

from six previous clinical trials of enzyme potentiated desensitisation in seasonal rhinitis, we searched for any reason why we were unable to detect a treatment effect but were unable to find one, except for the suggestion that the desensitising potency might be subject to variation. This possibility should be taken into account in the design of any future trial. In the meantime, the evidence of efficacy from the previous clinical trials of enzyme potentiated desensitisation in seasonal rhinitis should be viewed with caution.

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Competing interests: MJR was funded by a grant from McEwen Laboratories and has received fees for lecturing and consulting from the same source. GTL is funded by a grant from the Maurice Laing Foundation. STH has consultancies with several pharmaceutical companies in relation to asthma research and

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Impact of supplementing newborn infants with vitamin A on early infant mortality: community based randomised trial in southern India

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Abstract

Objective To assess the impact of supplementing newborn infants with vitamin A on mortality at age 6 months.

Design Community based, randomised, double blind, placebo controlled trial.

Setting Two rural districts of Tamil Nadu, southern India.

Participants 11 619 newborn infants allocated 24 000 IU oral vitamin A or placebo on days 1 and 2 after delivery.

Main outcome measure Primary outcome measure was mortality at age 6 months.

Results Infants in the vitamin A group had a 22% reduction in total mortality (95% confidence interval 4% to 37%) compared with those in the placebo

group. Vitamin A had an impact on mortality between two weeks and three months after treatment, with no additional impact after three months.

Conclusion Supplementing newborn infants with vitamin A can significantly reduce early infant mortality.

Introduction

Ocular signs of vitamin A deficiency are associated with increased mortality among children aged 6 months or older. Supplementation with vitamin A can significantly reduce total mortality, but the impact is only clear in children aged 6 months or older. It was assumed that breast feeding protected infants from vitamin A deficiency, but recent evidence has challenged this. Infants are born with low stores of



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A table on cause specific mortality appears on bmj.com

vitamin A, and if the mother's breast milk has a low concentration of vitamin A—as found in many women in developing countries—the infant will be unable to meet daily requirements and increase body reserves.¹⁻³

Supplementation of women post partum can improve the concentration of vitamin A in their blood and breast milk, but data on the impact of supplementing infants early with vitamin A on survival are conflicting.⁴⁻⁹ We aimed to determine the impact of supplementing infants with vitamin A within 48 hours of delivery on early infant mortality.

Methods

Our study was a randomised, placebo controlled, community based trial conducted between June 1998 and March 2001 in two rural districts of Tamil Nadu, southern India.

Eligibility and randomisation

Liveborn infants that resulted from all pregnancies within participating villages were eligible for participation. Pregnant women were identified for recruitment from a variety of sources. Project staff explained the study to them and attempted to recruit them before delivery. Baseline information on personal and socioeconomic characteristics was collected by interview. Pregnant women in this area of India traditionally move in with their parents for delivery and for up to six months after delivery. Eligibility was therefore determined by where the woman delivered her child.

Randomisation was at the individual level, stratified by geographical area. Because births were likely in a variety of locations, randomisation was conducted at the time of recruitment. Exclusions after randomisation were stillbirths, miscarriages, delivery more than 20 km outside the study area, and infants who died before our study team arrived.

Intervention, data collection, and primary outcome

The infants were randomly assigned to receive either 24 000 IU of vitamin A twice within a 24 hour interval, beginning within 48 hours of birth, or placebo. The treatment doses were in an edible oil solution packaged in identical gelatin capsules. Mothers were encouraged to breast feed their infant immediately after treatment to ensure consumption of the full dose. Investigators, study staff, and mothers were masked to the assigned treatment.

Village based staff notified their supervisor when a birth had occurred. The supervisor travelled to the site of the delivery to provide the assigned treatment, weigh the infant, and collect information on the delivery. Supervisors had a target to begin treatment within 48 hours of birth or as soon as possible if this was not achievable.

The day after the first dose, the supervisor revisited the household to collect any comments on treatment and to provide the second dose. In the case of adverse events, a report was completed and the child visited daily for seven days.

Project staff visited the household every two weeks to assess the vital status of the child and any morbidity. Infants were followed until 6 months of age. Before discharge the infants had anthropometric measurements taken and were given a 100 000 IU dose of vitamin A. We considered as censored those infants aged

less than 6 months who were being followed at the end of March 2001. The primary outcome was mortality within the first six months of life.

Statistical analysis

Our sample size calculation showed that we required 4500 live births per group (see [bmj.com](#)). Treatment groups were compared on baseline household, maternal, and infant characteristics for all deliveries and for liveborn infants who were enrolled. We used three approaches for the primary analysis of treatment effect on mortality. Firstly, we estimated the incidence density of mortality with person time as the denominator. This permitted use of all data, including infants who were censored at the time follow up was completed. Secondly, we estimated the infant mortality at age 6 months, with live births as the denominator. We include in this analysis only infants who were followed to 6 months. Thirdly, we performed a survival analysis.

Results

Overall, 13 294 infants were born; 6670 (50.2%) were allocated placebo and 6624 (49.8%) were allocated vitamin A. After exclusions, 11 619 liveborn infants were enrolled and followed; 5833 (50.2%) in the placebo group and 5786 (49.8%) in the vitamin A group (see [bmj.com](#)).

Baseline characteristics of the families, mothers, and infants were similar between the treatment groups. This applied to all deliveries and to those infants who were enrolled. Five to 6% of women reported a history of night blindness, a clinical symptom of vitamin A deficiency. The mean birth weights were 2675 g in the placebo group and 2673 g in the vitamin A group (31% of infants weighed less than 2500 g). Similar proportions of mothers in both groups began breast feeding within 12 hours of birth and reported expressing colostrum. Mortality of infants born alive but not enrolled was similar in both groups. Eighty per cent of infants were first dosed within 48 hours of birth (median time to first dosing, 25.5 hours in placebo group and 26.4 hours in vitamin A group).

Supplementing newborn infants with vitamin A was associated with a 22-23% reduction in mortality during the first six months of life (table and figure). Similar estimates of relative risk were obtained by using the incidence density analysis (0.78, 95% confidence interval 0.63 to 0.96), infant mortality at six months (0.77, 0.62 to 0.96), and an estimate of the hazard ratio (hazard ratio 0.78, 0.63 to 0.97). The survival curves began to diverge at around two weeks of age and con-

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Relative risk of mortality in newborn infants receiving placebo or supplementation with vitamin A according to sex

Sex and treatment group	Infant years	No of deaths	Mortality rate/1000	Relative risk (95% CI)
Total:				
Placebo	2719.1	188	69.1	0.78 (0.63 to 0.96)
Vitamin A	2713.0	146	53.8	
Males:				
Placebo	1412.3	100	70.8	0.70 (0.52 to 0.94)
Vitamin A	1378.2	68	49.3	
Females:				
Placebo	1306.7	88	67.3	0.87 (0.65 to 1.17)
Vitamin A	1334.8	78	58.4	

tinued to separate until three months of age (figure). After three months the curves remained parallel, indicating no further treatment effect.

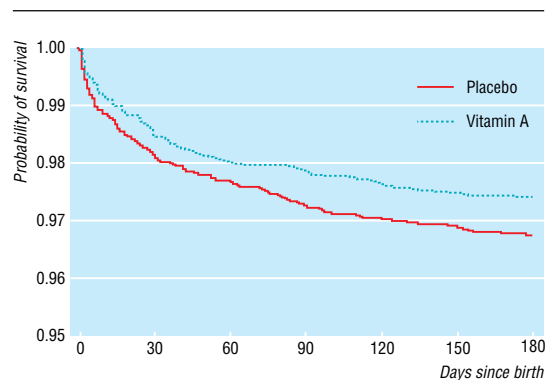
Little evidence was found for effect modification by sex (table, test for interaction, $P=0.33$). The impact of vitamin A on survival was limited to infants who were treated before 14 days, although the strength of evidence for this interaction was low (test for interaction, $P=0.68$). The effect was also limited to infants of low birth weight. In this group, vitamin A reduced mortality at six months by 37%. In contrast, there was no effect of vitamin A on mortality among infants weighing 2500 g or more at birth (test for interaction, $P=0.02$).

Discussion

Giving newborn infants two doses of 24 000 IU of vitamin A within 48 hours of birth significantly reduced early infant mortality. Our results agree with those from a hospital based study in Indonesia, which reported a 64% reduction in infant mortality associated with giving newborn infants 50 000 IU of vitamin A.⁹ As in our results, the impact of vitamin A on survival was limited to the first three or four months of life. The greatest impact in the Indonesian study was among infants who weighed 2500 g or more at birth. In contrast, we found the greatest effect among infants of low birth weight.

The discrepancy with studies that supplemented infants later in the first six months suggests something unique about receiving a large dose of vitamin A shortly after birth.⁶⁻⁸ Although the underlying mechanism for this differential impact by age is unknown, two explanations are plausible. Humans are born with marginal reserves of vitamin A and depend on breast milk or other sources to meet their metabolic demands in the first few months of life. Premature infants have even lower reserves of vitamin A, and correction of the deficiency has been shown to reduce the respiratory complications of preterm birth.¹⁰ A large bolus of vitamin A early in the neonatal period may provide a stimulus to rapid maturation of both gut and respiratory epithelium. This matured epithelium may be more resistant to invasion by pathogens or may clear such organisms more efficiently.

Another potential mechanism relates to the role of vitamin A in the development and maintenance of



Kaplan-Meier survival curve for enrolled infants. Log rank test: $\chi^2=5.12$, $P=0.02$, hazard ratio 0.78 (0.63 to 0.97)

What is already known on this topic

Supplementation with a large dose of vitamin A reduces mortality among children aged 6 months to 5 years in many developing countries

The effect of supplementation on mortality in newborn infants under 6 months of age is unclear

Periodic treatment with vitamin A beyond the first month of life has no impact on mortality

What this study adds

Supplementing infants with vitamin A in the first few days after birth significantly reduced infant mortality

The greatest impact was observed between 2 weeks and 3 to 4 months of age

immunocompetence. Vitamin A deficiency causes alterations in T cell subsets, impaired phagocytic activity, and reduced antibody response to antigen challenge.¹¹⁻¹³ Retinoic acid is an important regulator of gene expression and cell differentiation, and vitamin A deficiency can cause alterations in the balance of Th1 versus Th2 type cytokine response.^{14 15} However, these effects have been observed in animal models and humans after the newborn period.

Our study had limitations. The need to maintain control over delivery of the assigned treatment, and the variation in locations and time at which deliveries took place, resulted in a delay in arrival at the place of delivery. We therefore missed several children who were born alive and were subsequently moved, whose parents refused participation, or who died before the arrival of our staff. Although there was no difference in survival between the treatment groups before enrolment, the delay prevented estimation of the effect of supplementation on total six month infant mortality.

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Effect of strategies to reduce exposure of infants to environmental tobacco smoke in the home: cross sectional survey

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Abstract

Objective To examine parents' reported knowledge and use of harm reduction strategies to protect their infants from exposure to tobacco smoke in the home, and the relation between reported use of strategies and urinary cotinine to creatinine ratios in the infants.

Design Cross sectional survey.

Settings Coventry and Birmingham.

Main outcome measures Parents' reported knowledge and use of harm reduction strategies and urinary cotinine to creatinine ratios in their infants.

Participants 314 smoking households with infants.

Results 86% of parents (264/307) believed that environmental tobacco smoke is harmful, 90% (281/314) believed that infants can be protected from it in the home, and 10% (32/314) were either unaware of measures or reported using none. 65% of parents (205/314) reported using two or more measures, but only 18% (58/314) reported not allowing smoking in the home. No difference was found in mean log e transformed urinary cotinine to creatinine ratio in infants from households that used no measures compared with households that used less strict measures. Mean log cotinine to creatinine ratios were significantly different in households banning smoking in the home compared with those using less strict or no measures. Banning smoking in the home was independently associated with a significant reduction in urinary cotinine to creatinine ratio by a factor of 2.6 (1.6 to 4.2) after adjustment for average household cigarette consumption, tenure, and overcrowding.

Conclusions Less than a fifth of parents in smoking households ban smoking in the home. Banning smoking was associated with a small but significant

reduction in urinary cotinine to creatinine ratio in infants, whereas less strict measures compared with no measures had no effect on the infants' exposure to environmental tobacco smoke.

Introduction

Exposure of infants to environmental tobacco smoke is associated with an increased risk of sudden infant death syndrome, asthma, and other respiratory conditions.¹ In England, children's exposure to tobacco smoke has decreased since the late 1980s, but there is little evidence of reduced consumption of tobacco by parents in the presence of their children.² Smoking cessation among household members is the only effective way of reducing passive smoking among young people. Changing smoking practices in the home and in the presence of young people has been suggested as a means of reducing exposure to tobacco smoke when cessation is not possible. To date the evidence on the use and effectiveness of such measures is limited and confusing.

We report parents' knowledge and use of measures to reduce exposure of their infants to environmental tobacco smoke and the impact of harm reduction measures on urinary cotinine to creatinine ratios in infants. Our sample was community based and representative of UK smoking households with infants (mean age 12.8 weeks).

Participants and methods

We used a cross sectional survey design to collect data from a sample of parents of infants living in households with one or more smokers. The parents of



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