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PREVENTION OF XEROPHTHALMIA BY ORAL MASSIVE DOSE VITAMIN A (A PRELIMINARY REPORT)*

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Untuk menilai efektivitas pemberian vitamin A dosis tinggi (200.000 IU vitamin A dan 40 IU vitamin E) secara masal dalam usaha pencegahan xerophthalmia, dilakukan penelitian terhadap seluruh anak umur 1–5 tahun di tujuh RK kotamadya Salatiga dan lima desa kabupaten Semarang, oleh suatu team ophthalmologi.

Pada pemeriksaan awal ditemukan 132 penderita xerophthalmia diantara 2812 anak (4,7 persen). Kepada 2680 anak yang tidak menderita xerophthalmia sebagian diberi kapsul vitamin A dosis tinggi dan sebagian lain diberi kapsul placebo yang identik, secara "double-blind" diperiksa ulang sesudah enam bulan. Ternyata bahwa 7 diantara 1286 anak penerima vitamin A yang diperiksa (0,5 persen) menunjukkan tanda-tanda xerophthalmia. Sedang diantara 1183 anak penerima placebo yang diperiksa ternyata terdapat 43 penderita xerophthalmia (3,6 persen). Secara statistik bedanya amat bermakna.

Tanda-tanda utama yang ditemukan adalah kombinasi dari buta-senja, xerosis conjunctiva, dan bercak Bitot. Kedua tanda yang terakhir ini terdapat pada 90 persen dari penderita, sedang buta-senja hanya 15 persen. Pada pemeriksaan ulang 132 anak penderita xerophthalmia yang telah diberi kapsul vitamin A dosis tinggi ternyata bahwa 91 persen dari yang diperiksa tidak lagi memperlihatkan tanda-tanda xerophthalmia. Jumlah anak yang tidak dapat diperiksa kembali jauh dibawah angka perkiraan. Sebagian besar karena telah pindah alamat, sebagian kecil meninggal.

Antara golongan placebo dan vitamin, jumlah anak yang tidak dapat diperiksa kembali ini sama besar.

Penelitian ini membuktikan bahwa kapsul vitamin A dosis tinggi efektip sekali untuk mencegah timbulnya xerophthalmia dan menyembuhkan gejala-gejala xerophthalmia ringan.

Vitamin A deficiency clinically expressed by signs of xerophthalmia is considered to be a significant public health problem in Indonesia. The prevalence rates range from 4 to 17 per cent of certain pre-school age population groups. Eye signs related to vitamin A deficiency are also felt to be related with high mortality rates at these ages.

At the WHO Consultation on Prevention of Xerophthalmia in Hyderabad in March 1973, various studies showed evidence suggesting that massive dose of vitamin A resulted in adequate serum levels of vitamin A for up to six months, with the implication that these levels were sufficient to prevent the development of eye signs of deficiency.

Based on these facts, the Government of Indonesia has undertaken a pilot project of distribution of oral massive dose vitamin A to pre-school children in selected areas of Java. Because of the implications of opportunity cost as well as direct costs for personnel and material, it was deemed advisable to concurrently carry out controlled observation on the biological effectiveness of the massive dose capsule in term of availability to prevent the occurrence of clinical eye signs.

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* This paper is presented by Slamet Santoso at the WHO Meeting on the Control of Vitamin A Deficiency, Jakarta November 25—29th 1974.

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Evaluation of both aspects operational and biological aspects of preventive program has been an agreement with the American Foundation for Overseas Blind.

MATERIALS AND METHODS

The sample of children studied consisted of all children aged 1–5 years residing in seven urban kampungs and five rural villages in Central Java, an area where xerophthalmia is known to occur although the exact prevalence was unknown prior to the study.

A preliminary census and registration of all children was performed.

A double-blind prospective experimental/placebo study was designed with determination of xerophthalmia by examination teams at six months interval following an initial baseline examination with removal of cases. The study was intended to demonstrate a 50–70 per cent reduction in point prevalence of xerophthalmia resulted from the administration of massive-dose vitamin A. The sample was calculated accordingly on the basis of an estimated prevalence figure of 7 per cent, with an overage of 56 and 30 per cent for urban and rural respectively to account for possible dropout from mortality, migration, uncooperation, xerophthalmia occuring during the study.

At the initial baseline examination, children with xerophthalmia were treated with vitamin A capsule and removed from the study, although they were observed for response to the capsule. The remainder of the children were numbered and dosed with either vitamin A (200.000 IU vitamin A with 40 IU vitamin E in oil) or placebo in identical capsules, according to their code number. Dosing was repeated at six months interval with eye examination.

Two teams, urban and rural, conducted the examination. Each consisted of an ophthalmologist, two eye nurses, and local administrative aides.

Both teams were under close supervision of a principal investigator.

Those children indicating one or a combinating of signs of night-blindness, conjunctival xerosis, corneal cerosis, Bitot's spot, Keratomalacia were documented as xerophthalmia cases. No member of the team knew before the code was broken which was the experimental and which was the control group.

Examination were conducted at selected points in each village. Clinical examination forms were completed for each child. The forms for identified cases were tabulated for age, sex, diagnostic findings, and site of residence.

RESULTS AND DISCUSSION

The results of initial baseline examination are shown in tables below. Table 1 shows the prevalence rates of 4.5 and 5.2 per cent in urban and rural respectively, with an overall prevalence of 4.7 per cent.

Table 1. Baseline examination: total xerophthalmia cases among examined children aged 12 – 60 months.

	Urban n=1438	Rural n=1374	Total n=2812
Xerophthalmia cases	61	71	132
Prevalence rate percent	4.3	5.2	4.7

Table 2 indicates the number of xerophthalmia cases by age and place of residence. There are apparently more cases in older children.

As shown in table 3 there is an obvious difference in the prevalence rate between boys and girls.

Table 2. Baseline examination: Total xerophthalmia cases by age and place of residence.

Age / Residence	12-24mo n=667	25-36mo n=732	37-48mo n=748	40-60mo n=665	Total n=281
Urban	1	15	24	21	61
Rural	3	9	26	33	71
Total	4	24	50	54	132
Percent	0.6	3.3	6.7	8.1	

At the time of the repeat examination a strong effort was made to locate and examine those children who were initially identified as having xerophthalmia and treated with a massive-dose of vitamin A.

Table 3. Baseline examination: Total xerophthalmia cases by sex and place of Residence.

	Urban	Rural	Total
Boys n = 1409	37	47	84
Girls n = 1403	24	24	48

As shown in table 4 over 90 per cent of those examined were free from signs of xerophthalmia.

Table 4. Results of treatment with massive dose vitamin A: re-examination of xerophthalmia cases six months after baseline.

	Urban	Rural	Total
Total cases	61	71	132
Re-examined	57	61	118
Recovered	49	58	107
Per cent	85	95	91

The results of the repeat examination are presented in tables 5–7.

Table 5 indicates total cases of xerophthalmia in experimental and control group at six months after baseline. Seven cases were found among 1286 children (0.5 per cent) in the experimental group and 43 among 1183 children (3.6 per cent) in the control, the difference of which is highly significant.

The problem of sample size was the major distraction from the study design. As the exact prevalence in the study area was unknown, an estimated rate of 7 per cent was chosen, which was found later to be 4.7 per cent. The dropout from mortality, migration, uncooperation, and xerophthalmia was, on the other hand, much less than the average figure.

The clinical form for recording was found to be too long and detailed. Revision and improvement of this form represents a contribution to further field studies.

As in similar studies, the use of night-blindness unconfirmed by objective testing is a criteria of dubious value. Results of the initial baseline examinations indicated a need for more thorough inter examiner standardization on criteria.

Continuous surveillance of the study population would have been ideal, but was not possible.

Table 5. Repeat examination: Total cases of xerophthalmia six months ater baseline, by place of Residence and study group.

		Experimental	Control	Total
Urban	Xerophthalmia	3	16	19
	Examined	623	599	1222
Rural	Xerophthalmia	4	27	31
	Examined	663	584	1247
Total	Xerophthalmia	7	43	50
	Examined	1286	1183	2469

Table 6. Repeat examination: Total children missed six months after by study group and cause.

	Urban			Rural		
	Expr n=669	Cont n=678	Total n=1377	Expr n=691	Cont n=612	Total n=1303
Mortality	4	6	10	6	6	12
Migration	45	42	87	17	18	35
Uncooperation	27	31	58	5	4	9
Total	76	79	155	28	28	56
			11.2 per cent			4.3 per cent

Table 7. Repeat examination: Important diagnostic findings six months after baseline, by place of Residence.

	Urban n=19	Rural n=31
Nightblind	3 16 percent	4 13 percent
Conjunctival dryness, wrinkling, thickening	18 95 percent	30 97 percent
Bitot's spot	16 84 percent	31 100 percent

Although children found to have xerophthalmia were observed for the results of vitamin A treatment on the eye signs, there was no accumulation of detailed biologic and sociologic data on these children and their families. Such data might

be useful in assembling a protile of children at risk for xerophthalmia.

The development of an effective and efficient program depends on the understanding of the epidemiological aspects of the problem being attacked. Prevention of blindness a related to vitamin A deficiency has consisted of secondary prevention, i.e. the recognition of certain eye signs thought to be precursors of events which impair vision, and therapy with vitamin A to prevent such progression. Primary prevention would consist of assuring adequate intake and stores of the vitamin in population at risk.

For the purpose of this study, the assumption was made that xerophthalmia stands clearly within the spectrum of biological change denoting vitamin A deficiency, and that persons with xerophthalmia are at higher risk than others of progressing in some fashion to visual impairement including blindness.

Theoretically, the prevention of the lesser stages of xerophthalmia is well correlated with prevention of blindness. By stating this, it is meant that the present study measures the effect of vitamin A in preventing xerophthalmia, and only indirectly to the extent that xerophthalmia is in fact a precursor of blinding disease, its effect in preventing blindness.

The decision to base the study in observation of eye signs represents a compromise, in light of more recent data on serum levels of vitamin A. Serum studies are more objective than the rather subjective clinical examinations, but have also been difficult of interpretation, at least until studies of liver stores began to clarify the physiology of vitamin A and its pharmacodynamics. The highly significant difference between incidence in the experimental an control group suggest that oral massive-dose of vitamin A in oil is indeed effective in preventing clinical signs of xerophthalmia.

Although further studies are needed to elucidate the relationship between clinical signs and biochemical events, it is hoped that these data will be useful to decision makers contemplating preventive programs.

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