NEONATAL VITAMIN A SUPPLEMENTATION

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Vitamin A deficiency is a major public health problem throughout the developing world, affecting an estimated 124 million young children and accounting for more than 1 million child deaths each year.[1] A meta-analysis of eight controlled trials estimated that community-based vitamin A supplementation resulted in a 23% average reduction in child mortality rates.[2] Large-dose periodic supplementation of preschool children is an integral component of child survival programmes in many countries, and is well tolerated.[3] Supplementation of neonates with 50 000 international units (IU) vitamin A[4] has been recommended. The aim of this study conducted in Indonesia was to determine the risks and benefits of neonatal vitamin A supplementation. This work has been published elsewhere in three papers.[5-7]

ACUTE TOLERANCE STUDY

Methods

The study was carried out at Hasan Sadikin Hospital, a large public referral hospital in Bandung, Indonesia serving the urban and surrounding rural area. All infants born at Hasan Sadikin from 18 June 1992 to 2 June 1993 were considered for inclusion in the study. Infants unlikely to survive without aggressive medical treatment were excluded (i.e. birth weight < 1 500 g, severe respiratory distress, or major congenital anomalies). Of the 2 844 eligible live births, written informed parental consent was given within a 24-hour inclusionary period for the 2 067 infants who were enrolled. Baseline evaluations were carried out by a team of 12 nurse midwives and 4 paediatricians and included a morbidity history from birth (vomiting, diarrhoea, irritability), measurement of temperature and head circumference, and palpation of the anterior fontanelle. The first 973 infants also underwent a duplex Doppler examination of the anterior cerebral artery to determine the resistive index (RI). The RI is a reliable relative indicator of intracranial pressure.[8-11]

Following the baseline examination, infants were allocated to receive either one oral dose of 50 000 IU vitamin A (as retinyl palmitate) or placebo by simple randomisation. The supplements were dispensed directly into the infants' mouths. Mean age at dosing was 16.2 (SD 8.2) hours. Morbidity histories were repeated by the nurses at the end of each nursing shift, and at 12, 24 and 48 hours post-dosing by the caregiver of the infant for the respective period. Temperature was measured again at 12, 24 and 48 hours post-dosing. Palpation of the anterior fontanelle and measurement of head circumference were repeated at 24 and 48 hours post-dosing by the paediatrician. The RI was assessed again at 24 hours (our protocol stipulated that the RI be repeated again at 48 hours if the 24-hour examination was abnormal, but no infant required this 48-hour examination).

Findings

Treatment groups were comparable for all baseline characteristics including birth weight, birth length, gestational age and appropriateness of weight for gestational age, Apgar scores, maternal age, and maternal parity. In both groups 98% of the infants were breast-fed during the 48-hour period of observation. There were no differences between treatment groups in terms of rates of vomiting, excessive stooling, or fever over the 48-hour period. Mean head circumference in the two groups was virtually identical at each examination. The mean RI at baseline was 70.6% and 70.4% in the control and vitamin A groups, respectively. Reported RI values for healthy term infants are ~70% (range 60 - 80%)[8,12] and decline as infants age. At 24 hours the mean RI value had fallen to 68.4% and 68.3% in the control and vitamin A groups, respectively. We compared the RI values of infants who did and did not develop a bulging fontanelle to assess the relationship between the clinical findings of the fontanelle and intracranial pressure among infants for whom RI data were obtained. The mean change in RI was negative even among infants who developed a bulging fontanelle over the same 24-hour period. At 24 and 48 hours post-dosing there were excess rates of 1.8% and 2.1% for bulging fontanelle in the vitamin A group compared with the placebo (28/1 033 v. 46/1 034 at 24 hours, 25/1 027 v. 46/1 030 at 48 hours). Bulging of the fontanelle was an isolated sign: the presence of a bulging fontanelle was not associated with higher rates of any sign or symptom assessed at any time during the 48-hour follow-up period.

Conclusions

Acute side-effects of a single oral 50 000 IU dose of vitamin A given to neonates were limited to a 2% excess rate for isolated bulging of the anterior fontanelle. The absence of concomitant signs and symptoms and the expected mean decrease in RI among both groups — even those who developed a bulging fontanelle over the same 24-hour period — suggest that while intracranial volume may have increased due to the vitamin A, the compliance of the cranium was sufficient to prevent an increase in intracranial pressure. Furthermore, even the increase in intracranial volume was rare, occurring in only ~2.5% of placebo-treated infants and 4.5% of vitamin A-treated infants at both 24 and 48 hours post-dosing.

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ONE-YEAR FOLLOW-UP STUDY

Methods

Infants were assigned to one of two follow-up studies. The first 1 597 infants enrolled in the trial were followed up once at their first birthday (study I). The remaining 470 infants were followed up at 4, 6 and 12 months of age (study II). The majority of these visits (91%) were conducted in the infants' homes by study nurses; the remaining visits were conducted in the hospital clinic. In both studies, vital status was recorded after the study nurse either saw an infant alive or confirmed his/her death with a family member. If an infant was not at home, but a family member could confirm that he/she was alive, vital status was classified as alive. A 1-week morbidity history was elicited from mothers of study II babies; respondents were also asked whether the infant had been taken for medical treatment of an illness since the previous visit, and if so to specify all signs and symptoms that had caused them to seek medical care.

Findings

Of the 2 067 infants, vital status could be confirmed for 1 839 children (89%) at 1 year of age. Follow-up was similar in the two treatment groups (89.5% and 88.5% in the vitamin A and control groups, respectively). There were 26 deaths: 7 in the vitamin A group and 19 in the control group, leading to mortality rates of 7.2 deaths per 1 000 child-years in the vitamin A group and 19.8 deaths per 1 000 child-years in the control group. Vitamin A supplementation was, therefore, associated with a 64% reduction in infant mortality (relative risk = 0.36; 95% confidence interval (CI) 0.16, 0.87). Vitamin A supplementation had its greatest impact on deaths occurring between 1 and 4 months of age (2 vitamin A infants v. 14 control infants); vitamin A had no impact on deaths occurring in the first month of age (5 vitamin A infants v. 4 control infants). Only one infant (in the control group) died after 4 months of age. One-week period prevalences of common morbidities among infants in study II were not significantly different between treatment groups at 4, 6 or 12 months. However, between birth and 4 months of age 50 control infants (24.6%) and 29 vitamin A infants (14.2%) were brought for medical treatment of cough ($P = 0.008$), and 42 control infants (20.7%) and 28 vitamin A-treated infants (13.7%) were brought for medical treatment of fever ($P = 0.063$). There were no differences between treatment groups in terms of the proportion of infants seeking treatment for diarrhoea, difficulty in breathing, ear infection, or flu. Between 4 and 6 months and between 6 and 12 months of age there were no differences between groups in medical care-seeking behaviour for any diagnosis.

At recruitment, blood was collected from mothers and archived. Serum retinol was measured in a random subsample of 150 mothers enrolled in the trial during a 4-month period, using the method of Bieri.[13] Mean serum retinol concentrations were similar among mothers in the control and vitamin A group (1.75 (0.56) μmol/l ($N = 73$) v. 1.79 (0.53) μmol/l ($N = 77$)), respectively. The distribution of serum retinol concentrations of these mothers coincided with that of the reference population of Caucasian women of reproductive age in the USA.[14] As such there was no evidence that these mothers were vitamin A deficient.

Conclusions

In this study, a single oral dose of vitamin A administered to infants on the first day of life reduced early infant mortality by 64%. Though the intervention had no effect on the prevalence of common illnesses reported in a 1-week history, it did reduce sick clinic visits associated with cough and fever, a symptom and sign of pneumonia and the leading cause of death among young infants[15-17] during the same 4-month period when mortality was reduced. These findings support the findings of others that vitamin A supplementation reduces the frequency of severe illnesses (those that are fatal or severe enough to lead families to seek medical care), but has less impact on the prevalence of mild more common disease.[2,18] These findings have important public health significance because the impact was observed during early infancy, when mortality is highest yet cornerstone child survival interventions such as oral rehydration therapy for diarrhoea and immunisations have little effect.

Two observations about this population make these findings surprising. Firstly, this was a breast-fed population, with more than 90% of infants in both groups still being breast-fed at 1 year of age; only 1 - 2% of infants had been breast-fed less than 1 month or not at all. Secondly, their mothers were not vitamin A deficient. It has been commonly believed that breast-fed infants of vitamin A-replete mothers are not at risk of deficiency. We speculate that early introduction of non-breast-milk foods, which is customary in Indonesia and common in many countries, may play a role. In our population, 82% of the infants were already being fed complementary foods by 4 months of age. Early introduction of non-breast-milk foods may reduce the volume of breast-milk consumed (reducing vitamin A intake) and increase gastro-intestinal infections, which may in turn increase vitamin A requirements.

This is the only study to date to demonstrate a reduced infant mortality rate after neonatal vitamin A supplementation. In a previous trial among infants less than 6 months of age carried out in rural Nepal, infants were given 50 000 IU or placebo during the first month of life. The relative risk of death for the vitamin A group compared with the placebo group was 1.07 (95% CI 0.66, 1.72), showing no effect.[19] The primary difference between our study and the Nepal study was the age at dosing. We dosed infants on the first day of life, while the Nepalese infants were not dosed until 2 - 3 weeks of age, after significant exposure to dietary and environmental risk factors

for mortality. To our knowledge no other mortality studies have dosed infants in the immediate postpartum period. However at least three such trials are currently underway in other settings, attempting to elucidate the conditions under which neonatal vitamin A supplementation may save infant lives.

LONG-TERM GROWTH AND DEVELOPMENT STUDY

Methods

Following the completion of the acute side-effect and mortality studies, lingering concerns remained about the long-term safety of neonatal vitamin A supplementation, especially when accompanied by a bulging fontanelle. Given the promise that neonatal vitamin A might hold for infant survival, we conducted a final study to search for developmental changes at 3 years of age that might be associated with neonatal vitamin A supplementation or bulging fontanelles.

The following children were included: those who had a bulging fontanelle (BF) at either 24 or 48 hours after treatment with either vitamin A (VA) or placebo (PL), and children in both treatment groups whose fontanelles were normal. Of the 2 067 infants enrolled in the original trial, 122 (45 PL and 77 VA) developed a bulging fontanelle at 24 and/or 48 hours post-treatment. Of these, 14 were lost to follow-up and 1 died by 1 year of age. The remaining 107 children who had bulging fontanelles were selected for the growth and development study. For each of the 107 BF children, 4 NF children were selected, 2 from each treatment group, matched to the BF children by age, sex, birth weight and paternal years of education. Children were tested by the Bayley's Scales of Infant Development[20] within 2 weeks of their third birthday. This test consists of a mental scale (MDI), a psychomotor scale (PDI) and a behavioral rating scale (BRS). Two Indonesian psychologists who were extensively trained and standardised, administered all the tests. The psychologists, nurses and all other study personnel in Indonesia remained masked to the treatment group and fontanelle status of the children until the study was completed. After developmental testing a study nurse measured the weight and height of the children.

Findings

Mean developmental scores for the MDI, PDI and BRS were not significantly different for treatment-fontanelle-specific groups. In regression models predicting each score, a bulging fontanelle had a small negative effect in all models; when one child who was injured from birth was removed from the analysis the effect of a bulging fontanelle was not significant in any model ($P \geq 0.35$). Vitamin A had a small beneficial effect on all developmental scores which was significant for one of the BRS subscales and also for a second subscale when the outlier child was removed from analyses. Compared with PL-NF children, we observed a small (not significant) 0.56 cm deficit in linear growth in VA-BF children, and a small but significant 0.68 cm increment in length in VA-NF children. The magnitude of both the length deficit in VA-BF children and the length increment in VA-NF children was small and neither is likely to be of biological significance since they represent z-scores of only - 0.13 and 0.18 for height for age of 3-year-old boys.

Conclusions

This 3-year follow-up study provided no evidence that neonatal vitamin A supplementation is associated with biologically significant adverse growth or developmental sequelae.

FINAL CONCLUSIONS

In this population, a single 50 000 IU oral dose of vitamin A administered to infants on the first day of life reduced early infant mortality by >60% and health care visits for signs and symptoms of pneumonia by >50%. Acute side-effects were limited to isolated bulging of the anterior fontanelle in <5% of the infants; these were not associated with a measurable increase in intracranial pressure or with long-term adverse developmental or growth sequelae.

Current studies are underway to confirm or refute our findings of a substantial impact of neonatal vitamin A supplementation on infant mortality. If our findings are confirmed, neonatal vitamin A supplementation may be one of the most cost-effective and feasible interventions available to reduce infant mortality, especially in the first 6 months of life.

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