A STUDY ON PREVENTION OF VITAMIN A DEFICIENCY BY ANNUAL ORAL MASSIVE DOSE VITAMIN A AND E EMULSION ADMINISTRATION *

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Suatu penyelidikan mengenai pencegahan dan pengobatan penyakit defisiensi vit. A. di Cibatok, Bogor, telah dilakukan dengan menggunakan oral massive dose vit. A. (retinol palmitate) 300.000 I.U. dikombinasikan dengan vit E (a tocopherol acetate) 50 I.U. dl.

Dua group anak-anak umur 1 – 6 tahun dipilih masing-masing sebagai group Experiment dan Control yang hanya diberikan placebo. Sedangkan masing-masing group dibagi lagi menjadi golongan-golongan penderita dan golongan Non vit. A. defisiensi (normal).

Ternyata setelah 6 (enam) bulan kemudian 90 per cent penderita yang mendapat pengobatan menjadi sembuh dan sebaliknya 88.9 per cent dari penderita yang mendapat placebo masih tetap menderita defisiensi vit. A. (table 2)

Table 3. Menunjukkan adanya pengaruh penyakit infeksi G.I. tract terhadap berhasilnya pengobatan dan juga pada umumnya dapat disimpulkan bahwa gizi penderita tidak mempengaruhi pengobatan. Table 4 Kadar Vit. A. didalam darah penderita setelah pengobatan ternyata jauh lebih tinggi dari semula. Sedangkan dalam group yang mendapat placebo tidak terjadi kenaikan.

Dari data penyelidikan tersebut dapat disimpulkan bahwa pemberian oral massive dose kombinasi dari vit. A dan E pada anak-anak sebelum sekolah dapat mencegah, mengobati gejala-gejala defisiensi vit. A. di mata.

Vitamin A deficiency is known to be a problem of public health significance in developing Asian countries. In its acute severe ocular manifestations particularly in preschool children xerophthalmia represents the largests single cause of preventible partial or total blindness and thus has social-economic implications.

Blindness rates are in general around or below 200 per 100.000 population in America and Europe. In developing countries, especially those in Africa and Asia rates are considerably higher and reach values above 1.000. It has also been estimated that half to two third of cases of blindness could have been prevented if they has been detected and treated in time (Boyche, V.S. 1967; Chowdhury, M.J. 1967)

The rate of blindness for East Java was estimated by Ten Doesschate to be ca 250 : 100.000 inhabits (Ten Doesschate, J. 1968), where keratomalacia was shown to be the most frequent cause of blindness in children.

These miserable facts which concern also Indonesia prompted us to undertake systematic invertigations for an immediate practical solution of vitamin A deficiency.

Earlier studies had demonstrated that the administration of oral massive dose of vitamin A 200.000 I.U biannually brought about preventive and curative effects on the vitamin A deficiency lesions and symptons (Darwin Karyadi 1973). Therefore the Ministry of Health of Indonesia has been just launched a pilot program for prevention of xeriphthalmia

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with a coverage of 200.000 preschool children 1 – 4 years of age in Java.

Another study conducted in India by Swaminathan et al. with a sirfgle administration of 300.000 IU vitamin A in oil annually indicate also prophylactive effect, however toxic manifestations were observed in a small proportion or 4% of the children which would affect the succesfull implementation of a public health prevention program.

Green writing on the relationship of vitamin A and E, cites the importance of the sparing effect of vitamin E on vitamin A under certain physiological conditions. Both vitamin A and E influence the structure and function of biological membrances according to Roels et al. Bauernfeind suggested therefore to administration a little vitamin E with the vitamin A to vitamin A deficient subject.

The present study which is still underway reports preliminary of a six months evaluation the preventive effects of an annual oral massive dose of the combination vitamin A 300.000 IU in an emulsion form and describes factors or implications of diseases of high morbidity, especially infectious diseases as conditioners which possibility might interfore the effect of the oral massive dose.

MATERIALS AND METHODS

The study was carried out in a rural village Cibatok about 20 km from Bogor, West Java Indonesia, with an estimated population of 6213 inhabitants from 1206 families of which 1424 were children under 7 years of age.

A preliminary clinical survey were conducted by three paediatricians to assess the health and nutritional status on 754 preschool children 1 – 6 year of age which is randomly samples of the total preschool children. There were detected 133 cases of xerophthalmia or 17.6 per cent of the children study population examined.

The vitamin A deficiency group were divided into two main groups, the first group who received oral massive dose and a matched control received placebo. Another similar socio-economic group of about the same number preschool children serve as parallel control were preschool children without vitamin A deficiency signs and symptoms who received also the oral massive dose and placebo.

Biochemical determinations were done on a basis of subsampling of vitamin A deficiency children and an approximately equal number of apparently healthy non deficient vitamin A children who had served as control group matched by age and sex.

An attempt was made to determine biochemically on the same subject of children at the various time intervals before and after oral administration. The preparation of vitamin A combined E emulsion is presented is sealed vial containing 300.000 IU retinol palmitate and 50 IU dl. α tocopheryl acetate. The vial which contain 3.5 cc is easily opened with a screw driver and ready administration orally without spoon. Before administration the preparation have been checked particularly on the vitamin A content of the emulsion. Prior administration, clinical and biochemical evaluation were conducted. The introduction and distribution were executed by paramedical personels of the City and Regency Health Services of Bogor supervised by the staff. The paramedical personnel assisted by local administrative aides made register and record on the identification of each child. The following parameters were used for evaluation.

I. **Specific** :

a) Specific lesions of vitamin A deficiency signs and symptons by using diagnostic according an International Classification recommended by Ten Doesschate.
Stages of xerophthalmia (as a clinical syndrome) in one or both stages:

X_0 – Only nightblindness present.

X_1 – Conjunctival xerosis with or without nightblindness and with or without Bitot's spots.

X_2 – Corneal xerosis, reversible changes of the corneal epithelium.

X_3 – a. Irreversible corneal changes, leading on to loss or substance, smaller or larger perforations.

b. Rapid softening and destruction of the whole, or large parts of the cornea (Keratomalacia).

X_4 – Seqalae and scars. seqnatal, smaller or larger leucomata, vascularized or pigmented total leucomata, Staphylomas composed of the scarred remnant of the cornea. Pthisis bulbi.

b) Serum vitamin A and carotene levels at the beginning and twice succesive 6 months intervals.

c) Acceptability of the emulsion and possible side effects after administration with a special notice on signs and symptoms of hypervitaminosis A.

II. **General**

Nutritional status assessment by clinical examination including anthropometric measurements by using Quack-stick method (Arnold 1969) assessment for other nutritional deficiency diseases and disease patterns, particularly conditioned infectious diseases. To assess the preventive effect of the oral massive dose the children were classified into 3 groups depending on the presence or absence of lesions of vitamin A deficiency both before and after the study examined. The groups represent the cured, unprotected and protected children as classified according to Swaminathan. The criteria for **cured** - lesions of vitamin A deficiency were present at the first examination but disappeared at the end of the sixth months. **Unprotected** - lesions of vitamin A deficiency were either present or not at the first examination but were present at the end of the sixth months. **Protected** - lesions of vitamin A deficiency were not present at the first examination and continued to be so even at the end of the sixth months.

Ultramicro procedures were used for all biochemical determinations hematocrit was measured in a 1.5 x 7 mm heparinized tube. Hemoglobin was determined with cyanmethemoglobin method. Vitamin A was estimated by the trifluoroacetic acid procedure of Neeld and Pearson. Total serum protein was determined by microbiurte method and the albumin was measured by precipitating the globulin with a solution of 23 per cent $NaSO_4$ (Knight E.M. 1972).

RESULTS AND DISCUSION

The following results obtained will be shown the base line data and preventive effects of the oral massive dose on the clinical and biochemical findings six months after the dose. Due to various reasons, especially the psychologic effects of taking the blood from the children there occured dropout during the reexamination.

Table 1 presents the results of vitamin A deficiency signs and symptons by age and stages. Most of the cases were X_0 and X_1.

Table 1. Vitamin A deficiency cases in age and stages.

Age in year	Number of cases	X_0	X_1	X_2	X_3	X_4
1	4	–	4	–	–	–
2	22	9	13	–	–	–
3	20	5	15	–	–	–
4	35	10	25	–	–	–
5	24	7	17	–	–	–
6	28	5	23	–	–	–
Total	133	36	97	–		

Table 2 shows the curative, protective on preventive effects of the oral massive dose after 6 months.

After the dose the proportion cured was 90 per cent and 10 per cent or 2 cases was still unprotected which revealed suffering from tuberculosis pulmonum. Those simular finding was also been observed in our previous study as one of important conditioners e.q. chronic state of infectious diseases. Next among the other Non deficiency vitamin A. Experiment group all children were 100 per cent protected. The reverse situation was found among the control who received placebo, vitamin A deficiency group 88.9 per cent was unprotected or uncured while there was one case which was cured "spontanously" or naturally, after examining the serum vitamin A and carotene

before and after, this case showed an increase of carotene and vitamin A, which is self explainatory might be due to an increase of dietary caroteneoid intake.

Finally the Non vitamin A deficiency control group showed 100 per cent protected clinical conditions, although their average serum vitamin A levels indicated higher values compared with the vitamin deficient A group especially at the initial levels.

Table 2. The effects of oral massive dose vitamin A after 6 months

Age in year	Experiment						Control					
	Vitamin A deficiency			Non Vitamin A deficiency			Vitamin A deficiency			Non Vitamin A deficiency		
	Number of children	Cured	Unprotected	Number of children	Protected	Unprotected	Number of children	Cured	Unprotected	Number of children	Protected	Unprotected
1	–	–	–	3	3	–	–	–	–	2	2	–
2	1	1	–	2	2	–	–	–	–	1	1	–
3	2	2	–	3	3	–	3	–	3	1	1	–
4	7	6	1	3	3	–	2	–	2	2	2	–
5	5	4	1	–	–	–	2	–	2	2	2	–
6	5	5	–	3	3	–	2	1	1	4	4	–
Total	20	18	2	14	14	–	9	1	8	12	12	–
Percentage		90	10		100			11.1	88.9		100	

Table 3 shows the procentage prevalence of PCM and important associated infectious diseases at the initial and after six months.

- PCM and associated infections which encountered the children, might interfere the effect of the oral massive dose e.g. the absorption during G.I. tract infections etc.
- In general the nutritional status and associated infectious diseases did not show significant differences before and after the oral massive doses comparing the respectively experiment versus the control even so the vitamin A deficiency and the Non vitamin A deficiency group.
- The same was true also concerning the mordibity pattern.

Table 4 demonstrated the biochemical values.

In general the parameters showed no significant differences, except the serum vitamin A values before and after the dose. Using ICNND recommended values in well nourished individuals usually will range between 30 – 50 ug/100 ml, while values ranging between 10 – 20 ug or more values below 10 ug then it should be regarded as a public health problem. Further interpretation of the data showed in Table 4 that in general the serum vitamin A levels at the initial levels are lower among the vitamin A deficiency group (10.8 – 11.2 ug/100 ml) compared with the Non vitamin A deficiency group (± 17.5 ug/100 ml). After the dosing at six months the serum vitamin A values showed a significant increase (p 0.01) particularly among the vitamin A deficiency group. While it is clear shown the control group using the placebo did not show a significant increase, but sustained about the same levels after the dose. The values of the control group should be regarded as a high risk conditions. The carotene levels in general by comparing the experiment and control group before and after the dose there were no dramatic increase except the vitamin A deficient experiment group which indicate that the recent past

Table 3. The percentage prevalence of P.C.M. and important associated infectious disease of children at initially and after 6 months.

Nutritional status and Infectious diseases	Experiment				Control			
	Vitamin A deficiency		Non vitamin A deficiency		Vitamin A deficiency		Non vitamin A deficiency	
	N = 20		N = 14		N = 9		N = 12	
	I	II	I	II	I	II	I	II
0	60.0	65.0	35.7	57.1	33.3	77.7	41.7	58.4
1	20.0	25.0	35.7	7.2	22.3	22.3	16.7	8.3
2	15.0	10.0	21.4	35.7	33.3	–	33.3	8.3
3	5.0	–	–	–	11.1	–	8.3	25.0
4	–	–	7.2	–	–	–	–	–
Infections diseases								
– Upp. Resp. Tract	65.0	65.0	57.1	50.0	88.8	77.7	50.0	91.6
– Lower Resp. Tract	5.0	5.0	–	–	–	–	8.3	8.3
– Gastro Intestinal Tract	15.0	–	14.3	–	11.1	11.1	–	25.0
– Skin	50.0	25.0	–	21.4	–	–	16.6	33.0

Note: I = base line data (Juni 1972), II = after 6 month (Pebruari 1973).

*) = By the quack-stick recommended by Arnhold, 1969 for the quick screening of borderline PCM and moderate severe PCM.
Upper arm = circumference (a Public health Index for protein calorie malnutrition).
0 = international standard or above, which is "fat" or "plumb"
1 = above 85 per cent of international standard, which is not suspected for PCM.
2 = 85 per cent of international standard and below, which is borderline.
3 = 80 per cent of international standard and below, which may be early cases of PCM (as moderate and severe PCM).
4 = 75 per cent of international standard and below, which is definite PCM including kwashiorkor or marasmus.

Table 4. Biochemical blood analysis of vitamin A deficiency and without deficiency after 6 months, oral massive dose vitamin A

Blood components		Experiment						Control					
		Vitamin A deficiency			Non vitamin A deficiency			Vitamin A deficiency			Non vitamin A deficiency		
		N = 19		Differences *	N = 13		Differences *	N = 8		Differences *	N = 17		Differences *
		I	II		I	II		I	II		I	II	
Vitamin A	ug %	11.2 ± 0.6	23.3 ± 1.3	S	17.5 ± 3.2	24.3 ± 2.4	N.S.	10.8 ± 0.6	14.6 ± 2.0	N.S.	17.5 ± 2.5	13.2 ± 2.6	N.S.
Carotene	ug %	16.3 ± 2.10	33.6 ± 2.59	S	28.1 ± 5.4	31.8 ± 3.1	N.S.	21.6 ± 3.9	21.6 ± 2.7	N.S.	15.7 ± 2.3	22.5 ± 4.1	N.S.
Hemoglobin	gr %	10.5 ± 0.22	11.3 ± 0.15	N.S.	9.9 ± 0.37	10.6 ± 0.21	N.S.	10.4 ± 0.36	11.4 ± 0.36	N.S.	10.5 ± 0.29	10.2 ± 0.3	N.S.
Hematocrit	%	36.2 ± 0.46	37.2 ± 0.32	N.S.	35.9 ± 0.46	37.1 ± 0.57	N.S.	37.0 ± 0.7	35.0 ± 1.6	N.S.	36.2 ± 0.5	34.9 ± 0.59	N.S.
Serum protein	gr %	6.6 ± 0.17	6.7 ± 0.11	N.S.	6.5 ± 0.1	6.6 ± 0.1	N.S.	6.2 ± 0.17	6.3 ± 0.20	N.S.	6.5 ± 0.14	6.5 ± 0.09	N.S.
Serum albumin	gr %	3.38 ± 0.12	3.44 ± 0.12	N.S.	3.1 ± 0.2	4.1 ± 0.2	S	3.0 ± 0.18	3.0 ± 0.09	N.S.	3.2 ± 0.06	3.3 ± 0.07	N.S.
Serum globulin	gr %	3.27 ± 0.09	3.28 ± 0.10	N.S.	2.9 ± 0.05	3.1 ± 0.08	N.S.	3.2 ± 0.12	3.0 ± 0.15	N.S.	3.2 ± 0.14	3.3 ± 0.07	N.S.
A.G. Ratio	–	1.05 ± 0.11	1.06 ± 0.03	N.S.	1.1 ± 0.1	1.1 ± 0.02	N.S.	0.96 ± 0.03	1.08 ± 0.06	N.S.	1.0 ± 0.02	1.0 ± 0.03	N.S.

* P 0.01 = Significance
S = Significance
NS = Not significance

dietary intake could be considered unchanged, however there were few cases exceptions especially among the older children consistently higher levels of carotenenoios were sustained. Finally it is important to note that the administration of the oral massive dose in the field occured without any difficulties.

Observations made during the week after the administration by home visits revealed so classical toxic manifestation. The nighblindness or X_0 symptons disappeared reported by their parents usually after 1 – 2 days.

SUMMARY AND PRELIMINARY CONCLUSIONS

Administration of 300 000 IU vitamin A mixed with 50 IU vitamin E in an emulsion form or oral dose had been given to preschool children with the primary objective to prevent xerophalmia.

The preliminary results six months after the administration indicate curative and preventive effects on ocular signs and symptoms of xerophthalmia, increase serum vitamin A levels. Further study is required to know the relationship of a chronic infection such as tuberculosis which might interfore the effect of the oral massive dose.

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