Issues and Controversies with Vitamin A in Childhood

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Abstract

Vitamin A deficiency is common in the developing world. Vitamin A supplementation (VAS) has been used to prevent or treat vitamin A deficiency and to decrease mortality and morbidity in children. However, there are still controversial issues in relation to the role of universal VAS in different populations. Thus, studies that look at mortality outcomes reveal that VAS decreases mortality in children >6 months of age; however, there is still controversy on the extent to which reduction in morbidity from diarrhea and respiratory infection, other than measles, decreases mortality. Studies in infants 1–5 months old show no protective effect of VAS on mortality; whether this is secondary to environmental influences (breastfeeding), or interactions with DTP vaccine, needs to be further investigated. Studies with VAS in newborns have resulted in contrasting results in countries in Africa and Asia; trials are underway to better understand this. VAS does not have a universal protective effect on lower respiratory tract infection in children; some studies reveal an increase in respiratory morbidity associated with VAS, especially in well-nourished children; in contrast, VAS may confer some protection to malnourished children. The interaction of VAS with different vaccines is under current debate; some discussions are presented.

Introduction

Vitamin A deficiency (VAD) is common in the developing world. About 190 million children under 5 years and 19.1 million pregnant women are vitamin A deficient (i.e. serum retinol <0.70 μmol/l), representing about 33% of children under 5 years in populations at risk of VAD. Xerophthalmia, a condition associated with VAD, is the world’s leading preventable cause of blindness [1].

Vitamin A has been described as an anti-infectious vitamin because of its role in regulating human immune function and epithelial integrity; studies in
animals and humans have reported an association between VAD and increased susceptibility to infections [2].

In addition to its preventive and therapeutic effect against xerophthalmia, vitamin A supplementation (VAS) has been used to prevent or treat VAD and to decrease mortality and morbidity in children. However, there are still controversial issues, especially in relation to VAS’s role in deaths or morbidity not related to measles in the pediatric population.

The WHO recommends VAS: 100,000 IU for infants 6–12 months of age and 200,000 IU for children over 12 months of age, every 4–6 months [3]. The international community recommends VAS for all children between the ages of 6 months and 5 years in all countries where over 70 in 1,000 children die before the age of 5 years, ‘as this is the internationally accepted proxy to indicate that VAD is a public health problem’ [4]. However, worldwide, a large proportion of children receiving it are not vitamin A deficient, stunted or wasted. The effect of such a public health policy on this population needs to be carefully assessed.

Mortality Outcomes: Vitamin A Supplementation in >6-Month-Old Children

In the 1930s, Ellison [5] first documented the protective effect of vitamin A on measles mortality. The first evidence of the role of prophylactic VAS in preventing death was demonstrated the 1980s in Indonesia; it concluded that children who received massive-dose vitamin A supplements had a 34% lower mortality from all causes than those not receiving the supplement [6]. These results were dramatic; however, no causes of death were reported. Also, the control children had more clinical signs of VAD and poorer growth than the children receiving VAS. During the following years, several other trials were performed. A meta-analysis of these initial studies concluded that VAS to patients hospitalized due to measles was highly protective against mortality. In addition, when given periodically to children at the community level, it decreased overall mortality (0.70; 0.56–0.879) [7]. It is important to emphasize that these studies were performed mostly in Asia, in countries with a high incidence of VAD and also in population with not universal measles immunization. Could it be that the significant reduction in mortality rates in children receiving vitamin A supplements in some studies was due to a reduction in measles deaths? This question has never been specifically addressed. Latham [8] suggested that the statistical difference in deaths might disappear if measles mortality were excluded from some studies of VAS. ‘The ‘causes’ of death in such studies were established by ‘verbal autopsies’. It appeared entirely feasible, based on many years’ experience in the field in Africa, that many deaths recorded as due to respiratory infections, diarrhea
or fever, might in fact be measles deaths. Measles can cause all of these symptoms”. Whether VAS might still have a positive effect in countries with high measles immunization coverage remains to be established, and is an area of controversy.

In a recent meta-analysis by Imdad et al. [9], including 43 trials, involving 215,633 >6-month-old children, there was an observed reduction in the risk of all-cause mortality (24%) and a 28% overall reduction in diarrheal mortality. Of interest, there was no effect on the mortality associated with lower respiratory tract infection (LRTI). Again, the authors stated that ‘the causes of morbidity and mortality were characterized by uncertainty’. So, the controversy of measles’ confounding action remains on the scene. Moreover, one of the largest studies exploring whether massive-dose vitamin A administration is associated with a reduction in childhood mortality was taken up in India between 1999 and 2004. In that study, children were given 6-monthly massive doses of vitamin A, 6-monthly deworming, or both, or neither. Approximately 1 million children were followed, and mortality rates in children 1–6 years of age were recorded. There was no significant difference in death rates between children who received the massive dose of vitamin A and those who did not [10]. Unfortunately, this trial has not been published to date, and details that might explain the difference between this study and previous meta-analyses are not available so far.

**Mortality Outcomes: Children 1–5 Months of Age**

Studies where children were supplemented with vitamin A between 1 and 5 months of age did not show any positive effect on overall mortality [11–14] (see tables 1 and 2). Plausible explanations for these findings have focused on differences in environmental influences on this age group in relation to older infants (e.g. the protection of breastfeeding against malnutrition and infection) or on differences among the populations studied (e.g. different prevalence rates of infectious diseases among study sites may affect underlying mortality rates). Whether this could be explained by the interactions of vaccines given at this age, such as inactivated diphtheria-tetanus-pertussis (DTP) vaccine, with vitamin A, needs to be further investigated (see below).

**Vitamin A in Newborns**

In developing countries, infants are born with low stores of vitamin A and depend on external sources. Sometimes breastfeeding is not enough and newborns and infants need VAS; however, results obtained with this strategy have been contradictory. Studies from Bangladesh [15], India [16] and Indonesia [17] have shown reductions in all-cause mortality (15, 22 and 63%, respectively)
in infants who received VAS relative to controls. Also, VAS has shown to reduce diarrhea case-fatality rates and the incidence of fever [18]. One study performed in Nepal showed no overall effect on early infant mortality, and there was a tendency for the relative risk of mortality among vitamin A recipients to rise with improved nutritional status [19]. Trials in Africa, in countries like Guinea-Bissau [20] and Zimbabwe [21] suggest a lack of benefit from VAS. A meta-analysis by Gogia and Sachdev [22] proposes that there is insufficient evidence to support neonatal supplementation with vitamin A, and there is an increased risk of acute respiratory infection or respiratory difficulty (1.11; 1.02–1.21). Although the study is appropriate, its application of general inclusion criteria may limit its ability to ascertain the role of the prevalence of VAD in infant mortality. Many speculations have so far been formulated in order to understand these controversial results. A recent meta-regression analysis performed by Rotondia and Khobzia [23] suggests that VAS to neonates within the first
2 days of life may confer benefit, especially in regions where the prevalence of vitamin A deficiency is 22% or more among pregnant women. This is an important finding given the current debate as to whether giving neonates vitamin A supplements helps reduce infant mortality in populations where endemic VAD and high infant mortality exist. However, not all neonatal VAS trials support a strong association between vitamin A status and baseline infant mortality, and the VAS effect. Thus, in the Indonesian trial mentioned above, mothers had a good vitamin A status, and infants a very good effect of VAS [17]. Biological and regional differences among populations need to be further studied to better understand contrasting results.

And finally, there has also been a debate in relation to a possible difference to neonatal VAS by sex. However, results from a recent meta-analysis performed by Kirkwood et al. [24] indicated that there is no differential effect of the intervention in boys and girls. Overall, there was no benefit from VAS.

From these results, it is clear more research is needed in this area before sound recommendations can be presented. It is possible that we will have better idea of the impact of this intervention by the year 2013 when information from ongoing trials in Ghana, India and Tanzania become available.

**Morbidity Outcomes: Diarrhea, Lower Respiratory Tract Infection and Measles**

In relation to morbidity, another controversy arises: to what extent is the decrease in mortality due to reduction in morbidity from diarrhea and respiratory infection (other than measles). One study in India, with measles-vaccinated and not severely malnourished children, concluded that VAS did not reduce respiratory and diarrheal morbidity as compared to the placebo controls [25].

The meta-analysis by Imdad et al. [9] revealed a reduced incidence of diarrhea (0.85; 0.82–0.87) and measles (0.50; 0.37–0.67) for VAS compared with control. But again, it included studies where it was difficult to control for measles comorbidity. Of interest, there was no effect on the incidence of respiratory disease or the incidence of hospitalizations due to diarrhea or respiratory disease. All of these studies were performed in developing countries, cointerventions were not analyzed, and there was statistical heterogeneity. Again, the controversy remains because of this and the uncertainty of morbid conditions.

Even more controversial, VAS has been shown to be detrimental in pediatric population. In a blinded, randomized controlled trial (RCT) performed in Mexico [26], where measles vaccination coverage is very high and mortality in children <5 years has been estimated at 17.4/1,000 live births (Information from DGIS, SS Mexico, 2009), VAS to infants 6–15 months old was associated with a
27% increase in diarrheal disease and a 23% increase in cough with fever (RR: 1.23; 1.02–1.47). The authors postulated that the increase in diarrhea in this study might reflect the effect of VAS to downregulate the Th1 response, which protects against rotavirus. Similarly, they speculated that negative respiratory outcomes might be explained by the adverse effect of VAS in respiratory syncytial virus infections [27, 28].

A meta-analysis by Chen et al. [29] concluded that VAS does not have a universal protective effect as prophylaxis for LRTI in children; indeed, three studies showed an increase in respiratory morbidity associated with VAS (table 3). There was also post-hoc evidence to show that VAS in children with poor nutritional status may decrease the incidence of LRTI while the opposite was true for well-nourished children.

Another systematic review by Mathew [30], which included 11 prophylactic and 9 therapeutic trials concluded that VAS has no benefit for childhood community-acquired pneumonia.

Wu et al. [31] published a meta-analysis involving six trials with 1,740 children, some of them <6 months of age. They concluded that disease severity after supplementary high-dose vitamin A was significantly worse compared with placebo (one study). However, low-dose vitamin A (10,000 IU twice daily for the first 6 days, followed by 1,500 IU/day administered for the next 20 days) significantly reduced the recurrence rate of bronchopneumonia (OR 0.12; 0.03–0.46). Moderate vitamin A doses (100,000 IU of vitamin A to children aged one year and older, and 50,000 IU to infants under the age of one year) significantly reduced the time to remission of signs in children with normal serum retinol (>200 μg/l).

**Table 3. Controversies surrounding VAS in children (diarrheal and respiratory morbidity)**

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Results</th>
<th>Controversial issues</th>
</tr>
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<tbody>
<tr>
<td>Incidence of diarrhea [9, 25, 26]</td>
<td>Decrease/increase/no change</td>
<td>Are these differences secondary to pathogen-specific responses to vitamin A? To what extent is this related to measles?</td>
</tr>
<tr>
<td>Incidence of respiratory infections [9, 26, 29]</td>
<td>No change/increase/decrease</td>
<td>Better results with lower nutritional status? Pathogen-specific responses?</td>
</tr>
<tr>
<td>Respiratory severity [29]</td>
<td>Therapeutic: no effect/increase Prophylactic: no effect/increase</td>
<td>Are these differences pathogen-specific? Are these results related to different doses? Lower doses better results?</td>
</tr>
</tbody>
</table>
Further RCTs, possibly with measured vitamin A levels and varying vitamin A doses, may provide sufficient evidence to clarify the role of vitamin A in non-measles pneumonia and other conditions.

**Measles and Vitamin A Supplementation**

A recent review which included eight trials (2,574 participants) revealed that there was no significant reduction in the risk of mortality in the vitamin A group when all the studies were pooled (0.70; 0.42, 1.15), and the pooled estimate from four studies suggested the risk of pneumonia-specific mortality (0.57; 0.24–1.37) was not significantly reduced in supplemented children. However, there was evidence of benefit with two mega-doses of VAS on consecutive days. This approach reduced the mortality in children aged <2 years (0.21; 0.07–0.66) and the risk of pneumonia-specific mortality (0.33; 0.08–0.92); it also reduced the incidence of croup by 41% [32, 33]. It is important to recognize that benefit was demonstrated in hospitalized children aged <2 years, given two doses of VA and in areas where the case fatality rate was greater than 10%. Controversy still remains as to whether these findings could be generalized to populations with high rates of measles immunization (low exposure), with low case fatality rates and in nonhospitalized children.

Apart from its role in decreasing mortality associated with measles pneumonia in children <2 years, the best target population for VAS in respiratory conditions, the best dosage, and the best timing are not clear yet.

**Effect of Vitamin A Supplementation on Vaccine’s Response: Good, Bad, Indifferent?**

The interaction of VAS with different vaccines may vary depending on the immunogen, the host, vitamin A dosage and many other factors. Benn et al. [34] have suggested that VAS could interact with the vaccines by amplifying their nonspecific effects. According to this thesis, VAS would have beneficial effects when administered with live vaccines such as BCG at birth or measles after 6 months of age, but no effect or even negative effects when administered with inactivated DTP vaccine between the age of 1 and 5 months. This hypothesis remains to be tested.

Some relevant findings related to VAS and immunizations are summarized in the following paragraphs.

**Bacille Calmette-Guerin Vaccine**

The effect of VA administered at birth along with this vaccine has been studied in a large (n = 1,894 and 1,426 in final analyses) randomized, placebo-controlled trial in Guinea-Bissau. The percentage of purified protein derivative of
Mycobacterium tuberculosis responders was significantly lower in 2-month-old boys who received VAS than in placebo recipients [35].

**Measles Vaccine**

There is some evidence that the effect of VAS is highly dependent on age at vaccination. One RCT study in Indonesia in which infants received the Schwarz measles vaccine (MV) and either the supplement (30 mg retinol equivalent) or a placebo at 6 months of age reported that supplemented infants had lower seroconversion rates at age 12 months, but only in infants with high levels of specific antibodies before vaccination (titers >8). It was suggested that the combined immune effects of VA and circulating maternal antibodies could neutralize the vaccine antigens [36, 37].

In children >6 months, there have been controversial results regarding the effect of VAS on MV rate of seroconversion or serologic titers. Some RCTs have shown higher seroconversion rates, some higher serum titers and other no changes associated with VAS [38–42]. Contradictory results from these studies may be explained by various factors, including preintervention VA status, age at vaccination and supplementation and hence presence/absence of maternal antibodies, vaccine strain, and antibody serological assays. There is some evidence to suggest that the most important factor responsible for the effect of VAS on MV response is the baseline-specific antibody titers. From a meta-analysis based on 3 studies in which this information was available [36, 42, 43], it was found that VAS was associated with reduced seroconversion rates in children having high baseline antibody levels [OR 0.57; 0.35–0.94]. In contrast, VAS did not affect seroconversion rates in children with low baseline antibody titers [44].

**Diphtheria-Tetanus-Pertussis Vaccine**

Most studies have not shown an improved tetanus-specific antibody response associated with VAS, as compared to controls [45, 46]. However, in an Indonesian study, the oral administration of 200,000 IU of vitamin A to tetanus-naive children 3–6 years of age resulted in significantly higher titers of anti-tetanus toxoid after immunization compared to those in the placebo group. In this study, vitamin A was given 2 weeks before immunization [47].

These controversial results may be related to differences in the VAS timing, basal vitamin A status or other factors that need to be further studied.

A group of researchers in Denmark have raised questions regarding the safety of VA administration with DTP vaccines. Thus, reanalyzing data from a study performed in Ghana, VAS had a negative effect in measles-vaccinated girls who were missing one or more doses of DTP at enrollment, a group who often received DTP during follow-up (mortality RR: 2.60; 1.41–4.80) [48]. The controversy regarding a potential detrimental effect of VA administered with DTP vaccines has led to considerable discussion. The possible negative
interaction is biologically plausible; however, the evidence produced so far is not abundant.

**Polio Vaccine**

VA has no effect on seroconversion to any of the 3 serotypes of poliomyelitis vaccine, although one study has shown a positive effect on seroprotection against poliovirus type 1 [49].

**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 and to inhibit the ability of vitamin D to prevent such demineralization [50]. The effect of supplementing with mega-doses of vitamin A vitamin D-deficient children born to malnourished or not sun-exposed women with a low calcium intake needs to be seriously addressed.

**Conclusions**

There is evidence that VAS in children >6 months of age decreases childhood mortality; however, there is controversy on the relation of the cause-specific protective effect. Could the difference in deaths possibly disappear if measles mortality were excluded from some studies of VAS? Might those in fact be measles deaths? If this is the case, could VAS still have a positive effect in countries with high measles immunization coverage? VAS in newborns and infants <6 months seems not to have a protective effect on mortality; however, there is controversy if newborn VAS could be useful in regions where pregnant women have a high prevalence of VAD. There is evidence to suggest VAS might be beneficial for diarrheal morbidity; however, this is controversial when considering measles comorbidity. Even though there are theoretical reasons that VAS might be effective for acute LRTI, most studies have not supported this concept or even have revealed the opposite. The reasons for these findings are not clear. The modulatory effects of vitamin A in the immune system, its potential interaction with the specific immune responses to different viral/bacterial pathogens, its role in several pathways of disease and the dose effect on disease development/protection remain to be elucidated to understand these complex results. VAS reduces measles mortality if mega-doses are given to children <2 years of age in regions with high case fatality rates. VAS improves immune response to MVs if circulating maternal antibodies are low or absent. There is controversy regarding the interaction between DTP and VAS; a single research group has reported possible adverse interaction; however, there is no conclusive evidence.
References


