

Research from the South

Vitamin A supplements and mortality related to measles: a randomised clinical trial

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Abstract

One hundred and eighty children admitted with measles were randomly allocated to receive routine treatment alone or with additional large doses of vitamin A (200 000 IU orally immediately and again the next day). Baseline characteristics of the two groups were virtually identical for age, severity of measles, and vitamin A and general nutritional states. In 91% of the children serum vitamin A concentrations were less than 0.56 $\mu\text{mol/l}$. Of the 88 subjects given vitamin A supplements, six (7%) died; of the 92 controls, 12 (13%) died ($p=0.13$). This difference in mortality was most obvious for children aged under 2 years (one death out of 46 children receiving supplements versus seven deaths out of 42 controls; $p<0.05$) and for cases complicated by croup or laryngotracheobronchitis. Mortality was several times higher in marasmic than in better nourished children, regardless of study allocation ($p<0.01$).

Introduction

Recent reports from Indonesia have shown that children with clinically mild vitamin A deficiency have a fourfold increase in mortality from all causes¹ and a threefold increase in the incidence of respiratory and diarrhoeal diseases.² Vitamin A supplements reduced preschool age childhood mortality by over 30%.³ After reviewing some 50 reports of the effect of vitamin A deficiency on bacterial, viral, protozoal, and helminthic infections in man and animals Scrimshaw *et al* concluded that "no nutritional deficiency is more consistently synergistic with infectious disease than that of vitamin A."⁴ At the time that they wrote this they were unable to find data concerning the interaction between vitamin A and measles.

Vitamin A is essential for the maintenance of normal epithelial tissues throughout the body. In the absence of vitamin A mucosal epithelium undergoes squamous metaplasia, with a concomitant decrease in cell turnover.^{5,9} Measles is a viral disease that infects and damages epithelial tissues throughout the body.^{10,11} The disease can also decrease serum concentrations of vitamin A in well

nourished children to less than those observed in non-infected malnourished children.¹² Measles probably increases utilisation of vitamin A, and children with marginal liver stores of the vitamin may thus develop acute vitamin A deficiency, resulting in eye damage and possibly increased mortality from respiratory and diarrhoeal causes. Indeed, measles is an important risk factor in the development of severe vitamin A deficiency and xerophthalmia in Asia.^{13,14} It is also a particularly virulent disease among African children, accounting for most cases of childhood blindness and for considerable mortality.^{10,11,15-17} Recent data suggest that vitamin A deficiency may be prevalent in areas of Africa, including Tanzania.^{16,18,19}

This hospital based study sought to determine the effect of high dose vitamin A supplements taken during early infection with measles on subsequent mortality in African children.

Patients and methods

Mvumi Hospital is a rural general hospital in central Tanzania related to the church. Paediatric patients are drawn almost entirely from the local population, which comprises subsistence farmers living in a fairly arid environment. The staple diet is millet eaten with a green vegetable relish.

There is only one harvest a year, in April to May, and that is dependent on good rains. The rains in 1982 were very bad, leaving conditions of near famine for many, but the rains and harvest in 1983 were good. Malnutrition is a great problem in children. About a quarter of all children admitted are severely malnourished, and only 30% have a weight for age above 80% of the standard.²⁰ Anaemia is also common. The general paediatric background is more fully described elsewhere (A J G Barclay, unpublished).

We attempted to include in this study every child with measles presenting to the hospital from September 1982 to November 1983, a period that included an entire measles season. Measles was diagnosed on clinical grounds that included a history of prodromal disease and the presence of a typical rash. On admission all children were given a full clinical examination by the paediatrician. Shortly after admission they were seen by a member of the eye department. They were all weighed and measured by the nurses and had their haemoglobin concentration measured and a blood slide examined by staff in the hospital laboratory.

A venous blood sample was taken on admission for estimation of vitamin A state. Half of the subjects were then randomly allocated to receive vitamin A (200 000 IU in oil orally immediately and again the next day); the other children were given standard treatment. Randomisation was accomplished by sequential assignment of single digits from a random numbers table, odd digits dictating one group and even the other. Which children received vitamin A was known to the paediatrician but not recorded in the general notes: study allocation was therefore not known by any other staff dealing with care of the children. Other main therapeutic sources of vitamin A—for example, multivitamins—are not routinely given and therefore were not received by any children in the trial. The two groups were treated identically in the ward, fed the same diet, and given antibiotics or further investigated as indicated by their clinical condition.

Deaths caused by measles were taken to be deaths occurring within one month of onset of the rash. Most patients were still in the ward when they died; three returned of their own accord and were readmitted with dysentery or diarrhoea and died quickly and two ran away moribund and died at home.

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Baseline blood samples were allowed to clot and were then spun down. The serum was separated and stored in a deep freeze within four hours of taking the sample. The serum was later shipped to Baltimore, where concentration of vitamin A (as retinol) was measured by high performance liquid chromatography.²¹ Because of losses in transport biochemical determinations are available for only 38 recipients of vitamin A and 47 controls.

As the study was designed to assess the beneficial impact of vitamin A supplements, and there was no biological, clinical, or epidemiological reason to suspect any deleterious effects from added vitamin A, results were assessed with a single tail normal deviate (*z*) and Fisher's exact test.

Results

Two hundred and twelve patients with measles were admitted during the trial. Thirty two were excluded from the trial, all but six before randomisation because of corneal ulcers (seven patients, who were automatically given vitamin A and are reported on separately²²); death within 24 hours of admission (five); running away within 24 hours (one); receiving vitamin A before admission (nine); and admission while the study coordinator was absent (10). Of the 180 children in the trial, 11 did not have their height recorded and 15 did not have their haemoglobin concentration measured.

The distribution of baseline characteristics of recipient and control children was similar, including age (mean recipient 29.5 *v* mean control 30.7 months), weight for age (72% *v* 75% of standard), weight for height (83% *v* 86% of standard), haemoglobin concentration (85 *v* 89 g/l), interval between onset of rash and admission (3.5 *v* 3.4 days), and serum vitamin A concentration (0.30 *v* 0.32 $\mu\text{mol/l}$). Only 9% of patients had serum vitamin A concentrations greater than 0.53 $\mu\text{mol/l}$.

Of the 88 children given vitamin A, six (7%) died (table I). Of the 92 controls, 12 (13%) died. Despite the large clinical difference small numbers limit its significance ($p=0.13$). The difference was most obvious for children aged under 2 years ($p<0.05$).

TABLE I—Mortality of children admitted with measles

Age (months)	No of children admitted		No (%) who died	
	Given vitamin A	Controls	Given vitamin A	Controls
<9	14	9		2 (22)
9-11	12	10		2 (20)
12-23	20	23	1 (5)	3 (13)
24-35	11	16	3 (27)	2 (13)
36-47	11	13	1 (9)	1 (8)
48-59	8	6	1 (13)	
≥ 60	12	15		2 (13)
Total	88	92	6 (7)	12 (13)

Twenty five children (14%) were marasmic, and 104 (58%) were underweight as assessed by weight for age (table II). The mortality of marasmic children was several times higher than that of better nourished children, regardless of whether they had received vitamin A or not ($p<0.01$, two tailed test). In every nutritional category mortality was lower for vitamin A recipients.

Complications, usually already present at the time of admission, were equally common in the two groups, but mortality from such complications was higher in the control group (table III). Pneumonia was the commonest complication, affecting 85 children. Croup complicated measles in 13 of the

TABLE II—Weight for age and mortality

Weight for age*	No of children in study		No (%) who died		Total
	Given vitamin A	Controls	Given vitamin A	Controls	
>80%	24	27	1 (4)	3 (11)	4 (8)
60-80%	47	57	1 (2)	6 (11)	7 (7)
<60%	17	8	4 (24)	3 (38)	7 (28)
Total	88	92	6 (7)	12 (13)	18 (10)

*Percentage of median National Center for Health Statistics standard.¹⁹

TABLE III—Complications and associated mortality

Complication	No (%) of children with complications		No (%) of children who died	
	Given vitamin A	Controls	Given vitamin A	Controls
Pneumonia	38 (43)	47 (51)	3 (8)	7 (15)
Otitis media	19 (22)	20 (22)	1 (5)	3 (15)
Croup or laryngotracheobronchitis	8 (9)	13 (14)		4 (31)
Dysentery	2 (2)	6 (7)	1 (50)	3 (50)
Haemorrhagic rash	28 (32)	34 (37)	1 (4)	4 (12)
Oral candidiasis	9 (10)	5 (5)	1 (11)	1 (20)

control group, of whom four (31%) died; in contrast, of eight children with croup given vitamin A, none died. Very few children had dysentery; of those who did, half died.

Discussion

Children randomised to receive vitamin A did not differ from the control group in baseline age, nutritional state, duration of illness, prevalence of complications, or haemoglobin or serum vitamin A concentrations. Mortality was twice as high in the control group as in the treated group, almost all of the difference being accounted for by children aged under 2 years ($p<0.05$).

Although the numbers were small, there was a remarkable consistency in the beneficial impact of vitamin A supplements on complicating illness and nutritional strata. This was especially obvious among children with croup or laryngotracheobronchitis. No child who received vitamin A died of laryngotracheobronchitis, whereas four in the control group died. Laryngotracheobronchitis is a particularly difficult condition to treat with limited resources. Because repair of epithelial surfaces in children with early vitamin A deficiency may be poor, with a tendency to develop into squamous metaplasia of the respiratory tract,^{5,7} they may suffer increased susceptibility to laryngotracheobronchitis or its consequences.

Malnutrition is common in and around Mvumi, and the nutritional state of this study group is not atypical of general paediatric admissions. Children with low weight for age (and weight for height, not shown) had the highest mortality in both study groups. Recent community studies have shown a varying relation between premorbid general nutritional state and death from measles, but most dealt with milder disease.²³⁻²⁶ Schrimshaw *et al* noted a decrease in mortality from measles in children fed a vegetable extract rich in protein that may have contained considerable amounts of vitamin A.²⁷ In our study vitamin A recipients suffered lower mortality in every nutritional stratum.

The vitamin A concentrations among the children in our study were all very low, much lower than that reported by workers in Nigeria.¹² This is explained partly by the different analytical methods, populations, and diet. Tielsch and Sommer found that children with vitamin A concentrations of less than 0.53 $\mu\text{mol/l}$, a category that would include over 90% of our study group, were at very high risk of developing corneal ulcers.¹⁴

Vitamin A deficiency may be a large factor in determining the outcome of measles in Africa, just as it seems to affect morbidity and mortality in Asia.¹³ When a child with marginal vitamin A stores gets measles available vitamin A is quickly depleted, presumably reducing the ability to resist secondary infections or their consequences, or both.²⁸⁻³² This would exacerbate the already reduced immunocompetence thought to be associated with measles infection.³³

Further trials in different parts of Africa are urgently needed to define the role of vitamin A deficiency in measles morbidity and mortality and the importance of vitamin A supplements in their control.

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MATERIA NON MEDICA

On the beach

The lights of Ardentiny across the waters of Loch Long go out one by one as the bleak November evening moves imperceptibly into night. Now and again a gap in the blackness above allows moonlight to sparkle on the lapping waves, a welcome relief from the soaking northerly squalls that chill and dishearten. On the foreshore a dozen oyster catchers are busily feeding as the tide ebbs. No sign of the rafts of eiders or the shags or even the gulls so conspicuous by day. A Scottish sea loch has its charms even on a winter's night.

But this is no birdwatchers' outing. This is Coulport beach, right next to the naval base that will act as home to Britain's Trident submarines. We are five members of the local peace group who have chosen to spend a Friday night here. Our vigil is peaceful but not silent. We sing hymns, we chatter, and the laughter pervades even those dreaded small hours which the doctor on call knows and hates so keenly. We watch the comings and goings of the base and the swarms of Ministry of Defence police—and they in turn watch us, but in a much more sophisticated way. Though we speak to two policemen, we are unable to speak to the majority of the workers as they are bussed in and out, and our protest is made simply by our presence.

Dawn slowly creeps over the pines, and the birds return. The day shift replaces the night shift and it is time to extinguish the driftwood fire.

Have we changed anything? Nuclear weapons are an emotive issue. For those of us who see them as the greatest danger to public health of our time it is vital to protest, and I remember Edmund Burke's words: "Nobody made a greater mistake than he who did nothing because he could only do a little." At the very least, for a short while we were at peace with our consciences.—KENNETH F MCLEAN, Denny, Stirlingshire.

Music buffs

Orpington has culture. Never mind that it has little history. In fact Queen Elizabeth I stayed at the manor once, and there is the Buff Orpington chicken, but until the railway was electrified it was only a small place, mentioned in the Domesday Book but overshadowed by the neighbour which it now dwarfs, St Mary Cray. Today it is a pleasant middle class dormitory suburb, perhaps slightly less refined than Petts Wood, with a fast train to London taking a mere 20 minutes, but only three miles from the real country—at least until the green belt is raped by the mushrooming plans for houses and out of town leisure precincts with which the developers hope to fill the green fields between us and the M25.

Opposite our house is St Olave's School, relocated from the shadow of

Southwark Cathedral. The hall, with its brick columns, gallery, and, clerestoried roof, has excellent acoustics and for some time now it has been the setting for a yearly recital programme featuring world famous musicians. You buy a ticket for the whole series, and it is always sold out. There is always a wonderful flower arrangement on the stage (our next door neighbour does them). To get the seat of your choice you must appear early—up to an hour early—and recently we were seated in the gallery for the first time to hear the Takacs String Quartet play Haydn and Bartok and then, with Michael Collins, Brahms's *Clarinet Quintet in B Minor*, with a little Mozart for an encore. It was a superb performance, but you come to expect this at St Olave's. We are lucky. Not many people can boast fine concerts less than a minute from their house.

It is interesting to observe a large audience from above. You can spot the people you know, run a detailed survey of the incidence of pattern baldness, watch the smaller children growing weary, and, above all, sense the absorption and enjoyment of a crowd in a way which is impossible when you are within it. The audience was spellbound by the Brahms and the Haydn. Not a cough barked, not a programme rustled. But Bartok's *String Quartet No 4* is not easy listening, and during that the throng seethed, wriggled, and fidgeted. There was manifest discomfort.

Oh yes, Orpington has culture. But perhaps it is not quite ready for Bartok.—ANDREW BAMJI, Orpington.

Some hosts ask their guests to take off their shoes when entering a carpeted house. Does this increase the spread of tinea pedis. What discreet prophylactic measures are recommended?

Whereas this is clearly the subject for a fascinating study, there is little information on the risks of transferring desquamated but infected skin scales to others via a carpet. Clearly many of the skin scales are exfoliated on to socks and into footwear and provided that socks are worn these should provide some sort of a barrier. One study from Belgium suggested that carpets were a potential source of desquamated hair from cats with ringworm infection.¹ The actual proof, however, that shed hairs could cause infection in members of the household is difficult to establish. Presumably, the best prophylaxis is that if guests are asked to take their shoes off they should be persuaded to leave their socks on.—R J HAY, consultant dermatologist, London.

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