Editorial

Randomized study of effect of different doses of vitamin A on childhood morbidity & mortality - claiming benefit when there is none!

Vitamin A deficiency (VAD), the most important cause of preventable blindness in young children, has long been a significant public health problem in India. It is principally a nutritional disease due to inadequate dietary intake of the vitamin or its plant-based precursors, and is often aggravated by low absorption from the intestine due to frequent infections and infestations. Administration of massive dose of vitamin A every six months is accepted to be an inexpensive, quick, and effective way to improve vitamin A status and even save children’s lives. India, perhaps, is the first country in the world, to initiate the national programme of biannual distribution of mega doses of vitamin A to children of 1-5 yr age as a prophylactic measure to control blindness due to vitamin A deficiency in 1970. In fact, the World Bank estimated that vitamin A supplementation was one of the most cost-effective interventions available (less than US $ 1 per disability-adjusted life year). The role of vitamin A supplementation in child survival received attention after Sommer and his colleagues demonstrated in Aceh province in Indonesia that biannual administration of vitamin A to young children could reduce child mortality significantly. Subsequently, a number of field trials were carried out in different countries to validate/verify these observations. A meta-analysis of eight field trials to assess the impact of vitamin A supplementation on child mortality indicated that improving the vitamin A status of children aged six months to five years reduced mortality rates by about 23 per cent in populations with low prevalence of clinical signs of vitamin A deficiency. The observed effect of supplementation did not differ by sex or age though the number of lives saved was greater at younger ages because of higher mortality. It has also been claimed that vitamin A supplementation of women of child bearing age can reduce maternal mortality from 40 to 50 per cent. Vitamin A supplementation is now considered as an effective way both to improve vitamin A status and save children’s lives.

Recently, Benn and coworkers published the results of a randomized trial, conducted in Bissau, the capital of Guinea-Bissau, to determine whether the dose of vitamin A currently recommended by the World Health Organization (100,000 IU to infants aged 6-11 months and 200,000 IU to children aged 12-59 months) or half this dose (50,000 IU and 100,000 IU respectively) gives better protection against childhood morbidity and mortality. They enrolled eligible (6,669) children aged 6 months to 5 yr during the country’s second polio vaccination campaign in November 2002 and offered WHO recommended dose of vitamin A to 2,525 children and half of the same to 2458 children 6-59 months of age. The effects of doses of vitamin A on mortality, admission to hospital and diarrhoea were examined to test the hypothesis if a lower dose would offer better protection. Initially the study was planned to last six months, the period in which vitamin A was
assumed to have an effect, it was extended by three months because of a sex differential observed after six months. After nine months, information on mortality and admissions to hospital on all the children enrolled in the study was obtained. However, the study has a number of lacunae and limitations some of which in fact have been pointed out in the rapid responses (Electronic letters to Editor) in the Journal14-16. The conclusions are of no real scientific significance for reasons enumerated below:

Absence of statistical significance between groups

By any statistical convention, the observations between two groups in an intervention study, which are not significantly different, should be considered as having no benefit at all. It is rather surprising, therefore, that even in the absence of any statistically significant differences between the groups in this study13 the authors have concluded that “half the dose of vitamin A currently recommended by WHO may provide equally good or better protection against mortality but not against morbidity”. It is rather surprising as to how such a discrepancy has been overlooked. One would have expected that during the peer review the discrepancy in the conclusion in spite of the results to the contrary would have been pointed out. The correct conclusion on the basis of the results should have been, “there was no statistically significant difference in mortality between the children who were administered the full dose as compared to those who had received half the recommended dose either at six months or nine months”.

Are the surmises justified?

The authors obviously have assumed, perhaps on the basis of results of the earlier studies, that even in Guinea-Bissau where xerophthalmia is not a problem, vitamin A supplementation at the WHO recommended dose would bring down child mortality. The authors might be right if there is evidence to the extent that the mortality with vitamin A is lower than that reported in the country since there is no routine vitamin A supplementation in the country. However, no information about the general mortality pattern in the child population of the country has been provided to verify the above. In the absence of comparable information it is difficult to comment on the validity of the data at the outset. It would have been more appropriate to have a placebo group as well in the study.

Sample size

When a meta-analysis10, based on earlier studies, had indicated only 23 per cent difference in mortality between placebo (who had not received any vitamin A) and vitamin A supplemented groups what is the rationale behind the assumption of 60 per cent difference between the groups for calculating sample size? In fact, larger sample might have been required if smaller difference was assumed. Under such circumstances, the actual statistical power of the results may have been affected.

Period of observation

At the outset, the duration of observation of nine months may not be adequate to draw conclusions on differences particularly between the doses and sexes. It should have at least been 12 months. Another advantage of 12 month observation is that seasonal differences would have been taken care as well. Moreover, at least two massive doses of vitamin A are recommended to control vitamin A deficiency in preschool children and to perceive the cumulative effect. It is also well recognized that the serum vitamin A levels fall gradually with time after 6 months of administration of massive dose of vitamin A. In addition, the protective period (of a 200,000 IU dose) is likely to vary with the frequency and severity of precipitating and contributory factors such as infection and protein-energy malnutrition. Therefore, the children should have been followed up for a period of at least one year. There would, then, not have been any need to resorting to estimation of years of risk and it would have been possible to estimate per 1000 children.

Confounding factors

The effects of any intervention depend upon the initial status of the community - with respect to mortality and nutritional (vitamin A) status - and
other confounding factors like provision of adequate nutrition and health care of study community. Similarly no data are given on consumption patterns of vitamin A and whether vitamin A deficiency is a public health problem at all in the community in general vis-a-vis the study community. It appears that in general the vitamin A status of the study community was satisfactory as there was no case of xerophthalmia. An important unanswered question is whether populations, without any evidence of clinical manifestations of vitamin A deficiency but with biochemical evidence of major depletion, would also be responsive to improvement of vitamin A status. To answer this, serum vitamin A should have been estimated at least in a subsample to assess whether subclinical vitamin A deficiency is a public health problem, particularly in the absence of clinical signs of vitamin A deficiency.

Thus, the conclusions of Benn et al, not only lack statistical validity but also have several limitations with respect to design, sample size and confounding factors. The authors’ contention that “language conventions may differ between countries or professions” cannot be accepted as such inferences may do more damage than good particularly when the role of vitamin A supplementation on child mortality is considered controversial by some in India. In countries like India, despite significant decline in the magnitude of clinical VAD, it still continues as a public health problem in rural and tribal areas. Ganguly Committee, appointed by the Government of India, recommended that the existing vitamin A prophylaxis programme should be effectively implemented until the nation is able to achieve dietary diversification.

It has since been well recognized that for controlling vitamin A deficiency and its consequences, the dose of vitamin A should be as suggested by the WHO. In fact, the dose is calculated based on the recommended dietary allowance (RDA) of vitamin A for preschool children. The Madurai study documented that regular provision of a supplement of vitamin A to children, at physiologic doses of vitamin A - corresponding to RDA - and at a level potentially obtainable from foods, in an area where vitamin A deficiency is a public health problem contributed substantially to children’s survival. In addition, most of the field trials, which were conducted in settings where VAD was a public health problem (as per the WHO definition), demonstrated the beneficial effect of WHO recommended dose of vitamin A supplementation on child survival with variable results. The existence of clinically apparent deficiency appeared to be a marker in all the field trials on vitamin A supplementation and child mortality. On the other hand, in the study children in Guinea-Bissau vitamin A deficiency did not appear to be a public health problem at all. Therefore, any conclusions based on such studies on distribution of vitamin A in reduced doses has no relevance particularly in any strategy of the Indian context where vitamin A deficiency continues to be a problem of public health significance.

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References


