Editorial

VITAMIN A SUPPLEMENTATION AND CHILD SURVIVAL

The intimate relation between nutrition and infection is recognized for a long time(1,2). A wide range of studies have been carried out in experimental animals and in human subjects to understand the underlying mechanism of this relationship. As a part of these studies, the influence of several nutrients on immune mechanism has been extensively studied both in experimental animals with induced deficiency and in human subjects with different degrees of nutrient deficiencies(3).

Besides, epidemiological studies to relate the prevalence of morbidity and mortality in the community with the concurrently present nutritional deficiencies have also been carried out. In the context of widespread prevalence of protein energy malnutrition (PEM) with the attended growth retardation, iron deficiency anemia, and vitamin A deficiency among children belonging to the underprivileged communities in the developing world, the influence of these deficiencies on immune function, morbidity and mortality have been extensively studied. Since, all these three differences occur concurrently in many communities, the interpretation of the results of human studies on the effect of a single nutrient is rendered extremely difficult, particularly in view of the associated poor socio-economic and environmental factors for which nutritional deficiencies are only proxy indicators.

Of the three nutritional deficiencies, PEM and iron deficiency anemia have been shown to affect some aspects of immune function(3). Based on the epidemiological studies, PEM with different degrees of growth retardation and iron deficiency anemia, have been shown to influence morbidity among pre-school children(2). On the other hand vitamin A although known to be an anti-infective vitamin(4), its deficiency, of the mild and the moderate types, has no influence on immune function(3,5). Vitamin A deficiency on the other hand is known to affect mucus membranes and mucus secretion leading to colonization of bacteria(6). Such non-specific effect on mucus membrane leading to bacterial colonization can also occur in iron deficiency anemia(2).

It is surprising that inspite of lack of specific effect of subclinical vitamin A deficiency on immune process, it is reported on the basis of epidemiological studies(7,8) that mild vitamin A deficiency increases child morbidity due to diarrhea, respiratory infection and measles among underprivileged population, and that intervention with vitamin A significantly reduces mortality among children below 5 years(9-12). These somewhat exaggerated claims on the effect of vitamin A administration on child morbidity and mortality has led to a lot of controversy and a lively debate. In view of the far reaching practical implications of these claims, they deserve a detailed critical examination.

The first of these intervention studies to test the effect of vitamin A on child mortality was carried out in Indonesia by Sommer and co-workers(9). Vitamin A was ad-

ministered to the experimental children in two doses of 200,000 IU each, at 6 monthly intervals. The control children were left alone without any placebo. In this study 34% reduction in mortality was reported among preschool children receiving vitamin A. A reanalysis of their data taking into consideration only those children who actually received vitamin A indicated a much higher reduction in mortality namely 75%(10). This study has been criticized on several counts, the most important one being with regard to its design. Since, it was not a double blind study with placebo control, it is argued that the observed effect of vitamin A administration on mortality among the experimental children, could be due to a contact effect. In view of this criticism three more studies(11-13) were carried in different locations using an improved experimental design. All were double blind with the control group receiving a placebo. Of the three studies one study each in India (Tamil Nadu)(11), and Nepal(12) confirmed the findings of the Indonesian study while the other study also in India (Andhra Pradesh)(13) did not. The main findings of the Tamil Nadu and the Nepal studies are enumerated below.

In the study reported from Tamil Nadu, South India(11) which had a double blind design, vitamin A was administered in small oral doses to the experimental children, the dose being 8 μ mole of retinol (*i.e.*, 8333 IU) per week. The control children received a placebo containing about 1.4 μ mole (300-400 μg) of vitamin A. A reduction of 54% mortality in the experimental group receiving weekly dose of vitamin A was reported, the relative risk compared to control was only 0.46. In the Nepal study(12) a large dose of retinol (65,000 μg) was administered to the children in the experimental area, once in 4 months. The control children received placebo. A 30% reduction in mortality among children receiving vitamin A has been reported, the relative mortality risk in the experimental group was 0.7.

All the above three studies which reported a large reduction in mortality on vitamin A intervention have been critically examined by several scientists. A number of criticisms(14-23) have been levelled against the Indonesian, South Indian and Nepal studies particularly with respect to the data presented and their interpretation. On the basis of all these criticisms the claim on high reduction in mortality on vitamin A administering becomes almost unacceptable. Some of the important criticisms which are common to all the three studies are:

1. The rates of child mortality reported for the study area, in all the three studies are very low in comparison with the corresponding national averages. The national average of 0-5 mortality rate is 97, 142 and 189 for Indonesia, India and Nepal, respectively(24). The child mortality rate in Tamil Nadu is usually higher than the National average. The corresponding observed rates in the study areas were 7.8, 16.4 and 8.1% respectively. It is surprising that mortality rates were so low considering the areas chosen for the study were backward and depressed ones in all the three studies. The consequence of such low mortality rates is that it makes unreliable and uncertain the data on the impact effect due to missed or misreported deaths. The observed low mortality rate is undoubtedly due to the well-known contact effect. A more appropriate mortality figure for comparison would have been the natural mortality rate in the study area which could have been collected for the preceding one year at the time of baseline survey. Such

data were apparently not collected in the Indonesian study but were collected in the Nepal and the Indian (Tamil Nadu) study, but it is unfortunate that these figures are not reported.

2. In none of these studies adjustments have been made for socio-economic differences, a very important determinant of child mortality. Random allocation of villages to control and experimental group does not necessary compensate for this factor.

3. Similarly, other confounding nutritional factors which also influence child mortality like growth status and micronutrient deficiencies have not been taken into consideration in the data analysis.

4. Some anomalies in the observed alterations in mortality in relation to disease, age and sex are also seen in the data presented.

(*a*) On the basis of available data the infectious diseases most influenced by vitamin A deficiency are respiratory diseases, gastro intestinal disorders *viz.*, diarrhea and measles, the former too being normally the most important causes of preschool child mortality in developing countries. However, the observed reduction in mortality on vitamin administration does not fall uniformly in these disease categories. For example, in the Indonesian study, mortality reduction according to disease is not given while in the Nepal study, vitamin A supplementation had an effect on mortality only among those with diarrhea and not in those with respiratory diseases. Similarly, in the Indian (Tamil Nadu) study vitamin A had no effect on mortality attributable to acute lower respiratory infection. In the Indian study, surprisingly deaths from respiratory diseases accounted for less than 5% contrary to all the available evidence on childhood mortality in rural India.

(*b*) There were also anomalies in the observed effect of vitamin A supplementation on mortality between the two sexes. In the Indonesian study, the impact of vitamin A was seen only among boys and not among girls and on the other hand girls of 12-72 months showed somewhat increased risk. In Nepal study both sexes showed equal response. In the Indian study also the reduced mortality risk was greater among girls than among boys. There is no explanation for the sex bias in the vitamin A impact.

5. There are also other criticisms levelled against these studies, with regard to differences in the baseline prevalence of xeropthalmia between control and experimental groups (Indonesian study) and the age and disease related mortality reduction (Nepal study).

All these inconsistencies in the reported observations raise doubts about the validity of the far-reaching conclusion drawn. In view of all the above criticisms of the three studies, the reported large reduction in mortality due to vitamin A intervention cannot be readily accepted as valid.

The other study which concludes that there was no effect of vitamin A supplementation on child mortality has been reported by the National Institute of Nutrition from India. There have been several comments on this study also(19,25-27). This study also a double blind one was carried out in a backward district of Andhra Pradesh. The children in the experimental village were administered 200,000 IU vitamin A in peanut oil orally once in 6 months and the children in the control village received only plain peanut oil as placebo. Morbidity data were collected every three months by the field workers and clinical

examinations of the children were done initially and after 6 and 12 months. It has been concluded that administration of vitamin A has no impact on child mortality as there were no differences between the control and experimental groups in the mortality figures.

A closer scrutiny of the paper reveals that this study also suffers from several of the limitations as pointed in case of the other three studies which have reported a positive impact of vitamin A. Also in this study there are a number of internal contradictions in the results presented. The important drawbacks of this study are:

1. The mortality rate reported in this study for a backward district is extremely low, *viz.*, 4.96/1000 among those with xerophthalmia and 2.26/1000 among normals, as compared to the national average, which in the case of the state of Andhra Pradesh must be even higher. In contrast to these two figures, mortality among those who did not receive any dose is reported to be 17.6 and 17.2 in the experimental and the placebo groups, respectively. It is rather difficult to reconcile these figures. The authors should have collected the normal mortality rate in the study area at the time of baseline survey for the preceding one year. It is not clear whether this has been done since no information on this is given in the paper.

2. Unfortunately, no detailed data on morbidity, mortality according to age, sex, nutritional grades and according to disease have been given for the experimental and control groups separately to enable the reader to make the comparative assessment of the data and the authors conclusion.

3. It is reported that mortality rate and the relative risk of morbidity were higher among children with xerophthalmia with respect to both diarrhea and respiratory infection (vide Table II of the study). On the other hand, it is stated that vitamin A supplementation which resulted in a reduction of vitamin A deficiency, did not influence either morbi-dity or mortality. It is reported that the prevalence of xeropthalmia came down from the baseline figure of 6.1 to 1.3% in the treatment area and to 2.9% in the placebo area. It is rather difficult to reconcile these results.

4. The most surprising of all are the results presented in Table III. It is surprising that there was a dramatic reduction in child mortality both in the experimental and the control areas both with one dose and two doses of vitamin A or placebo. Mortality rate decreased from 17.6 to 9.7 with one dose and to 2.3 with two doses in the vitamin A group, and in the placebo group from 17.2 to 10.8 with one dose and to 2.2 with two doses. The relative risk compared no dose group in the vitamin A and the placebo areas, respectively were 0.55 and 0.63 with one dose and 0.13 in both with two doses. A remarkable achievement in mortality reduction is indeed even with placebo. If the reported mortality reduction is not due to vitamin A, what is it due to? It cannot merely be due to increased contact by one or two over the 6 contacts made with all the groups or due to one or two doses of peanut oil. These data need to be looked at again to check whether there has been any error of reporting.

In view of the above cited serious limitation of the study, the conclusion that vitamin A administration had no effect on either morbidity or mortality cannot be accepted without serious reservations.

The foregoing critical scrutiny of reported studies on the effect of vitamin A on child mortality, the large effects of mortality reduction of 30-75% claimed in these

micro-scale studies cannot be accepted without serious reservation. The other study which has reported no effect of vitamin A on mortality also suffers from serious limitations. Thus the question of the effect of vitamin A supplementation in child mortality is still open. A more realistic assessment of the effect of vitamin A intervention on child mortality can be made only through studies on large population at the districts or the state level. Such studies would be prohibitively expensive. Since massive dose vitamin A programme is currently in operation in many countries, the impact of vitamin A intervention on child mortality after adjusting for other variables can be studied retrospectively, particularly in areas where the programme has been effectively implemented.

From our present knowledge on the lack of effect of vitamin A on immune function, vitamin A can have only a minor role in reducing child morbidity and mortality. On the other hand, the widely prevalent protein energy malnutrition and iron deficiency anemia which are know to have a definite influence on some aspects of immune process can be expected to be greater risk factors in childhood morbidity and mortality and any intervention to correct these deficiencies can have a better impact on morbidity and mortality. Vitamin A and other nutrients whose deficiencies are widely prevalent can have only a supportive role in reducing morbidity and mortality, in which a significant reduction can be effectively achieved only through improvement in health prarameters including immunization, improvement in environmental sanitation, safe drinking water supply, and access to health and medical facilities. The primary objective of nutrition intervention should be to correct expeditiously the existing nutrient deficiencies and the associated functional and biological disabilities. Any such intervention must be total covering all the prevailing nutritional deficiencies for a maximal impact in view of the known interrelationship between nutrients. Their contribution if any in reducing the child mortality should be considered as a bonus.

The much publicised claim on large effects of vitamin A intervention on child mortality to the extent of 30-70% may give wrong signals to the National and International Agencies concerned with programmes in the developing countries, for the improvement of the health and nutritional status of the deprived child population for which child survival is used as proxy indicator. There is a danger of their opting for this easy solution of periodical vitamin A administration which is less expensive than other health programmes, easy to operate, for achieving the targets of child survival without improving the health and nutrition and quality of life of the child population in the Third World countries. This danger must be avoided.

The most desirable strategy is the holistic approach to improve the nutrition and health of people in the third world, the former through dietary improvement and/or through specific nutrient intervention as an emergency measure, and the latter through immunization, improvement of environment including provision of safe drinking water, access to medical and health facilities and above all education.

B.S. Narasinga Rao,
Former Director,
National Institute of Nutrition,
Hyderabad.
11/4 M Block (1-2-62/3),
Kakateeya Nagar,
Habsiguda, Hyderabad 500 007.

REFERENCES

1. Scrimshaw NS, Taylor CI, Gordon JE. Interactions of Nutrition and Infection. World Health Organization, Geneva, 1968.
2. Tomkins A, Watson F. Malnutrition and Infection–A Review. ACC/SCN State of the Art Series, Nutrition Policy Paper No. 5, 1989.
3. Bhaskaram P. Two decades of nutritional immunology in India. New Delhi, Indian National Science Academy, Report of 1990.
4. Green HN, Mellanby E. Vitamin A as anti-infective agent. Br Med J 1928, 2: 691-696.
5. Bhaskaram P, Jyoti SA, Rao KV, Rao BSN. Effect of subclinical vitamin A deficiency and administration of vitamin A as a single large dose on immune function in children. Nutr Res 1989, 9: 1017-1025.
6. Rojanapo W, Lamb AJ, Olson JA. The prevalence, metabolism and migration of goblet cells in the rat intestine following the induction of rapid synchronous vitamin A deficiency. J Nutr 1980, 110: 178-188.
7. Sommer A, Katz J, Tarwotjo I. Increased risk of respiratory disease and diarrhea in children with pre-existing mild vitamin A deficiency. Am J Clin Nutr 1984, 40: 1090-1095.
8. Milton RC, Reddy V, Naidu AN. Mild vitamin A deficiency and childhood morbidity–An Indian experience. Am J Clin Nutr 1987, 46: 827-829.
9. Sommer A, Tarwotjo I, Djunaedi E, West KP, Loeden AA Tilden R. Impact of vitamin A supplementation on childhood mortality. Lancet 1986, 1: 1169-1173.
10. Tarwotjo I, Sommer A, West K, Djunaedi E, Mele L, Hawkins B. Influence of participation on mortality in a randomized trial of vitamin A prophylaxis. Am J Clin Nutr 1987, 45: 1466-1471.
11. Rahmathullah L, Underwood BA, Thulsiraj RD, Milton RC, Ramaswamy K, Rahmathullah R, Babu G. Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. New Eng J Med 1990, 323: 929-935.
12. West KP, Pokhrel RP, Katz J, *et al*. Efficacy of vitamin A in reducing child mortality in Nepal. Lancet 1991, 338: 67-70.
13. Vijayaraghavan K, Radhaiah G, Prakasam BS, Rameswara Sarma KV, Reddy V. Effect of massive dose of vitamin A on morbidity and mortality in Indian children. Lancet 1990, ii: 1342-1345.
14. Gopalan C. Vitamin A deficiency and child mortality. NFI Bulletin 1986, 7: 6-7.
15. Castello AML. Vitamin A supplementation and childhood mortality. Lancet 1986, ii: 161.
16. Gray RH. Vitamin A supplementation and childhood mortality. Lancet 1986, ii, 161.
17. Martinez H, Shekar M, Latham M. Vitamin A supplementation and child mortality. Lancet 1986, ii: 451.
18. Anonymous. Vitamin A supplementation and childhood mortality. Nutr Rev 1987, 45: 48-50.
19. Gopalan C. Vitamin A child mortality. NFI Bulletin 1990, 11: 1-3.
20. Cravioto J. Vitamin A supplementation and child mortality–Examination of a claim. NFI Bulletin 1990, 11: 5-6.
21. Ramachandran K. "Reduced mortality" with vitamin A supplementation. NFI Bulletin 1991, 12: 6-7.
22. Rajagopalan S. Vitamin A supplementation and child mortality–the Nepal study. NFI Bulletin 1992, 13: 4-5.

23. Gopalan C. Vitamin A child mortality—now the Nepal study. NFI Bulletin 1992, 13: 6-7.
24. UNICEF: The State of World Children, 1992. Delhi, Oxford University Press, 1992.
25. Editorial. Vitamin A and malnutrition/infection complex in developing countries. Lancet 1990, ii: 1349-1351.
26. Thurnham DI. Vitamin A and childhood mortality. Lancet 1991, i. 232.
27. Sommer A, West KP. Vitamin A and childhood mortality. Lancet 1991, i: 925.

NOTES AND NEWS

CRITICAL CARE PEDIATRICS–APPROPRIATE PRACTICE AND TECHNOLOGY

A Symposium-cum-Workshop on Critical Care Pediatrics–Appropriate Practice and Technology is to be held on *12th and 13th December, 1992* at St. John's Medical College, Bangalore 560 034.

For futher details, please contact:

Dr. Swarna Rekha,
Organizing Secretary, Pediatric Symposium,
Alumni Association Office,
St. John's Medical College,
Bangalore 560 034.