Selected Summaries

Vitamin A and Measles Vaccination

[Semba RD, Munasir Z, Beeler J, Akib A, Muhilal, Audet S, Sommer A. Reduced seroconversion to measles in infants given vitamin A with measles vaccination. Lancet 1995, 345: 1330-1332.]

Administration of 100,000 IU vitamin A at the time of measles immunization is currently recommended for infants in developing countries. However, the safety and value of giving vitamin A, a potent immune enhancer, with live measles virus vaccines are unknown. A randomized, double-blind, placebo-controlled clinical trial was conducted in Indonesia to evaluate the effect of simultaneous vitamin A Supplementation on the immune response to measles immunization at 6 months of age.

Three hundred and thirty six infants received either vitamin A (100,000 IU) or placebo when immunized with standard-titre Schwarz measles vaccine. Follow-up rates were 93% and 90% at 1 and 6 months post immunization, respectively. Infants in vitamin A group (n=169) and in the placebo group (n=167) were comparable in their age, maternal age, sex, and anthropometric measurements. Overall 12.4% of infants developed a generalized rash within two weeks of measles immunization. The rash developed in a significantly fewer infants who received vitamin A than in those who received placebo (8.7 *vs* 15.9%, $p<0.05$). Two hundred and fifty one (82%) of 306 infants were seroconverted to measles immunization. There was no significant difference in the seroconversion of children with baseline titres of <1:8. However, in the infants with baseline titre of >1:8, a significant proportion (33.7%) in the vitamin A group did not seroconvert in comparison to 22.8% in the placebo group ($p <0.04$).

A total of 38.2% in the vitamin A group and 22.8% in the placebo group did not have titres consistent with protection (>120) at 6 months post immunization ($p<0.03$), Stepwise multiple logistic regression models were used to examine the impact of vitamin A supplementation, baseline antibody titre, infant age, sex, maternal age and anthropometric measurements on seroconversion in all infants. Baseline antibody titres, vitamin A supplementation, and female sex were associated with a lower likelihood of seroconversion. In a multiple logistic regression model adjusting for maternal antibody titres, vitamin A supplementation was associated with a lower likelihood of seroconversion to measles (odds radio 0.40, 95% CI 0.19-0.88).

It was concluded that immunization with standard-titre Schwarz vaccine at 6 months of age in this study population is characterized by high seroconversion rates. However, simultaneous high dose vitamin A may interfere with seroconversion to live measles vaccine in infants with maternal antibody.

Comments

Vitamin A deficiency in young children is a global problem and since immunization programmes are well advanced in most of the countries where young children are at risk of vitamin A deficiency, a possibility of giving vitamin A supplements to children together with their routine immunization has been seriously considered for over a decade (l). WHO has advocated administration of 100,000 IU of vitamin A at the time of measles vaccination, which is usually given around 9 months of age.

In many developing countries 25,000 IU of vitamin A have been administered with each dose of DPT and Polio in the 6th, 10th and 14th weeks of infancy(2). Gopalan(3), however, has cautioned against this strategy in the absence of sufficient information regarding immunological response to vaccination in such cases as well as the status of their serum vitamin A levels following administration of vitamin A along with vaccination. This study has attempted to investigate and address this issue. Infants of 6 months age with baseline titres of <1:8 seroconverted (irrespective of vitamin A administration) following measles vaccination. Seroconversion was poor in both groups where baseline titres were >1:8, but more so with vitamin A group. The difference was significant even after adjusting for baseline difference in maternal antibody levels between the two treatment groups. The finding that geometric mean titres against measles were lower by 25% at 1 and 6 months after immunization in infants who received vitamin A than those who received placebo may have significant implications as far as longterm immunity against measles is concerned. The status of vitamin A levels in these cases has not been evaluated by the authors.

Immunization with live measles virus vaccine is usually followed by a subclinical infection with the attenuated measles virus and seoconversion to measles. But vitamin A is a potent immune enhancer and has long been known as the 'anti infective' vitamin(4). Immune enhancement by vitamin A may also limit the ability of live vaccine virus to establish a subclinical infection, thus rendering the measles vaccine less effective and contributing to primary vaccine failure. Vitamin A may limit measles infection, irrespective of whether it is due to wild-type or vaccine-strain measles virus (5). In the study under discussion, infants who received vitamin A were less likely to develop a generalized rash after immunization, suggesting thereby that vitamin A may be limiting the replication of vaccine-strain measles virus. But the question which is not clearly addressed is whether it is primarily the time of giving measles vaccination (with regard to titres of maternal antibodies) which is responsible for the disadvantageous immuno-stimulatory effect of vitamin A inhibiting the replication of vaccine virus. Results from this study seem to partly answer this question as the seroconversion was good in infants <1:8 maternal titres irrespective of vitamin A administration. Results of ongoing clinical trials in infants given 25,000 IU of vitamin A along with DPT and polio may also provide further evidence on this subject. Another question which needs to be answered is 'what is the most critical age during infancy when vitamin A stores are depleted'? This would probably help to decide at what age vitamin A prophylaxis (VAP) can be incorporated in the immunization schedule. One also needs to consider the effect of high dose vitamin A on the immune system of young infants with normal vitamin A status. Some of the animal studies and clinical trials have noticed rather adverse effects on humoral and cell mediated immune response to antigenic challenge following high dose vitamin A supplementation and possible effects similar to vitamin A deficiency(6).

Measles and vitamin A deficiency, both top ranking problems in pediatric practice need to be prevented with all possible means. Expecting a child to come to a health facility specifically for VAP does not seem to be practical. Is it feasible to give vitamin A to a child anytime around 6 months of age when he is brought to a hospital for some minor illness? With that policy, do we expect to protect the

vulnerable population at risk? Therefore, a strategy of riding vitamin A supplementation on immunization programme may be most logical approach for most of the developing countries provided that we are sure about the safety and efficacy of this cocktail. This study has clearly highlighted the problem of administering high dose vitamin A at 6 months of age when 206/ 306 infant (67%) had baseline titres of >1:8. In countries where age of measles immunization is around 9 months it remains to be studied if VAP has similar immunological effect on seroconversion in children with significant maternal antibodies. It has been suggested that maternal antibody level at 9 months may still exceed 1:8 in 30% in some populations (2). If VAP reduces the immu-nogenicity of measles vaccination as suggested by authors then one seriously needs to reconsider the wisdom of giving it with measles vaccine. Measles vaccines are one of the most effective single shot interventions to reduce morbidity and mortality on account of a serious childhood illness. VAP is an intervention which requires more than one visit. Therefore we should not shadow the bright prospects of measles vaccination programme, which still has to go a long way to eradicate the disease, with another intervention which may be partially effective but may have some undesirable effect on measles vaccination. The need and logistics of an extra visit to health facility for VAP should be weighed against any negative influence on the measles vaccination even if it is noticed in a small proportion of vulnerable population.

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