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Original Article

The effect of vitamin A supplementation on morbidity due to *Plasmodium falciparum*

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ABSTRACT

Objective To investigate the effect of vitamin A supplementation on malaria morbidity.

Methods The study was a randomized double-blind placebo-controlled trial, conducted in Panyabungan, Mandailing Natal, North Sumatera from April 2001 to April 2002. Children aged 6-60 months suffering from falciparum malaria were randomly assigned to high dose vitamin A or placebo every 4 months for a year. All children were treated in accordance with health center policy. Malaria morbidity was assessed from health center visit due to fever, diarrhea, cough, or abdominal pain. Parents gave reports if their child received malaria treatment from other health centers.

Results The number of febrile episodes (probable malaria illness) was lower in the treatment group than that of control, but not significant. The parasitemia was not different between both groups. There was a significant difference in spleen enlargement between the treatment group and control (p=0.04). There was no difference in health center visit between the two groups.

Conclusion The findings suggest that vitamin A supplementation has only effect on spleen enlargement in malaria. **[Paediatr Indones 2004;44:133-137].**

Keywords: *vitamin A supplementation, morbidity, Plasmodium falciparum.*

Malaria remains a major public health problem in Indonesia.[1] The mortality and morbidity of malaria are still high, especially in infants and under-five children.[2] The high mortality in children is caused by the exacerbation of malaria attacks accompanied with other diseases such as respiratory infections and diarrhea.

Many people living in endemic areas are at risk of having nutrient deficiencies that can impair the development of immunity against *P. falciparum*. Vitamin A is essential for normal immune function and several studies suggested that it could play a role in potentiating resistance to malaria.[4] It had been shown that supplementation of vitamin A can lower the morbidity of some infectious diseases.[5] Shankar *et al*[4] found the effect of vitamin A on malaria episodes and parasite densities in young children. In contrast, a sub study of a vitamin A trial on preschool children in Ghana found no effect of vitamin A on *P. falciparum* morbidity and mortality.[6] The aim of this study was to investigate the effect of vitamin A supplementation on malaria morbidity.

Methods

This study was a randomized double-blind placebo-controlled trial conducted in Panyabungan, North Sumatera Province, from April 2001 to April 2002. The inclusion criteria were age between 6 to 60

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months, planning to reside in study location for at least 1 year, and no ocular sign of vitamin A deficiency or history of night blindness. Children were excluded if they had chronic diseases or debilitating conditions. Consent forms were given and explained to the parents.

Children who came to the health center with complaints of fever, pale, and stomachache were examined to find ocular signs of vitamin A deficiency, axillary temperature by thermometer, spleen size by Hackett grade, height by stadiometer or length by microtoise (for children under 24 months of age), and weight by seca weight scale. Thick and thin blood slides were prepared and 3 ml venous blood was taken for serum hemoglobin level determination. Children who suffered from falciparum malaria, which were confirmed by blood slide examination, were randomly assigned to treatment group (vitamin A) or control group (placebo) in blocks of two (two vitamin A, two placebo). The control group was given placebo (contained honeybee in one teaspoon). Each child in the treatment group was given one soft capsule containing 200,000 IU vitamin A (opened and given in a teaspoon), or half for those younger than 12 months, every 4 months by the investigators. Children received treatment of malaria in accordance with health center policy.

The parents were suggested to go to the local health center if their child had an episode of fever and symptoms of cough, rapid breathing, diarrhea, and stomachache; the nurse would record it in a child clinic book. If the child had an episode of fever, then axillary temperature was recorded. If the temperature was 37.5°C or greater, thick and thin blood smear were performed. At the end of the study, malaria morbidity was assessed.

The primary outcome was the number of malaria episodes in a year, spleen enlargement after the first treatment, and parasitemia after the first 28 days of treatment. An episode of malaria was defined as temperature of 37.5°C or greater followed by clinical manifestations of malaria or by the finding of *P. falciparum* on the slide. The nutritional status was assessed by calculating height for age and weight for height according to the National Center for Health Statistic data reference based on Semiloka Ciloto 1991; χ^2 test was used to find differences in frequency of clinical episodes, parasitemia, and spleen enlargement between the treatment and control groups. The effect of vitamin A on clinical episode, parasitemia, and spleen enlargement was assessed using relative risk and confidence interval. Data were analyzed by means of SPSS version 11.0 computer program.

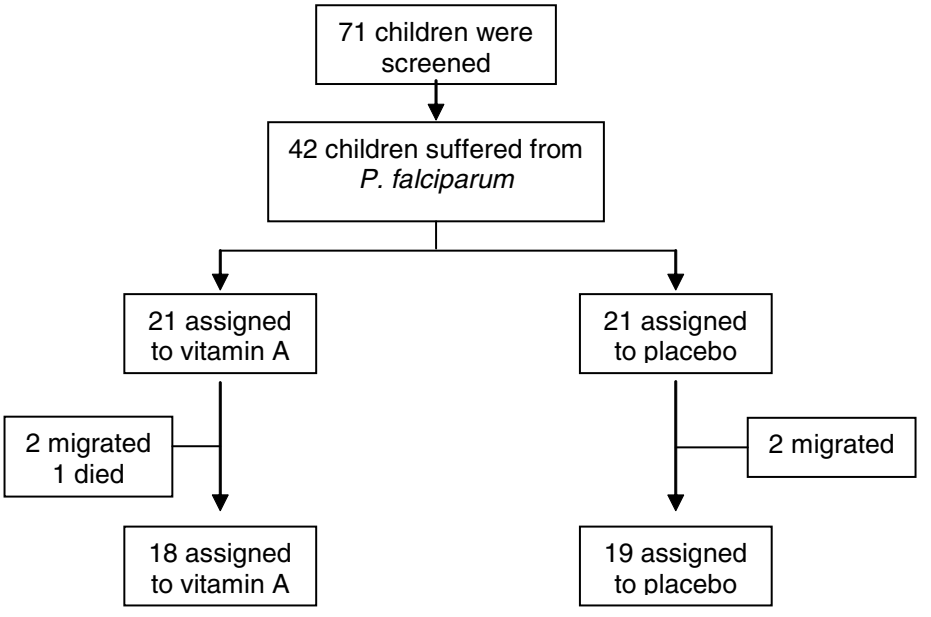

Figure 1. Trial profile

Results

Of 71 children, only 42 children aged 6-60 months had complaints of fever, pale, stomachache, and positive *P. falciparum*. The children were randomly assigned to treatment group (n=21) and control (n=21). No child had a history of night blindness or ocular signs of vitamin A deficiency. Five children were excluded from the study because 4 children left the study area and 1 died. At the end of the study only 19 children in the control group and 18 in treatment group were enrolled.

TABLE 1. SUBJECTS' CHARACTERISTICS

Characteristics	Control n = 19	Vitamin A n = 18
Age (Month)		
6-12	3	9
12-24	3	3
24-36	7	3
36-48	3	2
>48	3	1
Sex		
Male	11	11
Female	8	7
Weight (kg)	10.2	8.6
Height (cm)	76.6	72.7
Nutritional Status		
Good	1	2
Moderate	7	2
Mild malnutrition	9	13
Severe malnutrition	2	1
Hemoglobin (g/dL)	10.5	10.6
Parasitemia	3210.3	1947.8
Spleen enlargement	9	9
Liver enlargement	5	6

Table 1 shows that children in the treatment and control groups had similar baseline characteristics including age, sex, weight, height, and nutritional status. Malariometric indices i.e., hemoglobin, spleen enlargement, and parasitemia were also similar in both groups i.e., *P. falciparum* parasitemia were 1947.8 and 3210.3 respectively; spleen enlargement was found in 9 children in both groups; and hemoglobin concentrations were 10.6 g/dl and 10.5 g/dl, respectively.

Table 2 shows that the clinical manifestations of malaria were fever, pale, diarrhea, and spleen enlargement. There was no difference in clinical manifestations between the two groups (p>0.05).

In **Table 3**, we can see that the frequency of febrile episodes (probable malaria illness) was lower in treatment group than that in control, but not significant. There was no significant difference in parasitemia between both groups. After 28 days of treatment, the parasitemia was negative in both groups. There was a significant difference in spleen enlargement between the treatment group and control (p=0.04). There was no difference in health center visit between both groups.

Discussion

In this study, under-five children suffering from malaria were only 42 children, probably, because the study was done during the low malaria transmission season. It has long been acknowledged that population residing in malaria areas generally live under condition that leads to poor nutritional status.[7] Although the influence of nutrition on malaria is not clear yet,[7] we found that the incidence of malaria was higher in malnourished children. But in this study we did not assess the correlation between nutritional status and malaria.

Several studies had evaluated the effect of high-dose vitamin A every 3 or 4 months on children with falciparum malaria from communities

TABLE 2. CLINICAL MANIFESTATIONS

Clinical manifestations n=18	Control	Vitamin A n=19
Fever	17	18
Pale	12	14
Icteric	0	0
Diarrhea	8	12
Spleen enlargement	9	9

TABLE 3. THE EFFECT OF VITAMIN A SUPPLEMENTATION ON MALARIA AND GENERAL MORBIDITY

Morbidity indicatorControl	(n=19)	Vitamin A (n-18)	RR (95%CI)	p
Febrile episodes	8	5	0.8 (0.5;1.3)	0.49
Parasitemia	0	0	0	
Spleen enlargement	4	0	0	0.04
Health center visit				
Fever	11	10	0.9 (0.5;1.8)	0.57
Cough	8	8	1.1 (0.6;2.0)	0.57
Diarrhea	8	7	0.9 (0.5;1.8)	0.54
Abdominal pain	2	6	2.3 (0.7;8.1)	0.09

where vitamin A deficiency is a public health problem. The results of these studies varied although most pointed to a beneficial effect of vitamin A supplementation.[5] In Indonesia, vitamin A supplementation was given to under-five children every 6 months. In our study, either the treatment group or control had not have vitamin A for 8 months to eliminate the effect of previous administration of vitamin A. The effectiveness of supplementation does not wane during 4-month interval between doses but the effect could wane if the interval doses are longer.[5] Serum retinol has been found to be substantially lower in individuals with malaria than that in healthy ones. The low concentration of serum retinol was probably due to impaired release of retinol from the liver or increased use of retinol by the tissues.[8] Unfortunately, we did not perform serum retinol concentration due to unavailability of the reagent.

In our study the malaria episodes (probable malaria illness) were lower in the treatment group but not significant. Shankar *et al*[4] found the fever episodes were 30% lower in children with vitamin A supplementation than that in control group. Binka *et al*[6] showed that vitamin A had no impact on the rate of probable malaria illness. In this study, the diagnosis of malaria was not confirmed by blood slide. However, no longitudinal surveillance of slide-confirmed malaria morbidity was done.[4]

This study shows that after treatment, the parasitemia was not different between the treatment group and control, however spleen enlargement decreased in the treatment group. The mechanism by which vitamin A affected the reduction of spleen enlargement is unknown. One study in rats found that malaria and vitamin A deficiency acted synergistically in increasing spleen weight.[9]

Vitamin A supplementation in young children had been shown to decrease the mortality and the morbidity of some infectious diseases.[10,11] The effect of vitamin A on diarrhea and respiratory infection had been proved in some studies.[5,10,11] However, our study showed that the general morbidity was not different between the treatment group and control. Several factors may have contributed to these conflicting results. Although our study used control group and was randomized, error was embedded because reported morbidity was only based on recall. Another factor that may partly explain the various results is the different age group of children; some studies were conducted on older children. However, vitamin A alone is not enough to fight against malaria. Again, nutritional status plays a role in immune function and body resistance to diseases.

We concluded that vitamin A has effect on lowering spleen enlargement. However, the results might be interfered by the limitation of sample size, thus further studies with larger number of subjects are needed.

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