EDITORIAL

VITAMIN A SUPPLEMENTATION AND CHILD MORBIDITY AND MORTALITY

Deficiency of Vitamin A has long been recognized as a serious and preventable nutritional disease. Vitamin A is essential for normal vision, for maintaining the integrity of epithelial cells, and functions such as growth, reproduction and immunocompetence; the exact mechanisms of many of Vitamin A's functions remain still unknown. The most dramatic impact of acute Vitamin A deficiency–xerophthalmia is widely recognized as the leading cause of childhood blindness. It is estimated that in Asia alone, about 500,000 children under six years of age develop potentially blinding corneal xerophthalmia each year(1). Nearly 50% of them die within a few months after the blinding episode(2).

The role of Vitamin A in maintaining the integrity of the epithelial lining of the gastrointestinal, respiratory and genitourinary tracts is well recognized. *In vitro* studies have shown increased binding of bacteria to nasopharyngeal epithelial cells obtained from children with mild xerophthalmia(3). So far no strong immunological basis for the increased susceptibility to infection in Vitamin A deficiency has been demonstrated. Some studies suggest that Vitamin A may have a non-specific immunopotentiating effect(4,5); the functional significance is not clear. Vitamin A has been popularly referred to as 'anti infective vitamin', based on animal studies which had shown that hypovitaminosis A led to increased susceptibility to infections.

Since laboratory studies show that Vitamin A deficiency can alter the epithelial lining of the respiratory and gastrointestinal tracts, it is reasonable to assume that Vitamin A deficiency can increase susceptibility to morbidity and mortality due to certain mucosal infections. Recent studies indicate that even milder forms of Vitamin A deficiency like night blindness, conjunctival xerosis and Bitot spots are associated with a higher risk of morbidity.

Vitamin A Deficiency and Morbidity

In a longitudinal study in Indonesia, on children under the age of six years, Sommer *et al.*(6) showed that the relative risk for diarrhea and respiratory infections in children with night blindness, conjunctival xerosis and Bitot spots was higher than in those with normal eyes. The relationship between xerophthalmia and morbidity could not be attributed to the possible protein energy malnutrition in children with Vitamin A deficiency since it was maintained even after controlling, statistically, for weight for height status. But these conclusions have been questioned on the grounds that it was not possible, based on the data to decide whether Vitamin A deficiency led to the increased risk of morbidity or *vice versa*(7). In North Eastern Thailand, a follow up study revealed that in children with deficient serum retinol the risk of respiratory disease was greater, and no relation was found for diarrhea(8). In

another retrospective study in urban slums of Hyderabad though the risk of respiratory infection was higher in mild xerophthalmia, the risk of diarrhea was same in children with normal eyes(9). Similar results were observed in a prospective longitudinal study in rural areas around Hyderabad(10).

Vitamin A Supplementation and Morbidity

If Vitamin A deficiency *per se* increases the risk of morbidity it is reasonable to assume that Vitamin A supplementation should reduce the morbidity. However, Vitamin A supplementation did not have any impact either on diarrhea or respiratory infection in most of the intervention studies. In Hyderabad six monthly massive doses of Vitamin A did not have any impact on the incidence of either respiratory infection or diarrhea(10). Similarly in Baroda, massive dose of Vitamin A to under-privileged school children had no impact on diarrheal diseases(11). In the rural areas in Tiruchi, weekly supplements of Vitamin A (8,000 IU) to children between 6 months and 6 years of age for one year did not bring down the incidence of either diarrhea or respiratory infections(12). The Aceh study group(13) in Indonesia also concluded that Vitamin A supplementation was unlikely to produce rapid and dramatic effect on respiratory and enteric morbidity in the absence of changes in overall malnutrition and socio environmental factors. Thus, these studies show that Vitamin A supplementation singly did not bring down the morbidity in children. However, in North Eastern Thailand, administration of 200,000 IU to children of 1-5 years of age reduced the incidence of both diarrhea and respiratory infection for a period of atleast 2 months(8). A randomized double blind trial in hospitalized children in South Africa, indicated that treatment with 400,000 IU of water-miscible Vitamin A reduced morbidity and mortality in measles(14). The role of vitamin A in measles has been recognized and the WHO recommends routine use of Vitamin A in all cases of measles.

Vitamin A Deficiency and Mortality

A matter of considerable importance to pediatricians and public health policy makers is the relationship between mild Vitamin A deficiency and childhood mortality, and the impact of Vitamin A supplementation on child mortality. Researchers world over have been involved in providing answers to this aspect during the past five years. Sommer *et al.*(15) based on studies in Indonesia, reported that mortality risk in children with mild xerophthalmia was four times higher than with normals; the risk increased with the severity of the disease, and the differences persisted even after controlling statistically the effects of age, infection and weight for height. However, it has been argued that the relationship may have been due to stunting, *i.e.,* low height for age, and use of weight for height (wasting) to study the confounding effect of nutritional status was, therefore, not appropriate(16). The possible role of other confounding variables like socio-economic and dietary status has been pointed out as the poorer families may be more likely to encounter threats to child survival(17,18).

Vitamin A Supplementation and Mortality

Sommer *et al.*(19) subsequently made far reaching observations, based on an intervention trial carried out in another part

of Indonesia. They observed that mortality rate in randomly allocated programme villages, where two massive doses of oral Vitamin A (200,000) were administered, was 34% lower than in the control villages. The mortality rates were lower than the reported national averages. These observations projected almost overnight Vitamin A as a magic bullet for increasing child survival in developing countries where dietary intakes of Vitamin A are low. The study, however, generated considerable controversy, and the results have been questioned because it was not a double blind trial, and sufficient care was not taken to eliminate differential effects resulting from contacts between investigators and community in programme and control villages. Sufficient care was not taken in the ascertainment of deaths by active surveillance(18). There were also differences in the prevalence of xerophthalmia and severe malnutrition at baseline between control and programme villages(20). On further analysis of the data, the study group observed that mortality among non-recipients in the programme villages was considerably higher than even the controls. They concluded that the potential biological impact of Vitamin A supplementation on childhood mortality may exceed the 34% previously described(21).

Several large scale community trials have been initiated in India, Nepal, Sweden and Ghana to validate the findings of Aceh study group. The methodological issues were discussed in a workshop organized by the NRC Sub-committee on Vitamin A deficiency, prevention and control. In South India two large scale randomized double blind field trials with a placebo control were carried out. While in the Hyderabad study(14) the impact of six monthly massive oral doses of Vitamin A on preschool child mortality was measured, in the Madurai study(16) the impact of weekly supplements of 8,000 IU (equivalent to daily RDI) was estimated. The Hyderabad study showed that the child mortality was higher in children who had not received either Vitamin A or placebo. There was a significant reduction in mortality in the group which had received two doses of either Vitamin A or placebo compared with those who had received one dose or no dose. In other words, there was no effect of Vitamin A on mortality and any reduction in death rate was perhaps due to frequent contacts of investigators with the community both in the Vitamin A and placebo villages. The Madurai study however, indicated that regular provision of a supplement of Vitamin A to children, at a level potentially obtainable from foods, in an area where Vitamin A deficiency was a public health problem contributed substantially to children's survival; mortality was reduced on an average by 54%. There have been a number of speculations as to the reasons for the differences in the observations made in these studies. By and large the communities in Hyderabad and Madurai were essentially similar socio-economically though the prevalence of Bitot spots was higher in the Madurai study children. It has been argued that in the Hyderabad study, since the proportion of children receiving two doses of Vitamin A was lower, the impact of Vitamin A was absent. In fact, mortality was calculated for each cohort of children receiving different doses of Vitamin A or placebo and not for all the children of programme or placebo villages. In otherwords, differences in coverage of children with 2 doses (lower in Hyderabad) cannot explain the differences. A controlled trial in Indonesia also indicated that fortification of commercially

marketed monosodium glutamate (MSG)–a commonly used flavouring agent–brought down mortality in programme villages as compared to control villages(22).

Interestingly, in all the three studies in Aceh(13), Hyderabad(10) and Madurai(12), there was no impact of Vitamin A on morbidity which in turn was supposed to contribute to lowering of child mortality. This raises a question as to how can Vitamin A bring down the child mortality to such an extent. Sommer and West(23) propose that Vitamin A might act at a later stage and determine whether or not a child succumbs to infection, rather than earlier, to prevent clinical manifestations of a disease. Only carefully conducted studies on the effects of Vitamin A supplementation on childhood morbidity and mortality can provide answers. The conflicting opinions are likely to be resolved shortly as soon as the results from other countries are made available.

This, however, dose not deny the importance of Vitamin A supplementation to improve nutritional status. Presentation of blindness is a good enough reason to strengthen the continuing Vitamin A programme combined with other health care services, so that it can have a better impact on child health. The expectations that Vitamin A may be a magic bullet to increase child survival should not lead to false hopes among the health administrators. If controlled trials of Vitamin A supplementation show the association to be causal, interventions to improve Vitamin A status of at risk groups are likely to receive highest public health priority.

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