was obtained for all selected children.

Randomisation and dosing. As soon as discharged from hospital, children were randomly assigned to 3 groups. One group received an oral dose of 200,000 IU (International Units) of vitamin A (oily solution of retinyl palmitate) (100,000 IU for children under 12 months of age) at the start of the trial (day of discharge) and then every 6 months till the end of the one-year follow-up period. The second group received an oral dose of 500 mg of mebendazole at the start of the trial and then every 3 months till the end of the one-year follow-up period. The third group received no supplementation and served as control-group. The gelatinous capsules of vitamin A contained each 50,000 IU of vitamin A. Supplements were stored at room temperature. They were renewed every three months. All supplements were administered by two trained field-workers.

Data collection and management. Children were included just after discharge from hospital. They were then visited at home every two weeks during 3 months, then every 3 months until 12 months. They were then discharged from the trial.

At enrolment, field-workers visited each child's family and data were collected on the type of house, possessions, animals, access to drinkable water and access to health care. Other information collected included vaccination history, the survival status of siblings, parental education and principal activity, mother's age and marital status. On each visit, each child was recorded as being present, temporarily absent, moved

away, or dead. A child was classified as being temporarily absent if he or she was not in the compound when visited at least two times during a week. A child was dropped out of the study if he or she was temporarily absent on more than 2 consecutive programmed visits. This happened for 22 children. Overall, 6% of the children were lost to follow-up, with approximately equal proportions in each group. The average proportions of eligible children successfully dosed at each round were 97.2%. These figures were similar in the vitamin A and mebendazole groups. The great majority of the children who missed doses were away from home at the time of dosing. 25 children died during the follow-up period. The final sample included 311 children. On each visit, anthropometric (weight, height, mid-upper arm circumference (MUAC)) and clinical (presence of edema) indicators were collected. A blood sample was collected at enrolment.

Children were weighed naked on scales accurate to 50 g. The precision of the scales was checked regularly. Length or height was measured at the nearest mm using a calibrated scale comprising a wooden platform with a scale and a sliding head piece. Children under 2 years of age were measured lying; older children were measured standing. Midupper arm circumference (MUAC) was measured halfway between the elbow and the shoulder of the left arm with a non-expanding plastic tape and recorded to the nearest mm. In order to reduce intra-individual errors, each anthropometric measure was performed twice and the mean value was utilized for the analyses. The anthropometric measurements of the children were compared with standard values of the National Center for Health Statistics (NCHS)(17) and were expressed as Z-scores: height for age (HAZ), weight for age (WAZ) and weight for height (WHZ) Z-scores.

Blood samples (1 ml) were taken by antecubital venipuncture, protected from light and stored cold in cool boxes for less than 3 hours, then centrifuged at room temperature for 10 min at 2000 x g. The serum was distributed in two microtubes for the determination of retinol and serum proteins (albumin, Retinol Binding Protein (RBP) and C-Reactive Protein (CRP)) and then frozen at - 20°. The samples were transported to Brussels in cool boxes and stored at - 20° until analysed. Retinol was determined by high-performance liquid chromatography (HPLC) procedure adapted from Vanderpas (18). Albumin, RBP and CRP were measured using a nephelometric technique (19).

Fecal examinations: feces were examined from all children on admission and at 3, 9 and 12 months follow-up. Feces were collected in small plastic-covered cups by the mothers, stored in coolers and transferred to the laboratory within 3 hours. Fecal egg counts, measured in eggs per gram of feces (epg) were performed using the Kato-Katz method. Ascaris infection was considered as present if at least one egg of Ascaris lumbricoides was found in a stool sample. WHO criteria (20) were used to classify children according to severity of infection: light infection: 1-4999 epg, moderate infection: 5000-49.999 epg, heavy infection: >50.000 epg.

One week recall morbidity data were collected on household visits every two weeks during the first 3 months of follow-up. On each visit, a detailed interview was conducted about the occurrence on each day of the past week of 27 listed symptoms, signs, and conditions using locally defined terms where appropriate. The child's mother or caretaker was asked in particular about whether there had been any episode within the preceding week of diarrhoea (watery stools four or more times in one day), vomiting, mucus or blood in the stools, rhinitis, cough, difficult breathing, fever associated or not with cough or with rash measles. On their visits, field-workers were instructed to refer children to the health care center or to the hospital, according to specified criteria. On the basis of the above definitions the following child morbidity measures were derived: percent of time ill = number of days ill for a given condition for children having at least one day of symptom x 100 divided by total number of days of follow-up; percent children ill = number of children who did present the symptoms at least one day during the follow-up x 100 divided by total number of children followed.

Data quality control, processing, and analysis. Several methods were used both to improve and to check on data quality. These included weekly visits to each field-worker by a supervisor, who attended interviews, conducted full re-interviews on a sample of recently completed interview forms, re-collected anthropometric and clinical indicators. Before the start of the trial field-workers were trained by the external supervisor to minimize inter-individual differences. Both field-workers and supervisors received regular training courses. Data were entered locally into microcomputers by one and the same clerk. A 10% of the data entered by the clerk were checked by the supervisor. In addition, data were listed periodically for visual checks. About 26 weeks and again 52 weeks after the intervention started, an external data-monitoring committee reviewed the data.

For quantitative variables, means and standard deviations (SD) were presented except for CRP and for morbidity variables whose distributions were highly skewed. For morbidity data, median (min, max) have been presented. For some analyses, quantitative variables were dichotomized. The cut-off point chosen for weight for age, height for age and weight for height Z-scores was -2 SD of the reference median. For albumin and RBP, the lower limits of the laboratory norms: 35 g/l and 30 mg/L respectively, were taken as cut-offs. For CRP, the cut-off point chosen was 20 mg/L. Serum retinol concentrations were classified according to WHO criteria (21). Retinol values < 0.35 µmol/L (10mg/dl) between 0.35 and 0.70 mmol/L (10 and 20 mg/dl) and equal to or above 70 mmol/L (20 mg/dl) were classified as deficient, low and normal, respectively.

Statistical analysis and interpretation of data. Statistical analysis was performed using the SPSS 4.0 release for Unix (22) and SPIDA (23). The tests used to compare the admission data of the three groups were the Chi2, one way analysis of variance and the Kruskal-Wallis test. Odds ratios and standard errors to compare morbidity between groups were estimated from logistic regression models with repeated measurements that make use of generalized estimating equations (GEE). This method, which can take into account within-individual correlation, was specifically developed for the analysis of longitudinal sets comprised of repeated observations of an outcome in the same individuals over time.

Results

Demographic, socio-economic and nutritional characteristics were similar in the three groups (Table 1). The population under study was characterised by a high prevalence of stunting (low length/height-for-age) and underweight (low weight-for-age) but a relatively low prevalence of wasting (low weight-for-height). This indicated that chronic rather than acute growth deficit predominated. No child presented edema at enrolment.

Biological nutritional parameters at enrolment showed high proportions of children with values of serum albumin and RBP under the lower limit of the laboratory's norms.

Mean serum retinol concentration at enrolment was very low. Deficient serum retinol (<0.35 µmol/L) was found in 19.1 to 25.6.1% of

TABLE 1

Baseline demographic, socio-economic and nutritional characteristics by randomized supplement group [1]

	Group		
	Vitamin A (n=118)	Mebendazole (n=123)	Control (n=117)
Demographic features			
Age (mo)	23.6 ± 20.2	25.1 ± 18.4	22.5 ± 17.8
%<12	42.4	30.1	40.2
%12-23	16.1	22.0	22.2
%24-47	26.3	35.8	24.8
% Boys	48.3	59.3	56.4
%≥ 48	15.3	12.2	12.8
Duration hospitalization (d)	18.2 ± 20.8	17.4 ± 17.3	17.9 ± 18.3
Socio-economic status			
% Mother never attended school	60.2	59.5	57.3
Nutrition			
% currently breastfed	59.3	54.4	59.8
Anthropometric status			
WAZ			
%<-2	55.9	56.9	50.4
HAZ			
%<-2	65.3	65.0	65.0
WHZ			
%<-2	4.2	8.9	5.3
Serum values			
Albumin(g/L)			
%<35	61.3	69.4	74.2
RBP (mg/L)			
%<30	45.5	50.4	43.0
CRP (mg/L)			
%>20	19.8	11.2	17.8
Retinol (μmo/L)	0.53 ± 0.24	0.51 ± 0.23	0.56 ± 0.25
%<0.35	24.8	25.6	19.1
%0.35-0.70	51.3	53.0	51.8
%>=0.70	23.9	21.4	29.1
Fecal examination			
Ascaris infection %	14.2	9.6	10.5

WAZ = weight for age Z-score
HAZ = height for age Z-score
WHZ = weight for height Z-score
MUAC = mid-upper arm circumference
RBP = retinol binding protein
CRP = C-reactive protein
[1] Means ± standard deviation or percentage.
No data differed significantly in the three groups.

the study sample. Only about a quarter of the sample (21.4 to 29.1%) had retinol concentrations considered as normal. *Ascaris* infection was present in 9.6 to 14.2% of the children at enrolment. 80% of the children had light infections and 20% had moderate infections. The prevalence of coinfection with *Ascariasis* and *Trichuris* ranged from 2.8 to 4.8%. Hookworm was not found in any of the children at enrolment.

The proportion of children who died during the one-year follow-up period was respectively 5.4% for the vitamin A group, 7.9% for the mebendazole group and 9.0% for the control group. These proportions did not differ significantly.

The comparison of the various measures of morbidity for respiratory illness, diarrhoea and fever are presented in Table 2. The proportion of children who never presented the symptoms described was not statistically different between the 3 groups. No statistically significant differences were observed either between the three groups in percent time ill

TABLE 2

Relation between supplementation and morbidity over 3 months

	Group		
	Vitamin A (n=112)	Mebendazole (n=117)	Control (n=113)
Percent children who never presented the following symptoms (%)			
Diarrhoea	44.2	51.0	62.1
Cough	32.6	33.3	41.4
Cough and fever	51.2	46.9	46.0
Fever	38.4	38.5	33.3
Percent time ill (%) for the following symptoms			
Diarrhoea	13.9(5.6-44.4)[1]	12.5(2.8-50.0)	13.9(5.6-33.3)
Cough	16.7(2.8-50.0)	19.4(2.8-86.1)	13.9(3.3-61.1)
Cough + fever	12.5(2.8-41.7)	9.7(2.8-47.2)	11.8(2.8-55.6)
Fever	11.1(2.8-43.3)	11.1(2.8-50.0)	11.1(2.8-33.3)

[1] Median (min-max).
No statistically significant differences were observed between the groups.

among children who presented at least one day the symptoms described.

The GEE model showed that prevalence odds ratios of treatment group for cough, diarrhoea and fever were not significant (Table 3 to 5).

TABLE 3
Prevalence of cough: Generalised Estimating Equations (GEE) model

Variable	Odds ratio	95% CI	p
Group Vitamin A/Mebendazole	0.84	0.54-1.34	0.470
Group Vitamin A/Control	1.15	0.73-1.84	0.544
Albumin <35/>=35	0.65	0.44-0.96	0.032
HAZ <-2/>=-2	1.23	0.77-1.98	0.384
WAZ <-2/>=-2	0.80	0.50-1.26	0.326
WHZ <-2/>=-2	0.45	0.20-0.99	0.047

TABLE 4
Prevalence of diarrhoea: Generalised Estimating Equations (GEE) model

Variable	Odds ratio	95% CI	p
Group Vitamin A/Mebendazole	1.23	0.77-1.94	0.389
Group Vitamin A/Control	1.09	0.66-1.79	0.729
Albumin <35/>=35	0.74	0.50-1.11	0.146
HAZ <-2/>=-2	0.70	0.43-1.13	0.141
WAZ <-2/>=-2	1.26	0.79-2.01	0.340
WHZ <-2/>=-2	1.34	0.65-2.76	0.436

TABLE 5
Prevalence of fever: Generalised Estimating Equations (GEE) model

Variable	Odds ratio	95% CI	p
Group Vitamin A/Mebendazole	1.15	0.75-1.76	0.515
Group Vitamin A/Control	0.91	0.61-1.36	0.638
Albumin <35/>=35	0.84	0.59-1.20	0.338
HAZ <-2/>=-2	0.84	0.56-1.26	0.399
WAZ <-2/>=-2	0.80	0.54-1.20	0.282
WHZ <-2/>=-2	1.10	0.60-2.02	0.755

Prevalence odds for diarrhoea and fever were not significantly different according to nutritional status whereas odds for cough was lower in children with albumin < 35 g/L and in children with WHZ < –2.

Discussion

High-dose vitamin A supplementation did not reduce prevalence of common morbidity in this population of children recovering from malnutrition and with biological signs of vitamin A deficiency. However mortality rate in the vitamin A supplemented group was lower than in the control group, though not significantly.

The lack of impact of vitamin A supplementation on morbidity in spite of a benefit in terms of reduced mortality was found in several well-designed controlled studies (24, 25, 26, 27). In Ghana (26) and Indonesia (24), there were no significant differences between the vitamin A and placebo groups in the prevalence of diarrhoea and acute respiratory infections. In India (25, 27), vitamin A supplementation did not influence the incidence or duration of diarrhoea or respiratory infections.

An explanation for finding in the same data a vitamin A effect on mortality but not on symptoms of the two leading causes of childhood death: respiratory and enteric infections, was proposed in a recent meta-analysis reviewing major morbidity trials (3). Beaton et al. concluded that vitamin A functions primarily by reducing the severity of disease rather by preventing its occurrence. There is growing evidence that this is the case. In Brazil (5), a reduction of the incidence of severe episodes of diarrhoea was observed in children who received large-dose vitamin A supplements compared with children of the placebo group whereas severity of acute lower respiratory infection was not significantly different between the two groups. However, in this study no difference in mortality rates was observed between the supplemented and the placebo groups. In Ghana (26), the vitamin A group experienced fewer diarrhoeal episodes with high stool frequency. Ghana and Brazil study populations were only mildly vitamin A-deficient and free of xeropthtalmia. We were not able to test the hypothesis that vitamin A might protect against severe episodes of diarrhoea and respiratory illness as in our trial morbidity data were gathered during one week every two weeks.

In contrast, in studies in Haiti (28) and Indonesia (29), the vitamin A group was found to have an increased prevalence of diarrhoea and respiratory disease.

The conflicting results on the effects of vitamin A supplementation on morbidity compared with consistent findings for mortality may be partly due to variation in the methods used to collect morbidity data and to the presence more or less of other factors such as PEM and micronutrients deficiences.

Deworming did not have a significant effect on prevalence of common morbidity in this population. As deworming improved vitamin A absorption in India (7) and serum retinol concentration in Indonesia (9), we hypothesized it could be an interesting way of improving vitamin A status in this population of vitamin A deficient children. This strategy could be considered as equivalent to the administration of a daily low-dose supplementation of vitamin A. The lack of impact on morbidity could be explained by the fact that as children had just been discharged from hospital, baseline prevalence of *Ascaris* infection was low. More heavily infected children might have responded better. It is also possible that, as was observed by Tanumihardjo et al. in Indonesian children (10), deworming alone is not able to improve significantly vitamin A status as measured by changes in serum retinol concentrations and in the modified relative dose response test values.

Odds for cough was significantly lower in children in bad nutritional status (albumin < 35 g/L and WHZ < –2). These results are surprising as malnourished children are more liable to develop infections than children in satisfactory nutritional status. As odds for diarrhoea and for fever were not different according to nutritional status, the higher prevalence of cough in malnourished children might have occurred by chance. An other explanation could be that severely malnourished children are sometimes too weak to produce cough.

In conclusion, high-dose vitamin A supplementation and deworming did not reduce common morbidity in this population of moderately malnourished children with subclinical vitamin A deficiency. As vitamin A improvement appears to have benefits in terms of child survival, further analyses are needed to test the plausibility of reductions in the severity of infections. However, as a multiple-nutrient deficit rather than only vitamin A deficiency prevails in this region, vitamin A supplementation alone is probably unable to dramatically improve health and accordingly

more general strategies such as improved primary health care services and improving dietary intakes should be emphasized.

Acknowledgements

Résumé

Une étude prospective longitudinale d'intervention a été menée à l'est de la République Démocratique du Congo pour évaluer l'impact d'un programme de supplémentation massive en vitamine A et d'un programme de déparasitage sur la morbidité de 358 enfants d'âge préscolaire en malnutrition protéino-énergétique modérée à leur sortie de l'hôpital.

Les enfants des groupes traités recevaient soit une dose de vitamine A tous les 6 mois (200.000 UI, 100.000 < 12 mois), soit du mebendazole (500 mg) tous les 3 mois tandis que les enfants du groupe contrôle ne recevaient pas de supplémentation. A l'admission dans l'étude, des données anthropométriques et cliniques ont été récoltées et le rétinol sérique a été mesuré. Des données sur la morbidité ont été recueillies une semaine sur deux pendant les 3 premiers mois du suivi en utilisant une méthode de rappel hebdomadaire. Les 3 groupes étaient comparables à l'admission en ce qui concerne les données socio-démographiques, la distribution de l'âge et du sexe, l'état nutritionnel et le rétinol sérique. 23.2% des enfants présentaient un taux de rétinol sérique déficient (<0.35mmol/L) à l'admission. Les médianes du pourcentage de temps de maladie pour la diarrhée, la toux, la toux + la fièvre et la fièvre n'étaient pas significativement différentes dans les 3 groupes et les odds ratio de prévalence pour la toux, la diarrhée et la fièvre n'étaient pas significatifs. Une supplémentation par des doses élevées de vitamine A ou un déparasitage trimestriel ne réduisent pas la prévalence de la morbidité courante dans cette population d'enfants convalescents d'un épisode de malnutrition protéino-énergétique et présentant des signes biologiques de carence en vitamine A.

Samenvatting

Een prospectieve longitudinale studie werd in het Oosten van de Democratische Republiek Congo uitgevoerd om de invloed te evalueren van de toediening van een belangrijke dosis vitamine A en van een deparasiterings programma bij ontslag uit het ziekenhuis op de morbiditeit van 358 matig ondervoede kinderen jonger dan 6 jaar.

Drie groepen werden vergeleken: de kinderen in een eerste groep kregen vitamine A (200.000 IE; <12 maanden: 100.000 IE); de kinderen in de twede groep kregen meben-

dazole (500 mg) over de 3 maanden; de kinderen in de controle groep kregen geen behandeling.

Anthropometrische en klinische gegevens werden bij opname in de studie verzameld; serum retinol werd op hetzelfde ogenblik bepaald.

De gegevens over morbiditeit werden een week op twee gedurende de 3 eerste maanden van de follow-up verzameld door de methode van wekelijks herhaling.Sociodemografische gegevens, leeftijd en geslachts verdeling, voedingstatus en serum retinol waren vergelijkbaar in de 3 groepen bij opname in de studie.

Serum retinol bij opname in de studie was laag (<0.35mmol/L) bij 23.2% van kinderen.
Ziekteperioden van diarree, hoest, hoest met koorts en koorts (mediane van het percentage van de tijd) in de 3 groepen was niet verschillend. Prevalence odds ratios van hoest, diarree en koorts waren niet significant.

De programma's om de vitamine A status door toediening van hoge dosis van vitamin A of van deparasiterings te verbeteren verminderen niet de prevalentie van eenvoudige morbiditeit bij ondervoede kinderen met matige deficientie aan vitamine A.

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