Newborn Vitamin A Dosing Reduces the Case Fatality but Not Incidence of Common Childhood Morbidities in South India


Abstract

Vitamin A supplementation reduces mortality in young children in areas of endemic vitamin A deficiency. However, it has no impact on the incidence of common morbidities. This discrepancy has been explained by an impact on case fatality, although with the exception of hospitalized measles cases, there is little direct evidence to support this hypothesis. We assessed the impact of newborn dosing with vitamin A on the incidence and case fatality of common childhood morbidities in early infancy in a community-based, randomized trial in South India. Morbidity for each day in the previous 2 wk was assessed for the first 6 mo of life. A total of 11,619 live-born infants were enrolled and randomized to receive either 48,000 IU (50.4 μmol retinol) of oral vitamin A or placebo following delivery. There was no difference between treatment groups in the incidence of acute or chronic diarrhea, dysentery, or fever but a small increased incidence of acute respiratory illness (ARI). Case fatality for diarrhea and fever were significantly reduced in the vitamin A group compared with placebo (relative case fatality [95% CI] of 0.50 [0.27, 0.90] and 0.60 [0.40, 0.88], respectively). There was a trend in reduction of case fatality for various definitions of ARI, but the evidence for this effect was modest. Survival analysis among those with morbid episodes confirmed the case fatality analysis. This trial demonstrated that the reduction in overall mortality due to newborn vitamin A dosing was driven primarily by a reduction in case fatality among infants. J. Nutr. 137: 2470–2474, 2007.

Introduction

It is well accepted that both clinical and subclinical vitamin A deficiency is associated with increased mortality in preschool-aged children (1,2) and that universal supplementation of populations with endemic vitamin A deficiency can significantly reduce total mortality between 19 and 54% in children 6 mo–5 y old (3–8). More recently, it has been demonstrated that vitamin A supplementation in the first few days of life can reduce early infant mortality (0–6 mo) between 16 and 64% in South and Southeast Asia (9–11), although this effect is not observed if supplementation is delayed until after the first month of life during infancy or if provided during pregnancy (12–14).

A variety of studies, including those trials that have shown an effect on mortality, have demonstrated that vitamin A supplementation to young children has little, if any, impact on the incidence of illnesses such as diarrhea, measles, and acute respiratory infections, which are the most common killers of young children in developing countries (15–20). As a result, it has been assumed that the mechanism of action of vitamin A on mortality is mediated through a reduction in case fatality. The direct evidence for this effect on case fatality is limited except for measles, where case fatality in hospitalized measles is reduced by ~50% with vitamin A supplementation (19–21). To directly address this question for other common childhood illnesses, we collected daily morbidity information during a community-based trial of vitamin A supplementation of newborn infants in South India.

Methods

The detailed methods of the Vitamin A Supplementation in Newborns Study have been reported previously (10), a summary of which is provided here. The Vitamin A Supplementation in Newborns Study was a randomized, placebo-controlled, community-based clinical trial conducted between June 1998 and March 2001 in 2 rural blocks of south...
India. All infants born in participating villages were eligible for participation if they were alive at the time study staff conducted their first visit. Pregnant women were identified from a variety of sources in study villages and recruited for participation by local project staff. Verbal informed consent was obtained at the time of recruitment. At the recruitment visit, baseline information regarding family and household demographic and socioeconomic characteristics were collected by interview. Study staff also asked the women where they planned to deliver the child. Eligibility was determined by where the woman actually delivered her child. Women were excluded if the delivery occurred >20 km outside the study area.

Individual level randomization was conducted at the time pregnant women were enrolled, stratified by geographic area and in blocks of 4 to ensure equal numbers in each treatment group. This was done because births would occur in a wide variety of locations (homes, health centers, maternity homes, and hospitals) and at all times of the day or night. Therefore, cases of fetal loss, delivery >20 km outside the study area, or infant death prior to the time our study team could arrive at the site of the delivery were additional exclusions from participation that occurred after randomization.

Newborn infants were randomly assigned to receive either 24,000 IU (25.2 μmol retinol) of vitamin A twice within a 24-h interval (total of 48,000 IU or 50.4 μmol retinol) beginning within 48 h after birth or placebo. The treatment doses were in an edible oil solution packaged in gelatin capsules. Mothers were told to breast-feed the child immediately following the dose to ensure the entire contents were swallowed. Investigators, study staff, and subjects were fully masked to the treatment assignment.

When a birth occurred, local study staff notified their supervisor that a delivery had occurred. The supervisor traveled to the site of the delivery to provide the assigned treatment, weigh the infant, and collect information regarding the delivery. Field supervisors had a target of beginning dosing within the first 48 h of life. If logistical problems interfered with this schedule, they dose the child as soon as possible. Newborn weight was measured using a Seca Model 727 electronic infant weighing scale.

Project staff visited the household every 2 wk to interview the family regarding the vital status and morbidity history of the child over the previous 2 wk. Mothers were asked about the presence of specific signs and symptoms for each day of the preceding 2-wk period. The morbidities assessed included cough, fever, difficulty breathing, diarrhea, and dysentery. Field staff also recorded immunizations received and visits for health care for the child in the prior 2 wk.

Infants were followed until 6 mo of age at which time they received anthropometric measurements and a 100,000- IU dose of vitamin A (105 μmol retinol) and were discharged from the study. Subjects younger than 6 mo who were being followed at the end of the study in March, 2001 were considered censored alive. The anthropometric assessment at the 6-mo visit included measurements of weight, length, and mid-upper arm circumference (MUAC). Weight was measured using the same Seca scale as was used for birth weight. Length was measured to the nearest 0.1 cm using a Schorr wooden length board according to a standardized protocol. Length was measured 3 times and the median value recorded. MUAC was measured on the left arm using special arm circumference tapes according to a standardized protocol. MUAC was measured 3 times and the median value was recorded.

The primary outcome of interest for this study was 6-mo infant mortality. Infant deaths and infant morbidity were ascertained during the vital status and morbidity assessments were conducted every 2 wk at the home. A verbal autopsy instrument collected cause of death information for all infants who died during the preceding 2 wk. Causes of death were determined by the independent review of the verbal autopsy information by 2 pediatricians and a 3rd independent review if there was disagreement between the first 2 reviews.

The incidence, duration, and case fatality for diarrhea, chronic diarrhea, dysentery, and acute respiratory illness (ARI) are the subject of this report. These morbidities were based on parental report and defined as follows: diarrhea, 4 or more loose, watery stools on any day; chronic diarrhea, diarrhea with a duration of >14 d; dysentery, blood or mucus in the stool on any day; fever, parental report of fever or feeling hot to the touch; ARI-1, an episode of cough with fever on at least 1 d of the episode; ARI-2, an episode of difficulty breathing with fever on at least 1 d of the episode; ARI-3, an episode of cough and difficulty breathing with fever on at least 1 d of the episode. All episodes were separated by 3 or more symptom-free days.

All analysis was performed using SAS. Treatment groups were compared on baseline household, maternal, and infant characteristics to determine the success of the randomization. Incidence of morbidity was estimated using an incidence density approach with person-time as the denominator. All incidence rates were annualized for ease of interpretation. Case fatality was estimated for varying periods following each episode of morbidity. The periods were longitudinally cumulative and began with and included the period within the episode and extended through time intervals of 7, 14, 21, 30, and 60 d following each episode. The ratio of case fatalities between the treatment groups was used as the measure of treatment effect. We also examined the impact of treatment on survival among infants with morbid episodes using Cox proportional hazards models with robust variance estimation to account for multiple episodes for a child (22). All analyses were conducted using an intent-to-treat approach in infants who were enrolled and eligible to receive their assigned treatments. This did not include those who were excluded due to migration, death, or refusal prior to the time the study team first visited the infant after delivery.

This study received approval from the ethical committee of the Aravind Eye and Children’s Hospitals, Madurai, Tamil Nadu, the Department of Health, Tamil Nadu State Government and by the Committee on Human Research of the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland. An independent Data and Safety Monitoring Board reviewed the data for safety and efficacy.

Results

During the recruitment period, 14,035 pregnant women initially agreed to participate, 862 of which did not result in a delivery within the study area (10). A total of 13,294 infants were delivered, 358 of whom were stillborn. Twenty-three infants’ parents refused to participate after delivery, 1027 infants migrated out of the study area, and 267 died prior to our teams arriving at the household following the delivery (10). This left 11,619 live-born infants to be enrolled and followed, 5833 (50.2%) in the placebo group and 5786 (49.8%) in the vitamin A group (Fig. 1).

Previous results demonstrated that baseline characteristics did not differ between the vitamin A and placebo groups (10). In both groups, 80% of infants were first dosed with their assigned treatment within 48 h of birth with a median time to dosing of 25.5 h in the placebo group and 26.4 h in the vitamin A group.
Side effects, defined as morbidity of the infant associated close in time to the receipt of the study treatment, were uncommon, with 6 cases occurring in the placebo group and 3 cases in the vitamin A group.

The treatment groups did not differ in the incidence of diarrhea, dysentery, or fever. There were slightly higher rates in the vitamin A group for ARI using any definition and the CI just barely excluded 1.00 (Table 1). The mean or median duration of morbid episodes (data not shown) did not differ by treatment group. The analysis of case fatality among infants who had selected morbidities demonstrated reduced case fatality for children with episodes of diarrhea with relative case fatality ranging from 0.54 during the episode to 0.50 within 60 d of the onset of the episode (Table 2). There was no effect on case fatality for dysentery and there were too few cases of chronic diarrhea to make meaningful comparisons. The case fatality ratio for fever showed an increased benefit of vitamin A supplementation as time since initiation of the episode increased. The case fatality ratio went from 1.20 during the episode to 0.60 within 60 d of onset (Table 2). For none of the definitions of ARI was there a ratio went from 1.20 during the episode to 0.60 within 60 d of time since initiation of the episode (Table 2). The analysis of case fatality among infants who had selected morbid episodes (data not shown) did not differ by treatment group. The analysis of case fatality among infants who had selected morbid episodes (data not shown) did not differ by treatment group.

**TABLE 1** Incidence of common morbidities in children 0–6 mo of age in Vitamin A and placebo groups

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Placebo</th>
<th>Vitamin A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Episodes</td>
<td>Rate</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>n/child⁻¹y⁻¹</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2405</td>
<td>0.89</td>
</tr>
<tr>
<td>Dysentery</td>
<td>700</td>
<td>0.26</td>
</tr>
<tr>
<td>Fever</td>
<td>11,498</td>
<td>4.36</td>
</tr>
<tr>
<td>ARI-1</td>
<td>4942</td>
<td>1.90</td>
</tr>
<tr>
<td>ARI-2</td>
<td>993</td>
<td>0.35</td>
</tr>
<tr>
<td>ARI-3</td>
<td>712</td>
<td>0.26</td>
</tr>
</tbody>
</table>

1 Cough and fever.
2 Difficulty breathing and fever.
3 Cough, difficulty breathing, and fever.

Discussion

The lack of effect of vitamin A supplementation on the incidence and duration of diarrhea and dysentery in this trial is consistent with evidence from almost all previous supplementation trials in older children (15–18). Similarly, the slightly increased incidence of respiratory morbidity in the vitamin A group has been shown previously (17). The difference in impact on the incidence of morbidity and the well-established salubrious effect of vitamin A supplementation on child mortality has led to the tenet that the impact of vitamin A supplementation on mortality is mediated through an effect on case fatality. However, evidence supporting this hypothesis has been available only from severe cases of measles where vitamin A supplementation during the acute phase of measles illness can reduce case fatality by approximately one-half (19–21). Measles-related mortality comprises a relatively small proportion of the total <5-y mortality and is decreasing over time as immunization programs continue to improve measles vaccine coverage. Prior population-based studies of mortality outcomes were unable to collect incident morbidity information on the entire study population and were, therefore, unable to directly address this hypothesis. Our study was able to directly estimate case fatality, because morbidity data were collected continuously on all infants enrolled in the trial. The beneficial effect on case fatality for diarrhea and fever, the trend of benefit for ARI case fatality, suggests that the physiologic mechanism involved may not be as strongly related to the development and maintenance of epithelial integrity as originally hypothesized. This effect may be dominated by vitamin A’s role in local and systemic immunocompetence, but further study is required to understand the balance of physiologic mechanisms through...
which vitamin A supplementation exerts its beneficial effects on case fatality (23).

This trial has demonstrated that community-based distribution of vitamin A within the first few days after birth has no effect on the incidence of gastroenteritis and results in a slightly increased risk of mild to moderate respiratory illness in young children during the first half of infancy but can substantially reduce case fatality for diarrhea, fever, and acute respiratory infections. Whether the impact on case fatality observed in this trial of newborn vitamin A supplementation is reflective of similar mechanisms of action for supplementation in children over 6 mo of age is unknown, but the distribution of causes of death in this older age range suggests a common pathophysiologic mechanism. Yet to be explained is the apparent lack of effect of vitamin A supplementation on child mortality when the supplements are administered during the mo 2 through 4 of life.

**Literature Cited**


