

Dr K N Rao Memorial Oration

Low-quality Scientific Evidence for the Continuation of Universal Vitamin A Supplementation among under 5 Children in India

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Summary

Vitamin A supplementation (VAS) is presently being undertaken in India among under 5 (U5) children for two possible benefits (i) to prevent nutritional blindness due to Vitamin A deficiency (VAD) and (ii) to reduce U5 mortality. The existing scientific evidence suggests that nutritional blindness due to VAD has been virtually eliminated and also the difference between U5 mortality rate and infant mortality rate is very low for VAS to have any meaningful impact. On the contrary, scientific evidence indicates that there could be side effects of the administration of mega dose of Vitamin A (MDVA). These side effects of MDVA have not been systematically investigated. The universal VAS should be discontinued immediately as there are no likely benefits to U5 children.

Keywords: Mega dose of Vitamin A, nutritional blindness due to Vitamin A deficiency, Vitamin A deficiency, Vitamin A supplementation, under 5 children

Introduction

Vitamin A is an essential nutrient needed in small amounts for the normal functioning of the visual system, growth and development, maintenance of epithelial cellular integrity, immune function, and reproduction.¹ Although Vitamin A deficiency (VAD) can occur in any age group, the most serious effects are seen in the preschool children.

In 1970, the Government of India initiated the National Prophylaxis Programme against Nutritional Blindness due to Vitamin A Deficiency (NPPNB) as during the seventies, the magnitude of VAD was high.² The main objective of the program was to prevent nutritional blindness due to VAD among under 5 (U5) children.

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In India, at present, under NPPNB, all children in the age group of 6 months to 5 years are administered the mega dose of VA (MDVA) as per the following schedule:³ a total of 9 doses of MDVA are given till the child reaches 5 years of age.

- 6–11 months - one dose of 100,000 IU
- 1–5 years - 200,000 IU for every 6 months.

During the past 50 years, there have been significant changes in the epidemiology of VAD. The causes of morbidity and mortality among U5 children and the overall health scenario have improved in the country. However, administration of MDVA is being continued without reviewing the scientific evidence available on VAD. The health administrators and planners are possibly continuing the administration of MDVA to U5 children to maintain the tradition and faith in the Vitamin A supplementation (VAS) program which was initiated in 1970.

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Cite this article as: Kapil U, Gupta A. Low-quality scientific evidence for the continuation of universal Vitamin A supplementation among under 5 children in India. Indian J Public Health 2016;60:176-80.

Access this article online

Website: www.ijph.in	Quick Response Code: 
DOI: 10.4103/0019-557X.188999	

In this communication, we will review the current scientific evidence on the need for MDVA supplementation and its possible side effects in U5 children.

Changing Scenario of Vitamin A Deficiency

There has been a gradual decline in the prevalence of clinical signs of VAD among U5 children from 1975 to 2012.^{4,5} The overall prevalence of Bitot’s spot (BS) among preschool children has declined from 1.8% (1975) to 0.2% (2012) [Table 1]. The cutoff to define VAD as a public health problem in a community is a prevalence of BS of $\geq 0.5\%$.⁶

The validity of BS in establishing VAD has been questioned. A prospective, community-based, cohort study with 12-month follow-up was conducted among children (1–5 years) with BS at a district from North India.⁷ Even after receiving two MDVAs, more than 40% of the BS did not respond to the administration of MDVA during the 12-month follow-up period. On follow-up, it was found that 61.8% of the children had reappearance of BS after a complete resolution. For programatic decisions and evaluation, the public health burden of Vitamin A deficiency should not be assessed solely through BS.⁷

Another national study conducted recently to assess the prevalence of VAD in the country by the Indian Council of Medical Research covering 16 districts in all five regions of the country documented that only three out of 16 districts had a prevalence of BS of $\geq 0.5\%$.⁸ The three districts, which had a higher prevalence were either draught-prone (Bikaner, Rajasthan) or had poor socioeconomic development indicators (Patna and Gaya, Bihar, India). The existing evidence suggests that possibly VAD is a public health problem only in isolated geographical pockets of the country. There are wide variations in the prevalence of VAD within the states.

Reasons for Reduction in the Clinical Signs of Vitamin A deficiency

There has been a very low coverage of the national VAS program in the country. Percentage of children who received at least one dose of Vitamin A within 6 months preceding the survey as projected by the National Family Health Survey (NFHS)-2 (1998–1999) and NFHS-3 (2005–2006) was 17% in 6–35 months age children and 18% in 6–59 months children, respectively.^{9,10} Hence, the VAS had no major effect on the reduction of VAD.

The reduction in VAD is possibly linked to (i) reduction in the prevalence of severe protein–energy malnutrition in children, (ii) increase in immunization coverage particularly with measles, (iii) better health infrastructure, (iv) reduction in the overall morbidity due to higher use of antibiotics, (v) overall improvement in the dietary intake of children, (vi) improvement in the water supply and sanitation, (vii) higher availability of Oral Rehydration Solution (ORS) for the management of diarrhea, (viii) higher utilization of health-care facilities and overall economic progress in the country along with better educational status among women. All these factors in combination may have improved the nutritional status of children in the country and may have resulted in the reduction of VAD.

Mega Dose of Vitamin A and Under 5 Mortality: Scientific Evidence from India

A landmark study conducted in Indonesia on the impact of MDVA supplementation on U5 mortality was published in 1986.¹¹ This study revealed that there was a reduction of 34% mortality among U5 children who received MDVA as compared to controls. Based on the results of this study, the UNICEF and other international organizations promoted VAS, as a major child survival intervention for U5 children in the developing countries. The health administrators and planners of the developing

Table 1: Prevalence of Bitot’s spot among preschool children

Year	Kerala	Tamil Nadu	Karnataka	Andhra Pradesh	Maharashtra	Gujarat	Odisha	Pooled (7 states)
1975-1979	0.1	2.9	2.3	3.1	0.4	0.9	1.5	1.8
1988-1990	0.5	0.6	1.1	1	0.3	0.5	1.1	0.7
1996-1997	0.1	0.7	0.5	0.8	3	0	0	0.7
2011-2012	0	0	0.6	0.1	0.4	0.2	0.3	0.2

countries were motivated to adopt VAS for reduction in U5 mortality.

During the 1990s, Indian scientists repeated the Indonesian study in Hyderabad to assess the effect of VAS on U5 mortality rate (U5MR). This study was implemented with an improved research design, better quality supervision, quality control, and efficient statistical analysis. It was found that MDVA did not reduce the U5 mortality.¹² Another study in 1992 repeated in Sudan to assess the impact of MDVA on U5 mortality did not show any impact.¹³

Later in 2000–2004, a study was conducted in India to assess the effectiveness of VA on U5 mortality in the programmatic conditions.¹⁴ One million preschool children were included. It was the largest randomized control trial ever conducted. VAS was done for every 6 months. It was found that the absolute risk of death amongst children in the age group of 1–6 years who received MDVA and who did not receive MDVA was approximately 2.5% and 2.6% respectively. There was no dramatic impact of VAS on the U5 mortality.

Can Mega Dose of Vitamin A have Impact on Under 5 Mortality in the Current Scenario?

In India, there has been a gradual reduction in U5MR from 191 (1970) to 48 (2015).¹⁵ Similarly, the infant mortality rate (IMR) has reduced from 80 (1991) to 38 (2015).¹⁶

An analysis of the data from NFHS-4 suggests that a very small proportion of deaths occurs between U5MR and IMR [Table 2].¹⁷ The difference between U5MR and IMR in the selected states is in the range of 0–14% points. The causes of these few deaths are accidents, genetic disorders, congenital anomalies, meningitis, pneumonia, etc., in which biologically it is not possible for MDVA to intervene and prevent deaths. The above evidence suggests that MDVA may not have any impact on U5 mortality in India.

Public Health Concerns on Vitamin A Supplementation

Mega dose of Vitamin A and diarrhea and acute respiratory tract infection-related morbidity and mortality

Universal supplementation of MDVA contains 200,000 IU to all children in the age group of 6–60 months irrespective

Table 2: National Family Health Survey-4 data on infant mortality rate and U5MR

State	Under 5 mortality rate	Infant mortality rate	Difference between U5MR and IMR	Proportion of IMR in U5MR (%)
Andaman and Nicobar Islands	13	10	3	77
Andhra Pradesh	41	35	6	85
Bihar	58	48	10	83
Goa	13	13	0	100
Haryana	41	33	8	80
Karnataka	32	28	4	88
Madhya Pradesh	65	51	14	78
Maharashtra	29	24	5	82
Manipur	26	22	4	84
Meghalaya	40	30	10	75
Puducherry	16	16	0	100
Sikkim	32	29	3	91
Tamil Nadu	27	21	6	78
Telangana	32	28	4	88
Tripura	33	27	6	82
Uttarakhand	47	40	7	85
West Bengal	32	27	5	84

IMR=Infant mortality rate, U5MR=U5 mortality rate

of their VA status. The RDA of Vitamin A per day is 1333 IU (0.3 mcg = 1 IU).¹⁸ MDVA provides VA which is 150 times the RDA. It is a pharmacological dose.

Studies have documented that VAS could lead to a significant increase in the rate of pneumonia in well-nourished children who received 10,000 IU of Vitamin A weekly. A meta-analysis of studies was undertaken to assess the impact of VAS program on U5 morbidity from diarrhea and respiratory infections. The results concluded that VAS had no consistent overall protective effect on the incidence of diarrhea. However, it slightly increased the incidence of respiratory tract infections (RTIs). For this reason, authors concluded that high-dose Vitamin A supplements are not recommended on a routine basis for all preschool children, and should be offered only to individuals or populations with VAD.^{19,20} The differential effect of VAS in pneumonia and diarrhea raised the question and concerns of serious public health implications.

A recent review of 9 randomized controlled trials enrolling 33,179 children with RTI (31,379 in the community and 1800 in hospital) concluded that VAS may not be helpful for preventing pneumonia in normally nourished children and may rather worsen the condition. According to investigators, the study results should force the policymakers of the countries to think twice before continuing or starting a universal VAS program.²¹

Antagonism with Vitamin D

Animal studies suggest that Vitamin A is an antagonist of Vitamin D action. Massive doses of Vitamin A have been shown to intensify the severity of bone demineralization by inhibiting the ability of Vitamin D to prevent such demineralization. Increasing the levels of retinyl acetate abrogates the ability of Vitamin D to elevate the level of serum calcium. Increasing amounts of retinyl acetate have been shown to produce progressive and significant decreases in total bone ash and increases in epiphyseal plate width.²²⁻²⁵

In poor community settings in India, there is a high prevalence of deliveries of low-birth weight infants because of high maternal malnutrition. Vitamin D content in breast milk is low. Due to small and dingy household constructions, these malnourished children may hardly get any exposure to sunlight. In addition, the calcium intake is also low. Supplementing the malnourished young children to MDVA being an antagonist to Vitamin D action may have a detrimental effect on the bone health. These effects have not been studied systematically.

Fontanels bulging

It has been documented that nearly 12% of the young children when administered with 50,000IU of VA developed fontanels bulging.²⁶ A significant part of the overall development of the brain takes place in young children below 3 years of age. In India, as per the NFHS-3 survey, 48% of the children suffer from moderate grade of undernutrition (below – 2 standard deviation). Subjecting these malnourished under 3 children to repeated episodes of increased intracranial tension could contribute to further retardation of their brain development. There is a lack of scientific evidence on the long-term ill effects of these repeated episodes of raised intracranial tension on brain development of intrauterine growth-retarded children who start their lives with psychomotor deficits.^{27,28}

Economics of universal Vitamin A supplementation

According to a recent evaluation, the annual cost per child dosed is US\$1.14 (Rs. 80) per dose.²⁹ In India, if we consider 160 million U5 children (15% of 1200 million), a total amount of Rs. 12,800 million is being spent for universal distribution of MDVA, which has questionable health benefits. Apart from the cost of Vitamin A, the distribution process consumes precious human and material resources meant for the delivery of primary health-care services.

Way Forward

A recent publication based on the trends and mortality effects of VAD in children in 138 low- and middle-income countries between 1991 and 2013 has documented that deaths attributable to VAD have decreased over time worldwide, and have been almost eliminated. This new evidence for prevalence, absolute burden of VAD, and expected mortality benefits of VAS should be used to reconsider and to possibly revise the MDVA supplementation program in the country.³⁰

The main causes of U5 deaths are neonatal mortality (52%), pneumonia (15%), injuries (4%), meningitis (2%), diarrhea (11%), measles (3%), and other causes (13%).³¹ Existing evidence suggests that VAS has no impact on the neonatal mortality, pneumonia, injuries, meningitis, and other causes. These causes constitute to 86% of the total mortality in U5 children. Since the 1980s, measles immunization has all but eliminated measles as a public health problem, including in India, and mortality from diarrheal disease has decreased with control measures including improved oral rehydration, plus the use of zinc and expanded rotavirus immunization in some parts of the world. Existing evidence suggests that periodic MDVA supplementation may have less relevance now with changing disease patterns (notably, reductions in measles and diarrhea). Recent reviews have suggested that MDVA can bring only reduction in U5MR in the range of only 2–3% by VAS.^{30,32}

Recently, the WHO has issued recommendations to discontinue VAS to neonates based on the new scientific evidence generated.³³ To conclude, there is a need to answer the specific issues (i) why we are continuing MDVA when we do not have unequivocal scientific evidence of health benefits to U5, (ii) what are the benefits of the money spent on MDVA supplementation, (iii) and why we are ignoring the current evidence in India. There is a strong evidence to discontinue VAS in the country.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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