Does Early Neonatal Vitamin A Supplementation Reduce Infant Mortality?

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SUMMARY

In this individually randomized, double-blind, placebo-controlled trial in Haryana, India, 44,984 neonates were randomly assigned to receive oral capsules containing vitamin A (retinol palmitate 50,000 IU plus vitamin E 9·5–12·6 IU; *n*=22,493) or placebo (vitamin E 9·5–12·6 IU; *n*=22 491) within 72 h of birth. The primary outcome was mortality between supplementation and 6 months of age. Between supplementation and 6 months of age, 656 infants died in the vitamin A group compared with 726 in the placebo group (29·2 per 1000 *vs* 32·3 per 1000; difference –3·1 per 1000, 95% CI –6·3 to 0·1; risk ratio 0·90, 95% CI 0·81 to 1·00). There was a small excess risk of transient bulging fontanelle (205 cases in the vitamin A group *vs* 80 cases in the placebo group; RR 2·56, 95% CI 1·98, 3·32).

COMMENTARY

Relevance: Mazumder, *et al.* [1] have presented a strong justification for conducting this trial of vitamin A versus placebo in a large cohort of newborn infants. Data from a limited set of previous trials suggested equivocal results with supplementation. Two Cochrane systematic reviews [2,3] provided diametrically opposite conclusions despite concordant literature search and inclusion of the same set of trials. The review by Haider and Bhutta [2] suggested a clinically significant reduction in early infant (<6 mo) mortality to the extent of 14% (RR 0.86; 95% CI 0.77, 0.97), although there was no difference in mortality at 12 months (RR 1.03; 95% CI 0.87, 1.23). In contrast, another Cochrane review by Gogia and Sachdev [3] published at the same time failed to demonstrate any benefit of vitamin A supplementation during early infancy on infant mortality (RR 0.94; 95% CI 0.79, 1.12) at any time point. Interestingly, the authors of the two reviews somehow managed to disagree even in the evaluation of methodological quality of the included trials! Besides reiterating that even best quality evidence can sometimes result in missing the forest for the trees [4], this discrepancy set the ground for re-evaluation of the subject. This was done through the recent Neovita trial conducted in India, Ghana and Tanzania [1,5-7). The data from the Indian trial [1] is briefly reviewed here and serves to highlight both the individual trial itself, and the data in the context of clinical equipoise with regard to the vexing issue of neonatal vitamin A supplementation to reduce infant mortality.

Critical appraisal: ***Table*** **I** summarizes the methodological aspects of the trial [1] using the Cochrane Risk of Bias tool [8]. The trial methodology was robust and developed through a well-planned [7] and well-documented process. In addition, there are several other noteworthy points. The randomization unit was the individual infant rather than a cluster of infants. The text contains a detailed description of the population demographics, health-seeking behavior, literacy rate, economic status etc; as well as several details of the enrolled infants. This makes it easier while considering generalizability of the trial results.

The trial procedures are described in detail, including participant enrolment, exclusion criteria, baseline data collection, administration of intervention, measurement of primary outcomes, and recording of potential adverse events. Other quality assurance measures included random monitoring of the research personnel, evaluation by an independent data safety monitoring board, and supervision of WHO. Serial evaluation of trial capsules for vitamin A content (indirect measure of potency and stability) was done with satisfactory results.

Outcomes were measured at serial intervals and several data variables were collected for analysis. A key adverse event (bulging fontanelle reported to be significantly more frequent with vitamin A supplementation in previous trials and systematic reviews) was evaluated by research staff, and also confirmed by a physician. Data were entered directly into

TABLE I ASSESSMENT OF METHODOLOGICAL QUALITY

Criteria	*Assessment*
Sequence generation	Adequate. The randomization sequence was prepared by independent personnel who were not involved in the trial conduct. Block randomization (with fixed block sizes of 20) was used.
Allocation concealment	Adequate. The allocation sequence code was not accessible to any of the investigators.
Blinding of participants, personnel and outcome assessors	Adequate. Elaborate precautions were taken to ensure that the intervention (vitamin A) and placebo capsules were physically alike. The packaging was also similar. Printed labels with participant serial numbers were affixed on the packages ensuring that no substitution was possible. Personnel measuring the outcomes were unaware of the allocations. However, there is no description of whether research personnel or participating families could guess the contents of the package at any time during the study.
Incomplete outcome data	There was a very small number of participants whose data were unavailable at the time of primary outcome assessment at 6 months (0.02% and 0.01% in the intervention and placebo arms respectively). At the longest follow-up (12 months), only 0.12% and 0.08% were unavailable for outcome assessment. The data were analyzed per protocol, rather than intention-to-treat.
Selective outcome reporting	All relevant outcomes have been reported viz mortality at 6 months (primary outcome), neonatal mortality, infant mortality, hospitalization for any cause till 6 mo, and several adverse events (mortality within 72 hours of intervention, bulging anterior fontanelle, vomiting, diarrhea, seizures, poor feeding, lethargy and various other local and systemic events).
Other sources of bias	No obvious bias.
Overall assessment	Low risk of bias.

computers reducing the risk of transcription errors, and facilitating immediate flagging of potentially incorrect entries.

Robust statistical methodology was used. Sample size was calculated *a priori* with stringent limits for type I and type II errors. The sample size was tweaked upward during the course of the trial, based on advisory recommendations. Appropriate statistical tests were used. However, *per protocol* rather than intention-to-treat analysis was used. Nevertheless, this may not adversely impact the results as very few participants were unavailable for outcome assessment.

The investigators measured serum retinol and C-reactive Protein (CRP) in a randomly selected subset of participants at two time-points (15 d and 3 mo). This data is useful for evaluation of a pathophysiologic mechanism for the observed results.

The trial did not show a statistically significant benefit of vitamin A supplementation on mortality at any time-point. Relative risk for mortality at 6 mo was 0.90 (95% CI 0.81, 1.00); at 12 mo 0.94 (95% CI 0.86, 1.02); and at day 28, it was 0.94 (95% CI 0.80, 1.11). There was no beneficial effect of supplementation on hospitalization within 6 mo of birth (RR 0.96, 95% CI 0.90, 1.04).

Despite multiple methodological refinements, there are some issues with data interpretation. For example, although the baseline infant mortality rate in the catchment population was 60 per 1000 live births, the recorded mortality in the trial population was only about half this value. This leads to the possibility that either the trial participants or trial catchment area or both were not truly representative of the local population. The other possibility is that the catchment area was popular for other research-based intervention strategies also, and hence had a pre-existing low infant mortality rate compared to the district average. Of course, Hawthorne effect wherein population behavior changes while under observation [9] cannot be ruled out.

The authors have suggested that vitamin A supplementation may reduce early infant mortality by almost 10%, and perhaps even more by 12 months (judging by the survival curves). This is difficult to grasp given that, even after supplementation, both groups had mean serum retinol levels below the cut-off level for vitamin A deficiency, despite an impressive *P* value for inter-group comparison. Similarly at three months, both groups had comparable mean retinol concentration, which was just at the cut-off level in both groups. There could be three explanations. Either the subgroup in which retinol levels were measured did not truly represent the

trial participants; or the dosage of vitamin A used was inadequate to raise retinol to a sufficient level; or serum measurements are inappropriate surrogates for tissue levels and/or body stores. More important, the absence of difference between the intervention and placebo groups suggests that the marginal differences in mortality at 6 and 12 months of age, as emphasized by the diverging survival curves, are unlikely to be related to vitamin A supplementation.

What does this trial add to the existing body of knowledge? On the one hand, the contrary opinions expressed in the two Cochrane reviews [2,3] led the WHO to strongly recommend against neonatal vitamin A supplementation in 2011 [10]. However, at the same time, WHO also led a set of three Neovita trials addressing the same issue [1,5,6], suggesting that it lacked confidence in its recommendation. Data from these trials is briefly summarized in ***Table* II** which shows some differences between the three sites. One additional recent trial by Benn, *et al*. [11] randomized 6048 neonates to receive either 50,000 units Vitamin A (*n*=2015), 25,000 Units vitamin A (*n*=2011) or placebo (*n*=2022) soon after birth. Mortality was primarily assessed at 12 months. The first and third arms are comparable to the Neovita trials; the respective mortality rates were 50/1378 infant-years and 45/1377 infant-years, suggesting the absence of any benefit with supplementation.

Haider and Bhutta have published an editorial with fresh meta-analysis [12], including the three Neovita trial data, but not the data from Benn 2014 [11]. Although the new meta-analysis (pooling data from 10 trials) showed no overall benefit with vitamin A supplementation, the authors suggested that trials in Asia showed reduction in infant mortality while trials from Africa did not. However, it is important to note that the authors clubbed together trials with varying durations of follow-up. Thus trials with 4 mo follow-up [13] were analyzed together with trials having follow-up of 6 mo and 12 mo. Interestingly, the authors chose to include the 6 mo follow-up data from the three Neovita trials rather than the 12 mo outcomes. Similarly, there are some errors in data extraction from other trials as well, making this meta-analysis unreliable. The authors conceded that contrary to their previous position, neonatal vitamin A supplementation may not be as beneficial as thought previously.

On the bright side, vitamin A appears to be safe as there was no increase in mortality or serious adverse events after supplementation. This may be particularly relevant because of recent concerns about a potential increased risk of mortality with vitamin A [14]. However as expected, the risk of bulging anterior fontanelle (necessitating observation of infants over a period of days, and possibly health-care interventions in some cases) was higher with vitamin A. It is interesting that the rates of this adverse event vary significantly at the three Neovita study sites; with India having the highest frequency in both arms.

Extendibility: The data in this randomized controlled trial (RCT) can be directly extrapolated to most Indian settings, although it must be emphasized that the infant mortality rate observed in the trial was about half of the expected rate; and hence the intervention could work differently in a setting with high(er) infant mortality.

TABLE II OVERVIEW OF THE TRIALS IN NEOVITA STUDY

Country		*India*		*Tanzania*		*Ghana*	
		Vitamin A	*Placebo*	*Vitamin A*	*Placebo*	*Vitamin A*	*Placebo*
Randomized		22493	22491	15995	16004	11474	11481
28 d	Dead	281	298	213	206	147	130
	LFU	0	0	318	294	27	22
	Alive	22212	22193	15464	15504	11300	11329
6 mo	Dead	375	428	194	166	131	1118
	LFU	4	3	249	246	102	106
	Alive	21833	21762	15021	15092	11067	11105
12 mo	Dead	223	213	159	174	93	80
	LFU	24	16	742	715	212	195
	Alive	21586	21533	14120	14203	10762	10830
Overall LFU		28 (0.12%)	19 (0.08%)	1309 (8.18%)	1255 (7.84%)	341 (2.97%)	323 (2.81%)

LFU=lost to follow-up

Although a trend towards better survival at 12 mo was evident, there is no plausible biological basis or explanation for this in relation to neonatal vitamin A supplementation.

Conclusions: This well-designed RCT confirms the absence of any benefit of neonatal vitamin A supplementation on neonatal mortality, early infant (6 mo) mortality and infant mortality; although vitamin A supplementation was reasonably safe barring increased risk of bulging anterior fontanelle.

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