Breast-Feeding Status Alters the Effect of Vitamin A Treatment During Acute Diarrhea in Children[1,2]

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ABSTRACT Vitamin A administration in children reduces the incidence of severe diarrhea during the subsequent few months. We therefore examined the effect of treatment with vitamin A during acute diarrhea on the episode duration and severity. In a double-blind controlled field trial, 900 children 1 to 5 y of age with acute diarrhea of ≤7 d duration were randomly assigned to receive vitamin A (60 mg) or a placebo. Children were followed up at home every alternate day until they recovered from the diarrheal episode. In all study children, those treated with vitamin A had a significantly lower risk of persistent diarrhea [odds ratio (OR) 0.30, 95% confidence interval (CI) 0.07–0.97], but there was no effect on the mean diarrheal duration or the mean stool frequency. In the subgroup of children who were not breast-fed, the mean diarrheal duration [ratio of geometric means (GM) 0.84, 95% CI 0.72–0.97], mean number of stools passed after the intervention (ratio of GM 0.73, 95% CI 0.56–0.95), the proportion of episodes lasting ≥14 d ($P = 0.002$) and the percentage of children who passed watery stools on any study day (OR 0.40, 95% CI 0.21–0.77) were significantly lower in those treated with vitamin A. We conclude that administration of vitamin A during acute diarrhea may reduce the severity of the episode and the risk of persistent diarrhea in non-breast-fed children. Similar benefit was not seen in breast-fed children. J. Nutr. 127: 59–63, 1997.

KEY WORDS: *vitamin A* • *acute diarrhea* • *severity* • *breast-feeding* • *children*

The current management of acute diarrhea is based on oral rehydration salts (ORS) solution for prevention and treatment of dehydration, continued feeding, and antibiotics only for the treatment of cholera and dysentery. Standard ORS solution does not reduce the average duration or severity of acute watery diarrhea or the risk of episode persistence.

Nearly 20% of diarrheal episodes last longer than 1 wk (Sazawal et al. 1995) and 10% longer than 2 wk (Bhan et al. 1989). When children revisit physicians because diarrhea has not ceased within 5–7 d, the latter often prescribe ineffective and potentially harmful anti-diarrheal drugs. In addition, mothers, often on the advice of physicians, change the frequency, amount and consistency of foods offered to the child, which severely curtails dietary intake. The subsequent lack of nutrients may convert marginal into severe malnutrition, delay intestinal epithelial recovery and further increase the duration and severity of diarrhea and malabsorption. The subset of persistent diarrhea episodes, although smaller in number than acute diarrhea, accounts for 23 to 62% of diarrhea-associated deaths in developing countries (Black 1993). Treatment approaches to decrease the average duration and stool output in acute diarrhea and to reduce the risk of episode persistence are therefore needed.

Further, vitamin A deficiency has been found to be associated with increased diarrheal morbidity (Shahid et al. 1988). A significant reduction in the incidence of severe diarrhea was reported in children given 60 mg of vitamin A at 4-mo intervals (Barreto et al. 1994). Vitamin A is absorbed in sufficient amounts during acute diarrhea (Reddy et al. 1986). It is therefore of interest to determine whether these effects of vitamin A treatment appear early enough following administration to be of significant benefit in the treatment of acute diarrhea.

We hypothesized that treatment with 60 mg of vitamin A during acute diarrhea reduces the average duration and severity of the treated episode and the risk of its persistence. This issue was examined in a randomized placebo-controlled field trial.

MATERIALS AND METHODS

The study was conducted in the urban slum of Govindpuri in New Delhi, which has about 30,000 inhabitants. Vitamin A prophylaxis had not been routinely given in this area during the preceding 3 y.

Children attending the solitary government health facility in the area with diarrheal duration of ≤7 d were considered for inclusion in the study if they were between 12 and 60 mo of age and their weight-for-height was ≥70% of the NCHS median for age. Diarrhea was defined as the passage of three or more loose or watery stools in the 24-h period preceding enrollment.

Of the 1258 children fulfilling these inclusion criteria, 900 were enrolled. The reasons for exclusion of 358 children were as follows:

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TABLE 1

Baseline characteristics of enrolled children treated with vitamin A or placebo[1]

Characteristic	Vitamin A (n = 451)	Placebo (n = 444)
Age, mo	26.7 ± 12.6	26.0 ± 12.6
Male	231 (51.2)	234 (52.7)
Weight-for-height ≤80% of NCHS Median	60 (13.3)	57 (12.9)
Breast-fed	207 (45.9)	221 (49.8)
Family per capita income, *rupees/y*	2259 ± 2444	2135 ± 1044
Literate mothers	85 (18.8)	84 (19.1)
Pre-enrollment episode characteristics		
Diarrheal duration		
≤3 d	301 (66.7)	288 (65.8)
Mean ± SD	3.12 ± 1.72	3.12 ± 1.74
Stool frequency in the previous 24 h	7.68 ± 3.3	7.64 ± 3.3
Watery stools during the episode	242 (53.7)	239 (53.8)
Visible blood in stools during the episode	49 (10.9)	61 (13.7)
Vomiting in the previous 24 h	77 (17.1)	82 (18.4)
Fever during the episode	154 (34.1)	164 (36.9)

[1] Values are n (%) or means ± SD. Differences between groups were not significant.

the presence of signs and symptoms of vitamin A deficiency (30; 8.4%), receipt of a large dose of vitamin A in the previous 6 mo (29; 8.1%), the likelihood that the subject would permanently leave the area (157; 43.9%), presence of associated systemic illness (82; 22.9%), prior enrollment into the study (28; 7.8%), weight-for-height <70% of the NCHS median (4; 1.1%), and non-consent (28; 7.8%). Of the 30 excluded children with clinical vitamin A deficiency, 14 had Bitot's spots and the remaining had night blindness alone. Among the 1258 screened subjects, the prevalence of clinical vitamin A deficiency was 1.0% in those aged 23 mo or less, 5.3% in those 24–36 mo of age and 3.2% in children older than 36 mo.

After informed consent was obtained, the child was examined by a physician. Details were sought on the socio-economic status of the family, features of the current illness and feeding practices.

The study was approved by the institutional and World Health Organization (WHO) ethics committees.

Randomization. The enrolled children were randomized to receive 60 mg of vitamin A or a placebo. The randomization code was drawn up by the WHO using a simple randomization scheme. The vitamin A and placebo capsules supplied by the WHO were labeled serially; each child was administered the contents of the capsule next in serial number, by a physician at enrollment. A replacement capsule was available for each child, to be given in the event that the contents of the main capsule were vomited within 30 min of administration.

Sample size estimates. The study was designed to detect a 20% difference in the post-intervention diarrheal duration between the treatment groups. The mean [3.6 d (SD 3.2)] diarrheal duration used for these calculations was based on an earlier investigation in similar patients (M. K. Bhan, unpublished data). We estimated that 438 children per group would be required to detect this difference with 90% power and 95% confidence.

Household surveillance. Each child was visited at home by a field worker every alternate day until the end of 72 consecutive hours during which the child passed two or fewer diarrheal (loose or watery) stools in each 24-h period. The first of these three consecutive days without diarrhea was defined as the day of recovery.

At each visit mothers were asked about the frequency and characteristics of stools, fever, vomiting, cough and other related symptoms, and visits to health care providers. Weights to the nearest 100 g and heights (lengths) to the nearest 0.1 cm were measured at enrollment and recovery.

Serum vitamin A was estimated in 40 randomly selected children in each group at baseline and 1 mo later. This sample was sufficient to allow detection of a 20% difference in post-intervention mean serum retinol concentrations between the two treatment groups with 80% power and 95% confidence. Vitamin A concentrations were determined by HPLC by using a reversed-phase column and water-methanol (ratio 5:95) eluant (Bieri et al. 1979).

The field staff was trained in measurement of respiratory rate, temperature, weight, height and hydration status and in giving standard instructions regarding fluids and feeding. Independent checks were made by supervisors for one third of all morbidity visits and half of the measurements obtained by field workers.

Diarrhea and dysentery were treated according to WHO recommendations. Two packets of WHO Oral Rehydration Salts (ORS) were provided to all mothers. Dysentery was treated with nalidixic acid for 5 d.

Analysis. Out of the 900 children enrolled, five did not complete the study because consent was withdrawn at the first post-enrollment visit; these children were excluded from the final analysis.

Student's t test (two-tailed) was used for comparisons of continuous variables between groups; those with skewed distribution were normalized by log transformation, and a two-tailed t test was applied to the transformed data. A paired t test was used to compare pre- and post-intervention serum retinol concentrations. The confidence intervals (CI) for means and difference in means were calculated (Gardner and Altman 1989). Categorical variables were compared using the chi square or Fisher exact test (Armitage and Berry 1987).

Episodes that lasted for 14 or more days post-enrollment were classified as persistent.

RESULTS

There were no significant differences in the age, parental literacy rates, nutritional status, feeding patterns or pre-enrollment illness characteristics between the treatment groups (**Table 1**). Only one child (vitamin A group) had signs of dehydration at enrollment.

The paired difference in mean serum vitamin A concentrations between baseline and 1 mo after treatment was 0.36 ± 0.71 μmol/L (95% CI 0.12 to 0.59; $P < 0.001$) in the 40 randomly selected children in the vitamin A group and 0.12 ± 0.7 μmol/L (95% CI−0.11 to 0.36; $P = 0.136$) in the 40 children in the placebo group. Comparison of the means of the change in serum retinol concentration between baseline and 1 mo after supplementation across the two treatment groups did not show significant differences ($P = 0.13$). Furthermore, the mean serum retinol concentrations 1 mo after supplementation were similar in the vitamin A (1.30 ± 0.44 μmol/L) and placebo (1.17 ± 0.42 μmol/L) groups ($P = 0.20$).

Subclinical vitamin A deficiency at baseline (serum retinol <0.7 μmol/L) was detected in 26.3% children: 31.6% in the vitamin A group and 21.1% in the placebo group (P = 0.30). The baseline mean serum retinol concentration was 1.0 ± 0.52 μmol/L in breast-fed children and 0.98 ± 0.38 μmol/L in those not breast-fed ($P = 0.83$).

TABLE 2

Post-enrollment clinical outcomes in children administered vitamin A or placebo

Illness characteristics: post-randomization to recovery	Vitamin A (n = 451)	Placebo (n = 444)	Ratio of geometric means or odds ratio (95% CI)
Duration of diarrhea (d)[1]	2.0 (1.9–2.2)	2.1 (1.9–2.3)	0.96 (0.86–1.07)
Stools during episode[1]	5.2 (4.6–6.0)	5.9 (5.1–6.7)	0.89 (0.73–1.08)
Episodes becoming persistent (≥14 d)[2]	4 (0.9)	13 (2.9)	0.30 (0.07–0.97)[4]
Children passing watery stools on any days[2]	44 (9.1)	61 (13.7)	0.68 (0.44–1.05)
Weight change as % of initial weight[3]	1.04 ± 2.8	1.09 ± 2.7	−0.05 (−0.41–0.31)

[1] Geometric means (95% CI) and their ratio.
[2] n (%) and odds ratio.
[3] Arithmetic means ± SD and their difference.
[4] P = 0.02 (Fisher exact test).

In the analysis on all children aged 1–5 y, the risk of persistent diarrhea was significantly reduced in the vitamin A–treated children (OR 0.30, 95% CI 0.07–0.97). However, the mean diarrheal duration, number of diarrheal stools passed during the episode and the weight changes during the study were similar in the two groups (**Table 2**).

Undernourished children and those that were not breast-fed may be expected to have a higher prevalence of severe subclinical vitamin A deficiency, so vitamin A may have a greater impact in these subgroups. A standard test of interaction (Pocock 1983) suggested a significant interaction between breast-feeding status and effect of vitamin A supplementation on the mean diarrheal duration (P = 0.01), whereas there was no such interaction for weight-for-height status categorized as ≤80% and >80% of NCHS median (P = 0.60). The children who received any breast-feeding in the 24-h period prior to enrollment were categorized as breast-fed.

In a secondary analysis, we therefore compared the outcomes in children supplemented with vitamin A or placebo within the subgroups of breast-fed and non-breast-fed children. Among the non-breast-fed children, there was a significant reduction in all the main study outcomes in the vitamin A–treated episodes: 16% in the average diarrheal duration, 27% in the mean stool frequency, and 60% in the proportion of children who passed watery stools. Eight (3.6%) episodes in the placebo and none in the vitamin A group became persistent (**Table 3**). Among the breast-fed children, there were no significant differences in any of these outcomes between the two groups.

The mean diarrheal stool frequency segregated by study day in the non-breast-fed children is shown in **Figure 1.** Compared with the placebo group, the vitamin A–treated non-breast-fed children had a 11% reduction in stool frequency on d 1 (P = 0.12), 20% on d 2 (P = 0.03), 16% (P = 0.16) on d 3 and 27% on d 7 (P = 0.01).

To confirm that the favorable effect of vitamin A in non-breast-fed children was not the result of confounding, we performed a multiple linear regression analysis restricted to this subgroup. In this analysis, the outcome variable was diarrheal duration on a log scale (model 1) and the mean number of stools on a log scale (model 2). The explanatory variables were treatment group (placebo or vitamin A), age category (≤23 or >23 mo), sex (male/female), weight-for-height ≤80% of NCHS median (no/yes), pre-enrollment duration of diarrhea (≤3 or >3 d), blood in stools (no/yes), stool frequency in the 24 h before enrollment (≤median/>median), and consumption of ORS before enrollment (no/yes). All the variables entered in the models were those associated with either of the outcome variables in the univariate analysis at a significance level of $P < 0.20$, with the exception of sex and pre-enrollment diarrheal duration.

The beneficial effect of vitamin A, after adjustment, remained significant for both mean diarrheal duration (P = 0.03) and mean number of stools during the episode (P = 0.02). A high pre-enrollment 24-h stool frequency was also independently associated with an increase in the mean number of stools passed after supplementation (P = 0.03). No other covariates were significantly associated with either of the outcome variables.

DISCUSSION

In this study, vitamin A–treated children had a reduced risk of persistence of diarrheal episode, but no significant benefit in other primary outcomes.

Because of the significant interaction between breast-feeding status and vitamin A effect on acute diarrhea, we analyzed results by breast-feeding status. This showed that the effect of vitamin A treatment on acute diarrhea depends on breast-feeding status; vitamin A treatment significantly improves the outcome of the treated diarrheal episodes in the non-breast-fed children, whereas there was no significant effect in those who were breast-fed. In the non-breast-fed children, there was a significant reduction in all the primary outcomes, including stool frequency, days when watery stools were passed and the risk of persistent diarrhea.

These findings are consistent with reports that breast-feeding beyond the first year of life is protective against severe vitamin A deficiency (Cohen et al. 1983, Mahalanabis 1991, Stanton et al. 1986, Tarwatjo et al. 1982, West et al. 1986). The mechanisms underlying the observed effect may be that the correction of subclinical vitamin A deficiency results in a rapid and effective repair of the intestinal epithelium following an acute enteric infection, because of the role of vitamin A in regulating cell division (Semba 1994) or enhancing immune response. Vitamin A has been shown to potentiate the antibody response to a variety of antigens, including rotavirus, *E. coli* and cholera toxin (Ahmed et al. 1991, Friedman et al. 1991, Wiederman et al. 1993) as well as T cell function (Coutsoudis et al. 1992, Semba 1994).

Furthermore, among several recent studies in Brazil, India, Haiti and Ghana that examined the effect of routine large-dose vitamin A supplementation on subsequent diarrheal morbidity, a convincing reduction in diarrheal morbidity was shown only in the Brazilian study (Barreto et al. 1994, Bhandari et al. 1994, Ghana VAST Study Team 1993, Stansfield et al. 1993). It is noteworthy that in this study, only 13.5%

TABLE 3

Post-enrollment clinical outcomes in non-breast-fed children administered vitamin A or placebo

Illness characteristics: post-randomization to recovery	Vitamin A (n = 244)	Placebo (n = 223)	Ratio of geometric means or odds ratio (95% CI)
Duration of diarrhea (d)[1]	1.9 (1.7–2.1)	2.3 (2.0–2.5)	0.84 (0.72–0.97)
Stools during episode[1]	4.6 (3.9–5.5)	6.3 (5.2–7.7)	0.73 (0.56–0.95)
Episodes becoming persistent (≥14 d)[2]	0 (0.0)	8 (3.6)	p = 0.002[4]
Children passing watery stools on any days[2]	17 (7.0)	35 (15.7)	0.40 (0.21–0.77)
Weight change as % of initial weight[3]	1.1 ± 2.8	1.2 ± 2.8	−0.09 (−0.60–0.42)

[1] Geometric means (95% CI) and their ratio.
[2] n (%) and odds ratio.
[3] Arithmetic means ± SD and their difference.
[4] Fisher exact test.

of the enrolled subjects were breast-fed, compared with 47.8% in the Indian study and 58% in the Haitian study.

The observed reduction in the risk of persistent diarrhea is extremely important because the risks of growth faltering and a fatal outcome are high with this disorder. Reduction in the risk of developing persistent diarrhea may be one of the ways by which vitamin A decreases childhood mortality. The relatively low rates of persistent diarrhea in this study compared with earlier studies at the same site may be due to early treatment of dysentery and standard case management of diarrhea. Furthermore, the enrolled children could have been suffering from diarrhea for 7 d prior to the intervention, leading to an underestimate of persistent diarrhea.

The only other trial in which the therapeutic efficacy of vitamin A (60 mg) for acute non-cholera watery diarrhea was examined showed no effect of such treatment on stool output or average diarrheal duration (Henning et al. 1992). However, it is noteworthy that in this study 89% of patients were breast-fed and the sample size of 83 children was sufficient to detect only a 55% difference in the mean stool output between the two groups.

On the other hand, vitamin A administration during acute measles has been shown to reduce the risk of diarrhea and its severity (Hussey and Klein 1990, Ogaro et al. 1993). In the study by Hussey and Klein (1990), children with measles had a significant reduction in complications including pneumonia and diarrhea following vitamin A supplementation; the mean duration of diarrhea was 5.6 d in the treated children and 8.5 d in the controls.

Some limitations of the study need to be emphasized. First, for ethical reasons, all the children were given ORS packets and parents instructed on their use, making it difficult to assess the effect on the risk of developing dehydration. The 27% reduction in the mean stool frequency and the fact that vitamin A–treated children were 60% less likely to have watery diarrhea suggest that vitamin A may reduce stool output and the risk of dehydration in non-breast-fed children. Second, the most significant findings of the study are based on subgroup analysis and need to be confirmed by others.

The effect of vitamin A, although restricted only to the non-breast-fed children, is important because in many developing countries breast-feeding is practiced only during the initial few months, and in other countries breast-feeding rates decline by the end of the first year (Popkin et al. 1982, WHO 1981). In addition, the majority of episodes of severe persistent diarrhea occur in children who are not breast-fed (WHO 1988).

In conclusion, vitamin A treatment during acute diarrhea substantially reduced the episode severity, including the risk of its persistence, in non-breast-fed children. A similar effect was not observed in breast-fed children. These results need to be confirmed in other studies.

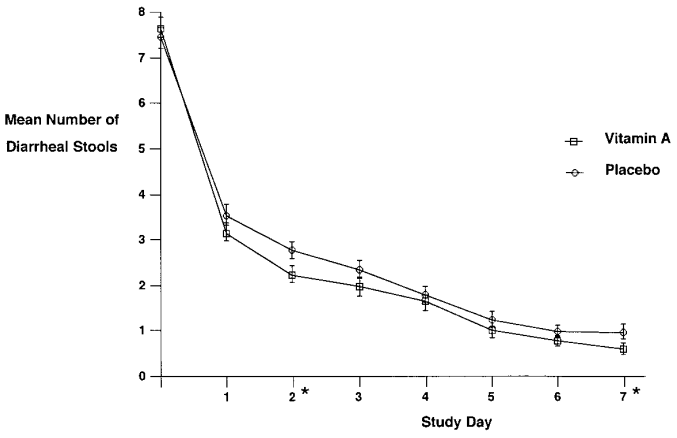

FIGURE 1 Diarrheal stool frequency in non-breast-fed children following treatment with vitamin A (n = 244) or placebo (n = 223). Values are means ± SEM. *Means on days with an asterisk are significantly different ($P < 0.05$).

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