

EFFECT OF VITAMIN A SUPPLEMENTATION TO MOTHER AND INFANT ON MORBIDITY IN INFANCY

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Objectives: To assess the impact of Vitamin A supplementation to the mother soon after delivery and to the infant at six months on morbidity in infancy. **Design:** Randomized double blind placebo controlled field trial. **Setting:** 51 villages in two contiguous Primary Health Centers in Villupuram Health Unit District of Tamil Nadu, South India. **Subjects:** 909 newly delivered mother-and-infant pairs. **Interventions:** Both mother and infant received Vitamin A (300,000 IU for mothers and 200,000 IU for children) in 311 instances (AA); mother received Vitamin A but infant received Placebo in 301 instances (AP); and both mother and infant received Placebo in the remaining 297 instances (PP). **Main outcome measures:** Incidence of diarrhea and Acute Respiratory Infection (ARI); distributions of infants by frequency of episodes and number of infected days. **Results:** 233 in the AA Group and 228 each in the AP and PP Groups were followed up regularly. The incidence of diarrhea in these infants was 97.4%, 96.9% and 94.7% in the three groups, mean number of diarrheal episodes was 4.4, 4.6 and 4.2 and median number of days in infancy with diarrhea was 26, 26 and 22 days, respectively. For ARI, the incidences were 96.6%, 95.6% and 96.1%, means were 4.8, 5.1 and, 4.8 episodes, and the medians were 32, 34 and 34 days, respectively. **Conclusions:** Prophylactic administration of mega doses of Vitamin A to the mother soon after delivery and to the infant at six months do not have any beneficial impact on the incidence of diarrhea and ARI in infancy.

Key words: Vitamin A supplementation, Diarrhea, Acute respiratory infections.

THE role of Vitamin A supplementation in reducing morbidity among children has been the subject of some controversy in recent years. Observational studies (1-3) have reported an association between Vitamin A deficiency and increased risk of morbidity. If Vitamin A deficiency *per se* increases the risk of morbidity, it is reasonable to assume that Vitamin A supplementation will reduce the incidence of morbidity. With this expectation, Vitamin A supplementation trials in

preschool age children have been conducted in different parts of the world, but the results have not been unequivocal (3-7).

Clinical Vitamin A deficiency is mainly seen in pre-school age children. However, sub-clinical Vitamin A deficiency can also occur in infants due to lower level of Vitamin A content in breast milk or due to increased demand on account of rapid growth. This deficiency may be further aggravated during infancy by recurrent infections which are common

in rural populations. Vitamin A supplementation to pregnant women has limitations due to a possible teratogenic effect, and has therefore to be administered in low and repeated doses. To overcome this, synthetic Vitamin A preparation can be prophylactically administered to the lactating mother soon after delivery (8,9).

A randomized controlled trial to determine the impact of Vitamin A supplementation to the newly delivered mother, with or without Vitamin A supplementation to the infant at 6 months, on the incidence of acute respiratory infections (ARI) and diarrhea in infancy is reported in this paper; the study was initiated in April 1991 and completed in May 1993.

Subjects and Methods

The trial was conducted in two contiguous Primary Health Centers (PHC) viz., Vikravandi and Thokkavadi, in Villupuram Health Unit District in Tamil Nadu, South India covering a total population of about 53,000 in 51 villages with 11,484 households.

Study Groups

A newly delivered mother and her infant formed a pair of subjects. Each pair of subjects enrolled for the study was randomly allocated to one of the following three groups: (i) AA-Both mother and infant received Vitamin A, the former soon after delivery and the latter at 6 months; (ii) AP : Mother received Vitamin A but her infant received a placebo (Sesame oil); and (iii) PP : Both mother and infant received placebo, the former Vitamin E and the latter Sesame oil.

Mothers received a dose of 300,000 IU(8,9) of Vitamin A or 600 mg of Vitamin E (placebo) in 6 capsules that were similar in color. Infants received 2 ml of syrup containing 200,000 IU of Vitamin A (as per

the programme in Tamil Nadu) or 2 ml of Sesame oil (placebo); the syrup and the oil being matched for color and consistency. The consent of the local health authorities and the village leaders was obtained for the study.

Trial Size

Taking the proportion of infants with at least one episode of diarrhea in a year to be 80%(10), the sample size was determined such that the trial would have a power of 90% to detect, at the 5% significance level (2-tail), a difference of 20%. The computed figure was 105 for each series. To allow for losses in follow-up, it was decided to admit double the number, i.e., 210 infants to each of the three series.

Survey Procedures

A camp office was set up in Villupuram town for conducting the study, with a Medical Officer, ancillary staff and transport facilities. The area covered by each PHC was divided into four sub-areas having approximately 5,000 to 7,000 population and each sub-area was allotted to a female graduate field investigator. By continuous monitoring of all the antenatal cases in the study area, the field investigators reported all live births to the Medical Officer. On a convenient day between 7 and 14 days after delivery, the Medical Officer recorded the infant's weight and administered the appropriate capsules to the mother from the sealed envelope supplied by the Statistical Section at the Camp Office. At the age of 6 to 6VI months, the infant was weighed again and given the appropriate syrup by the Medical Officer from coded bottles, supplied again by the Statistical Section at the Camp Office. In both instances, the Medical Officer revisited the household after 3 days to record side-effects, if any.

Data on morbidity was collected for each day until the child attained one year of age (together with immunization status and infant feeding practices), by field investigators at home visits. These were undertaken once a fortnight in the early stages of the study (April-December 1991, for operational reasons), but intensified to once a week subsequently (January 1992-April 1993). A case was considered as regularly followed-up if at least 90% of the folio wed-up days had a recall period of 17 days (14+3 days grace) or less.

All severe cases (for definition, see below) were referred to the Medical Officer for confirmation of the symptoms and appropriate action. The field investigators were trained intensively for a period of one month prior to the start of the trial, and standardized during field-testing of proforma. In the initial stages, a field supervisor checked a 10% random sample of the morbidity data once a fortnight. Subsequently, spot checking was done once a week by the Medical Officer to ensure the quality of data.

Definitions of Morbidity

The following definitions of morbidity were adopted

(i) *Diarrhea*: Passing of 3 or more loose motions within 24 hours.

(ii) *ARI*: Episodes of ART consist of episodes of acute upper respiratory infections (AURI) or acute lower respiratory infections (ALRI). *AURI* was defined as the presence of cough or running nose or ear discharge for a period not exceeding 14 days. *ALRI* was defined as difficulty in breathing for not more than 30 days in the case of infants aged less than 2 months, and difficulty in breathing together with cough for not more than 30 days for infants aged 2 months or more. For both diarrhea and ARI, episodes of

illness that were separated by a period of at least 2 days with no complaints were treated as two separate episodes(11,12).

(iii) *Severe episode*: All episodes of ALRI were regarded as severe. In addition, episodes of AURI or diarrhea that required hospitalization, and episodes of diarrhea that were associated with vomiting and inability to take feeds were considered as severe.

Statistical Methods

The Chi-square test was employed for comparing proportions, the Kolmogorov-Smirnov test for comparing distributions, the 't'-test for comparing mean number of episodes, and the median test for comparing the median number of days with ARI or diarrhea.

Results

Numbers in the Study

In all, 1,335 live births were reported between April 1991 and May 1992. Of these, 426 could not be included in the trial; in 291 this was because the mother had gone to her parents' home for delivery, a normal cultural practice in South India. Of the remaining 909, 311 were randomly allocated to the AA group, 301 to the AP group and 297 to the PP group. There were 3, 8 and 9 infant deaths in the AA, AP and PP groups, respectively (see below); 4 each in the AA and AP groups and 5 in the PP group were withdrawn from the trial on medical grounds such as congenital abnormalities, epileptic fits or jaundice. Migration accounted for the loss of 34 infants in the AA group, 25 in the AP group and 20 in the PP group while 7, 9 and 7 were excluded due to other miscellaneous reasons. Of the remaining 263, 255 and 256 infants in the three group, 233 in the AA group and 228 each in the AP and PP groups

were followed-up very regularly and form the basis for analyses in this report.

Infant Deaths

Of the 20 infants (3 AA, 8 AP, 9 PP) who died during the year, the available history suggested that 6 (5 AP, 1 pp) died of ARI and 4 (2 AP, 2 PP) of diarrhea; 5 (4 AP, 1 PP) of the former died within the first 6 months while all of the latter died between 6 and 12 months.

Baseline Characteristics

About 50% of the infants in the study were males and 52% were exposed to passive smoking; 69% of the mothers were illiterate and 81% were aged less than 30 years. The parity was 1 or 2 in 40%, 3 or 4 in 42% and 5 or more in 18%. The household size was 5 or less in 50% of the families and 6-10 in 46%. Over 75% of the families had a kutcha dwelling and virtually all used fire-wood for fuel. The three groups (AA, AP and PP) had very similar distributions with respect to all the above baseline characteristics. Further, 78 AA, 73 AP and 69 PP infants who were excluded from analysis for a variety of reasons (see above) had base-line characteristic distributions that were similar to those for the 233 AA, 228 AP and 228 PP infants included in the report, except in the case of parity in the AA group; mothers with a parity of 1 or 2 being more common among the exclusions than among the inclusions ($p < 0.05$).

Other characteristics such as the immunization status and the breastfeeding habits which may have influenced morbidity in the infants, were also monitored throughout. The overall coverage for the four important immunization schedules, namely, BCG, DPT, OPV and measles were 75%, 58%, 83% and 56% respectively, and were similar in the AA, AP and PP groups.

Practically all the infants in the study (99.7%) received breastfeeding for at least 6 months. The weight of the infants was similar at intake in the three groups. The distribution of the recall periods in the three groups was also similar. To sum up, the three groups were similar in all relevant characteristics, thereby validating the comparison of the outcome variables.

Side-Effects

No case of hypervitaminosis was observed in the study, nor was any side effect reported to the Medical Officer when he visited the household 3 days after Vitamin A administration.

Effect of Supplementation

Diarrhea: The incidence of at least one episode of diarrhea was 97.4% (95% CI 95.4% to 99.4%) in the AA group, 96.9% (95% CI 94.7% to 99.1%) in the AP group and 94.7% (95% CI 91.8% to 97.6%) in the PP group ($p > 0.2$). Further, the distribution of infants according to the number of episodes of diarrhea was similar in the three groups (*Table I*), and the means were 4.4, 4.6 and 4.2, respectively ($p > 0.2$). The corresponding means for severe episodes were 1.1, 1.3 and 1.2, respectively ($p > 0.2$).

The distribution of the infants according to the number of days with diarrhea during the year was similar in the three groups (*Table II*), with the median being 26 days in the AA series, 26 days in the AP series and 22 days in the PP group ($p > 0.2$). The corresponding medians for days with severe diarrhea were relatively low, namely 5, 7 and 5, respectively, since appreciable proportions of infants (40%, 37%, 36%) did not have a severe episode.

ARI: The incidence of at least one episode of ARI was 96.6% (95% CI 94.3% to 98.9%) in the AA group, 95.6% (95% CI 92.9% to 98.3%) in the AP group and 96.1% (95% CI

93.6% to 98.6%) in the PP group ($p > 0.2$). Further, the three groups had similar distributions for the number of ARI episodes in infancy (Table I), and the means were 4.8, 5.1 and 4.8 episodes, respectively ($p > 0.2$). The corresponding mean for severe episodes was 0.1 in each of the three groups, the incidence of AURI was 94.0%, 94.3% and 93.9% and that of ALRI was 19.3%, 14.5% and 16.7% in the AA, AP and PP groups.

The number of days in the year with ARI is given in Table II. Again the distributions are similar, the medians being 32, 34 and 34 days for AA, AP and PP groups ($p > 0.2$). As regards severity, the proportions of infants with at least one day with severe ARI were 11%, 8% and 9% in the three groups.

Findings in 0-6 and 6-12 months

Further analyses were undertaken to examine whether Vit A supplementation

to the mother had any impact on diarrhea or ARI in the infant in the first 6 months. For this purpose, the experience in the AA and AP groups combined was compared with that in the PP group. The incidence of at least one episode was 70.5% and 65.3% for diarrhea, and 86.3% and 86.5% for ARI. The mean number of episodes was 1.4 and 1.3 for diarrhea and 2.8 and 2.6 for ARI, while the median number of days was 8 and 7 for diarrhea and 1.7 and 1.6 for ARI. The differences are small and, moreover, in the wrong direction, demonstrating that the Vitamin A supplementation had yielded no benefit.

The findings in the second 6 months were also examined separately. The incidence of diarrhea (at least one episode) was 94.7%, 93.2% and 92.3% in the AA, AP and PP groups, the mean number of diarrheal episodes was 3.1, 3.2 and 2.9, and

TABLE I—Number of Episodes of Diarrhea and Acute Respiratory Infections in Infancy

| Number of episodes | Diarrhea | | | ARI | | |
|-------------------------|----------|------|------|------|------|------|
| | AA % | AP % | PP % | AA % | AP % | PP % |
| 0 | 2.6 | 3.1 | 5.3 | 3.4 | 4.4 | 3.9 |
| 1 | 6.4 | 7.9 | 8.3 | 9.9 | 9.6 | 9.2 |
| 2 | 12.4 | 12.7 | 12.7 | 12.4 | 12.7 | 14.0 |
| 3 | 18.0 | 13.6 | 18.4 | 15.0 | 10.1 | 9.6 |
| 4 | 19.3 | 17.1 | 16.2 | 12.9 | 12.3 | 13.2 |
| 5 | 13.3 | 14.5 | 13.2 | 12.0 | 8.3 | 13.2 |
| 6 | 7.7 | 7.5 | 6.6 | 8.6 | 11.4 | 9.6 |
| 7 | 8.2 | 9.2 | 9.2 | 6.0 | 6.1 | 7.0 |
| 8 | 6.4 | 5.7 | 3.5 | 7.7 | 8.8 | 9.2 |
| 9 | 2.1 | 3.1 | 2.2 | 4.3 | 7.9 | 5.3 |
| 10 | 1.3 | 2.2 | 1.8 | 1.3 | 2.6 | 1.8 |
| ≥11 | 2.1 | 3.5 | 2.6 | 6.4 | 5.7 | 3.9 |
| Total infants | 233 | 228 | 228 | 233 | 228 | 228 |
| Mean number of episodes | 4.4 | 4.6 | 4.2 | 4.8 | 5.1 | 4.8 |

TABLE II—Number of Days with Diarrhea and Acute Respiratory Infections in Infancy

| Number of infected days | Diarrhea | | | ARI | | |
|-------------------------|----------|------|------|------|------|------|
| | AA % | AP % | PP % | AA % | AP % | PP % |
| 0 | 1.7 | 3.1 | 3.5 | 3.4 | 4.4 | 3.9 |
| 1-7 | 13.3 | 11.0 | 13.2 | 6.9 | 7.0 | 4.4 |
| 8-14 | 17.2 | 11.0 | 19.3 | 9.9 | 10.1 | 10.5 |
| 15-21 | 10.7 | 18.0 | 11.8 | 10.3 | 9.6 | 9.6 |
| 22-28 | 10.7 | 11.8 | 11.8 | 15.0 | 12.3 | 14.5 |
| 29-35 | 10.7 | 11.4 | 11.0 | 9.0 | 9.2 | 11.0 |
| 36-42 | 10.3 | 7.0 | 7.0 | 14.6 | 8.3 | 12.3 |
| 43-49 | 5.6 | 7.0 | 5.3 | 6.9 | 11.0 | 9.6 |
| 50-56 | 3.9 | 5.3 | 2.2 | 3.4 | 7.9 | 6.1 |
| 57-90 | 12.4 | 10.1 | 11.8 | 18.0 | 18.4 | 16.7 |
| >90 | 3.4 | 4.4 | 3.1 | 2.6 | 1.8 | 1.3 |
| Total infants | 233 | 228 | 228 | 233 | 228 | 228 |
| Median days | 26 | 26 | 22 | 32 | 34 | 34 |

the median number of days with diarrhea was 16, 18 and 13, respectively. In the case of ARI, the incidence was 82.0% in the AA group, 75.6% in the AP group and 80.7% in the PP group ($p > 0.2$), the mean number of episodes was 2.2, 2.3 and 2.4 ($p > 0.2$), and the median number of days was 14, 15 and 15, respectively ($p > 0.2$).

Weight Changes

The mean weight gain in the first 6 months was 3.41 kg in the Vitamin A series (AA and AP combined) and 3.44 kg in the placebo series (PP); in the second 6 months, the mean weight gain was 1.0 kg in each of the three series.

Discussion

The randomized trial reported here had some interesting features. The unit of randomization was the individual pair (mother and infant), and not the village or a cluster of households, and this increased substantially the power of the statistical design.

Indeed, with the numbers studied, the experimental design had a *post-facto* power of 90% for detecting a difference of even 10% in the incidence of diarrhea or ARI. The trial was conducted double-blind, and quality control of the morbidity data collected by the field investigators was undertaken throughout. As long recall periods pose problems, the collection of morbidity data was intensified from once a fortnight to once a week when the study had been in progress for 9 months. A Medical Officer was permanently stationed in the study area, and reassessed all severe cases reported by field investigators. Finally, detailed analyses were undertaken over different time periods, in terms of the incidence, the number of episodes and the number of days with morbidity. In the circumstances, the consistently similar findings in the three groups indicate that Vitamin A supplementation was not effective in reducing morbidity. The lack of effect was not due to the absence of Vitamin A

deficiency in the study area, for an unpublished study of ours, based on 1,620 children aged 5-10 years from a random sample of six Municipal schools in this area, showed the prevalence of Bitot spots to be 2.1%, and that of conjunctival xerosis to be 1.0%.

Two other double-blind randomized controlled studies undertaken in South India also found no evidence of lowered morbidity in children receiving Vitamin A supplementation(5,6). It has been pointed out, however, that the dosage employed in the former study(5) was probably too low, considering the fact that 72% of the children were undernourished and 11% had clinical Vitamin A deficiency(13). The latter study(6) had a substantially higher proportion of losses from follow-up in the control group, indicating that the results may have been biased towards the null hypothesis(14). In contrast, the dosage employed in our study was high, and the coverages were similar in the test and control groups. In a double-blind randomized placebo controlled trial in Ghana(15) that was published after the commencement of our study, no differences were detected between the Vitamin A and placebo groups in the incidence of diarrhea and ARI. It would be pertinent to note that all these studies were conducted on preschool children.

Our study was not designed to assess the impact of Vitamin A supplementation on mortality, and the small numbers of deaths reported did not suggest any differences between the groups. Another study in South India also reported no impact(6). A study in Delhi reported no impact on ALRI or ALRI related mortality, though there was an indication of a possible reduction in the severity of diarrhea(16). However, several other studies(7,15,17-19) including a meta analysis(19), have reported substantial

reduction in mortality from Vitamin A supplementation.

It is concluded that in the area under study, mega doses of Vitamin A to the mother soon after delivery and to the child at six months do not result in a reduction of incidence of diarrhea or ARI in infancy.

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REFERENCES

1. 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.
2. Milton RC, Reddy V, Naidu AN. Mild Vitamin A deficiency and childhood morbidity-An Indian experience. *Am J Clin Nutr* 1987, 46: 827-829.
3. Bloem MW, Wedel M, Egger RJ, *et al.* Mild Vitamin A deficiency and risk of respiratory tract disease and diarrhea in pre-school and school children in Northern Thailand. *Am J Epidemiol* 1990, 131: 332-339.
4. Pinnock C, Douglas RM, Martin AJ, Badcock NR. Vitamin A status in children who are prone to respiratory tract infections. *Aust Pediatr J* 1986, 22: 95-99.
5. Rahmathullah L, Underwood BA, Thulasiraj RD, Milton RC. Diarrhea, respiratory infections, and growth are not affected by a weekly low-dose Vitamin A supplement: A masked, controlled field trial in children in Southern India. *Am J Clin Nutr* 1991, 54: 568-577.
6. Vijayaraghavan K, Radhaiah G, Prakasam BS, Sharma KVR, Reddy V. Effect of massive dose Vitamin A on morbidity and mortality in Indian Children. *Lancet* 1990, 336:1342-1345.

7. Rahmathullah L, Underwood BA, Thulasiraj RD, *et al.* Reducing mortality among children in Southern India receiving a small weekly dose of vitamin A. *N Engl J Med* 1990, 323: 929-935.
8. World Health Organization. Nutrition in Preventive Medicine. WHO Monograph Series No. 62. Geneva, WHO, 1976, p 109.
9. Oomen HAPC. Disturbances of Nutrition: Xerophthalmia *In: Diseases of Children in the Sub tropics*, 3rd edn. Jelffe DB, Stanfield J. London, ELBS and Edward Arnold, 1978, pp 221-227.
10. National Institute of Cholera and Enteric Disease, Calcutta. Annual Report, 1988, pp 1-4.
11. Morris SS, Cousens SN, Lanata CF, Kirkwood BR. Diarrhea: Defining the episode. *Int J Epidemiol* 1994, 23: 617-623.
12. Narain JP, Banerjee KB. Acute Respiratory Infection in India: Public Health Significance and Epidemiology. New Delhi, Directorate General of Health Services, 1988, pp 3-8.
13. Thurnham DL. Comments. *Trop Dis Bull* 1992, 89: 518-519.
14. Loevinsohn BP, Solter SL. Vitamin A supplementation: Correspondence. *Lancet* 1991, 338: 701.
15. Ghana VAST study team. Vitamin A supplementation in Northern Ghana effects on clinic attendances, hospital admissions and child mortality. *Lancet* 1993, 42: 7-12.
16. Bhandari N, Bhan MK, Sazawal S. Impact of massive dose of Vitamin A given to preschool children with acute diarrhea on subsequent respiratory and diarrheal morbidity. *BMJ* 1994, 309:1404-1407.
17. Sommer A, Tarworjo I, Djunaedi E, *et al.* Impact of Vitamin A supplementation on childhood mortality: a randomized controlled community trial. *Lancet* 1986, 1: 1169-1173.
18. West KP Jr, Pokhrel RP, Katz J, *et al.* Efficacy of Vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991, 338: 67-71.
19. Glasziou PP, Mackerras DEM. Vitamin A supplementation in infectious diseases: A meta-analysis. *BMJ* 1993, 306: 366-370.

NOTES AND NEWS

HUMAN LACTATION MANAGEMENT TRAINING

A three day course is being planned for Rajasthan in the first week of May 1996 at Mount Abu. Forty candidates shall be taken for the training on first come first served basis. Interested pediatricians and practitioners may write (latest by 30th April) to Dr. C.B. Dass Gupta, Senior Pediatrician, State Coordinator BPNI, 1, Gulab Bari, Arya Samaj Road, Kota-6 (Rajasthan).