ORIGINAL ARTICLE

Clinical and Head Ultrasound Findings in Neonates after Administration of High Dose of Vitamin A

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ABSTRACT Vitamin A deficiency is a major cause of blindness and severe morbidity and mortality in young children. Supplementation of vitamin A in the community might reduce child mortality rates. The safety of high dose of vitamin A administered to neonates is not clear. We randomized 2058 neonates to receive either a single dose of 50 000 IU oral vitamin A (n=1031) or placebo (n=1027). Bulging fontanel and head circumference were assessed before and throughout 48 hours following dosing. Cranial ultrasound examination was carried out in 972 infants before and 24 hours after dosing to rule out intracranial hemorrhage and determine resistive index (RI) of the anterior cerebral artery. Slight bulging fontanel occurred in 2.7% and 4.4% of the infants at 24 hours. Moderate bulging fontanel was seen in 0.1% of study group, no severe bulging was observed. At 48 hours slight bulging fontanel was observed in 2.4% of control group and 4.5% in study group. No intracranial hemorrhage was found. Mean RI values were normal in both groups at baseline or 24 hours. Bulging fontanel was not associated with increased signs or symptom, or with increase in RI. Single oral dose of 50 000 vitamin A may cause a small increase in intracranial volume in a small proportion of infants, without increase in intracranial pressure. **[Paediatr Indones 1994;34:197-208]**

Introduction

Vitamin A deficiency is the leading cause of blindness[1] and a major cause of severe morbidity and mortality among young children in the developing world.[2] A recent meta-analysis of eight controlled trials estimated that community-wide vitamin A supplementation resulted in an average 23% reduction in child mortality rates.[3] Accordingly, signatory nations of the 1982 World Declaration and

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Plan of Action for Nutrition have pledged to eliminate vitamin A deficiency by the year 2000.[4]

The literature on vitamin A toxicity in infants consists of case reports and small series, dating mostly before 1970. One of the most informative of these reports on acute hypervitaminosis A is that of Marie et al.[5] They reported 4 cases of infants aged 2 to 7 months who received single large vitamin A of 300 000 to 350 000 IU. They came under medical care for symptoms of irritability, lethargy, and vomiting within 24 hours of dosage. They received supportive care and observation, had all improved by 48 hours, and completely resolved by 72 hours. In addition, on six infants less than six months of age, a clinical trial of vitamin A administration (350 000 IU once) was undertaken. Only three out of these six infants became symptomatic, and further study showed lumbar puncture opening pressures of 15-23 mmHg. in comparison to 11-23 mm Hg in healthy infants served as control. All symptoms resolved in this study population. The investigators commented that a dose of 70 000 IU was tolerated in this study group with no neurologic signs or symptoms. No long-term follow-up was reported.

Another study by Toomey reported the case of chronic hypervitaminosis A in an infant who had multiple symptoms, including irritability and macrocephaly. After discontinuing the vitamin A intake, his neurologic symptoms disappeared, and by 1 year his growth and development were normal. No cases of death or permanent disability due to neurologic injury from hypervitaminosis A have been reported.

The mechanism of vitamin A-induced neurologic symptoms is unknown. The clinical picture in adults and children in the literature is compatible with cerebral pseudotumor. This disorder causes increased intracranial pressure without abnormalities in the structure of the brain or composition of CSF. If untreated it results in blindness due to papiledema and optic atrophy, and symptomatically associated with headache, mild lethargy or irritability, and occasionally cranial neuropathies. It is usually treated by reducing CSF volume (acutely by lumbar puncture, and chronically by surgery or drugs) and by removal of suspected causative agents.

A major constraint in establishing vitamin A supplementation program for infants is the paucity of data demonstrating safety. This trial was conducted to detect potential acute side effects (neurologic aspects) among newborn infants given one 52 μmol oral dose vitamin A.

Methods

The study was carried out at Hasan Sadikin Hospital in Bandung, West Java, a large public referral hospital serving the urban and surrounding rural area.

Safety Trial

All infants born at Hasan Sadikin Hospital from June 18, 1992 through June 2, 1993 were considered for enrollment. To aid in interpretation, infants unlikely to survive in the absence of medical care were excluded. These included infants with birth weights of less than 1500 g, those with severe respiratory distress

syndrome, major congenital anomalies, paralysis, hypoglycemia (< 1.66 μmol/L), hypocalcemia (< 2.0 μmol/L), clinical evidence of ischemic hypoxia (5 minute APGAR scores < 7 which did not improve by 24 hours), or clinical evidence of sepsis (hypothermia which did not resolve within 24 hours). The first 819 infants were restricted to infants > 2500 g. Following an interim review by a Data Safety and Monitoring Committee, smaller infants were enrolled in two stages: infants with birth weights between 2000 and 2500 g were included beginning on December 7, 1992; infants with birth weights between 1500 and 2000 g were included beginning on January 25, 1993. Fever (temperature > 37.5°) was initially an exclusion criterion, but was dropped on January 25, 1993. Similarly, 5 minute APGAR scores less than 7 was initially an exclusion criteria, but on January 25 we began enrolling these infants if their status improved by 24 hours. Enrollment was limited to infants of birth weights 1500 to 2500 g between May 15 and June 1, 1993, to increase the sample size of that birth weight stratum. Of the 2844 live births occurring between June 18, 1992 and June 2, 1993 which met birth weight criteria in force at the time, 2058 infants (72%) were successfully enrolled. Those not enrolled either met one or more medical exclusion criteria or did not give consent.

Following written informed consent, baseline examination was carried out by one of 12 study nurse midwives and on of four study pediatricians. Physicians and nurse examinations were carried out independently. A unique identifying number was assigned to each infant and written on a bracelet worn by the infant throughout the study.

Nurse midwives palpated the anterior fontanel. The historian was the care giver of the infant during the period between baseline and birth (either the mother if the infant was roomed-in, or the staff nurse for infants in the nursery). The fontanel was graded as normal, or having a slight, moderate, or severe bulge. Demographic data, obstetric information, APGAR scores, and birth weight and length were taken from medical records.

The physician also palpated the anterior fontanel, grading it as normal or having a slight, moderate, or severe bulge, and made three repeated measures of head circumference. Midway through the trial, inter- and intraphysician error in head circumference measurement was assessed among the 4 study pediatricians. Each pediatrician independently measured the head of the same 20 babies 3 times on the same day. Of the total variability, 0.03% was due to differences within physician, 0.30% to differences between physicians, and 99.6% to differences between infants.

The first 972 infants underwent a cranial ultrasound study to rule out intracranial hemorrhage, and a duplex Doppler examination of the anterior cerebral artery to determine the resistive index (RI). Each infant was examined in standard coronal projection through the anterior fontanel using a high-resolution unit equipped with a 5 MHz sector transducer for imaging, and Doppler studies (ACUSON 128 XP, Mountainview, CA). Every infant was examined with the head in midline position in order to avoid alterations in intracranial

venous drainage and intracranial pressure (ICP). The pericallosal artery (a branch of the anterior cerebral) was identified with color Doppler and the range gate was placed over the artery as it coursed anterior to the genu of the corpus callosum. The RI is a relative measure of cerebral vascular resistance and is an indirect indicator of intracranial pressure.[7] It was calculated automatically by the ultrasound unit as follows: The RI was determined on three representative Doppler waveforms using a built-in spectrum analyzer. The mean of the three values was reported. All examinations were performed at power output settings less than those recommended in current FDA guidelines (< 94 mW/cmPT2PT).[8] The estimated maximum in situ SPTA (spatial peak temporal average) intensities in water were < 94 mW/cm^2 during color and pulsed Doppler mode.

All ultrasound studies were recorded on video cassette tape. Examinations for the first 295 infants and a randomly selected 82 additional infants were reviewed by a specialized pediatric radiologist (GAT) who was unaware of the treatment group, interpretation of the ultrasound study by the study pediatricians, or clinical signs and symptoms experienced by the infant. The purpose of the review was to determine if the correct artery (the anterior cerebral) had been studied; to confirm the presence or absence of intracranial hemorrhage; to detect ventricular dilatation; to evaluate the quality of the sonographic images (good, poor, or none obtained); to evaluate the quality of the wave forms achieved by the duplex Doppler for calculation of the RI (acceptable or poor); and to confirm the representativeness of the three waves forms selected for RI determination.

Following baseline examination, infants were randomly allocated to receive one oral dose of 52 μmol vitamin A (as retinyl palmitate) + 23 μmol vitamin E (as dl-alpha-tocopherol), or placebo (< 0.10 μmol vitamin A + 23 μmol vitamin E). The supplementation was administered directly into the infant's mouth by a study nurse. Capsules were analyzed throughout the study. The dose administered to the first 383 of the 1031 infants in the vitamin A group averaged 62 ± 6 μmol (59 449 ± 5 700 IU). Contents of the capsules given to the remaining 648 infants had the average of 53.7 ± 0.08 μmol (51 234 ± 78 IU).

Morbidity histories were repeated by study nurses at the end of each nursing shift and at 12, 24, and 48 hours post-dosing from the care giver of the infant for the prospective period. Measurement of the anterior fontanel was also repeated by the nurse 12, 24, and 48 hours after dosing. Physician's examinations were repeated 24 and 48 hours post-dosing. Our protocol stipulated that ultrasound examinations be repeated at 48 hours if the 24 hour examination was abnormal; no infant required a 48 hour examination.

Group differences were tested by t-test for continuous variables; differences in proportions were tested by X^2 or Fisher's exact test as appropriate. Anova was used to compare means of more than two groups.[9] Agreement between nurse and physician fontanel examinations was evaluated by the Kappa statistic.[9]

Results

Groups were comparable in all baseline characteristics (Table 1). The mean age at dosing was 16.1 hours and 16.3 hours in the control and vitamin A groups, respectively; 88% of infants were dosed within the first 24 hours of life. Groups were similar in maternal age and parity.

At baseline, we identified 13 cases in the control group and 3 cases in the vitamin A group with slightly bulging fontanels (Table 2). There were excess rates of slightly bulging fontanel at 24 and 48 hours 1.8% and 2.1% respectively in the vitamin A group.

Among infants in the vitamin A group, all 46 cases with bulging fontanel at 24 hours represented incident events; none had been bulging at baseline. Of the 46 cases at 48 hours 15 (32.6%) were persistent from 24 hours and 31 (67.4%) were incident.

Among infants in the control group, 25 (69.3%) of the 28 cases with bulging fontanel at 24 hours were incident cases; 8 (17.4%) persisted to 48 hours. Thus, 17 of the 25 cases at 48 hours (68.0%) were incident.

Mean head circumference in the two groups was virtually identical at each examination (Table 3). Differences in the proportions of infants with an enlarged head circumference (> 0.5 - < 1.0 cm) within each 24 hour period were small and insignificant: 4.0% versus 5.2% (p = 0.22) between baseline and 24 hours; 5.8% versus 6.8% (p = 0.40) between 24 and 48 hours for the controls and vitamin A groups, respectively. During both 24 hours intervals, the slight excess in enlarged head circumference in the vitamin A group was confined to the 0.5 to 1.0 cm increase category. The two treatment groups had nearly identical rates in the more severe category of > 1.0 cm increase. Fewer than 10 infants were judged to be irritable by the pediatricians at any examination and there were no differences between treatment groups (data not shown).

Hemorrhage was not detected by ultrasound examination in any infant at baseline or 24 hours post-dosing (Table 4). One infant had a hemorrhage at baseline, and was excluded from the trial. The mean RI at baseline was 70.6% and 70.4% in the control and vitamin A groups (Table 5), respectively [reported RI values for healthy term infants 70% (range 60-80%)].[7,10] At 24 hours, the mean RI had fallen to 68.4% and 68.3% in the control and vitamin A groups, respectively. There was no treatment group difference in the mean change between baseline and 24 hours ultrasound studies were reviewed by the pediatric radiologist, 184 were in the vitamin A group, and 191 in the control group. Three of these infants had a bulging fontanel at baseline and 6 had a bulging fontanel at 24 hours. The anterior cerebral artery was correctly studied in 353 (94%) of the baseline studies. The errors made were balanced between treatment groups (p = 0.54). Among the 24 hour ultrasound studies which were reviewed, the anterior cerebral artery was correctly studied in 90% of the cases. There was again no difference between treatment groups in which artery was studied (p=0.47). The arteries studied in error were internal and middle carotid and branch of the anterior cerebral artery. These arteries

Table 1. Baseline characteristics by treatment group (n = 2058 cases)

Characteristic	Group	
	Control (n = 1027)	Vitamin A (n = 1031)
Male (in %)	530 (51.6)	542 (52.6)
Birth weight (g)(mean, SD)	3006.6 (430.4)	3002.6 (436.2)
Birth length (cm)(mean, SD)	48.3 (1.9)	48.4 (1.9)
Gestational age (in %)		
< 38 weeks	56 (5.4)	66 (6.4)
38-42 weeks	971 (94.6)	964 (93.5)
> 42 weeks	0 (-)	1 (0.1)
Appropriateness of weight for gestational age		
AGS [n (%)]	946 (92.1)	948 (92.0)
SGA [n (%)]	55 (5.4)	50 (4.8)
LGA [n (%)]	26 (2.5)	33 (3.2)
5-minute Apgar score (mean, SD)	9.0 (0.5)	9.0 (0.4)
Maternal age (yrs) (mean, SD)	27.3 (5.5)	27.5 (5.9)
Maternal parity (mean, SD)	2.4 (1.8)	2.4 (1.8)

Table 2. Status fontanel by treatment group[a]

Fontanel [n (%)]	Baseline		24 hours		48 hours	
Bulging Fontanel (physician exam)[a]	Control (n=1027)	Vit.A (n=1031)	Control (n=1027)	Vit.A (n=1031)	Control (n=1026)	Vit.A (n=1030)
Slight	13 (1,3)	3 (0,3)	28 (2,7)	45 (4,4)	25 (2,4)	46 (4,5)
Moderate	0 (-)	0 (-)	0 (-)	1 (0,1)	0 (-)	0 (-)
Severe	0 (-)	0 (-)[b]	0 (-)	0 (-)[c]	0 (-)	0 (-)[b]

[a] : Missing 1 case in control group at baseline; [b] : Groups significantly different, $p \leq 0.01$;
[c] : Groups significantly different, p = 0.05

Tabel 3. Head circumference and head circumference change by treatment group

Head circumference	Baseline		24 hours		48 hours	
	Control (n=1027)	Vit.a (n=1031)	Control (n=1027)	Vit.a (n=1031)	Control (n=1026)	Vit.a (n=1030)
Head circumference x cm (sd)	33.3 (1.3)	33.3 (1.3)	33.2 (1.3)	33.3 (1.3)	33.3 (1.3)	33.3 (1.3)
Head circumference changed	Base line to 24 hr		24-48 hours		Baseline to 48 hrs	
> 0.5 cm < 1.0 cm	21 (2.0)	37 (36)	41 (4.0)	54 (5.2)	59 (5.8)	70 (6.8)
> 1.0 cm	18 (1.8)	14 (1.4)	18 (1.8)	15 (1.6)	19 (1.9)	20 (1.9)

[d] missing 1 case in each group at 24 and 48 hours.

Table 4. Intracranial hemorrhage using duplex Doppler by treatment group

Intracranial hemorrhage [n (%)] [a]	Baseline		24 hours	
	Control (n=488)	Vit. A (n=484)	Control (n=481)	Vit. A (n=483)
Absent	488 (100)	484 (100)	481 (100)	483 (100)
Present	0 (-)	0 (-)	0 (-)	0 (-)

[a] Ultrasound studies were limited to 488 and 484 infants at baseline and 481 and 483 infants at 24 hours in the control and vitamin A groups, respectively.

Table 5. Resistive index using duplex Doppler by treatment group

Resistive index [a]	Baseline		24 hours	
	Control (n=488)	Vit. A (n=484)	Control (n=481)	Vit. A (n=483)
X (%) (SD)	70.6 7.1)	70.4 (6.8)	68.4 (6.4)	68.3 (6.8)
X - baseline			- 2.2	- 2.2
- 24 hours (SD)			(7.9)	(8.1)

[a] Ultrasound studies were limited to 488 and 484 infants at baseline and 481 and 483 infants at 24 hours in the control and vitamin A groups, respectively.

Table 6. Mean resistive index (RI), mean change in RI, and proportion of infants with increased resistive index by treatment group and fontanel status at 24 hours

Treatment Group	Fontanel status at 24 hrs (n)	Baseline RI (X, SD)	24 hour RI (X, SD)	X RI (X, SD)[a]	n (%) with Baseline RI Baseline RI
Placebo	Normal (471)	70.5 (7.1)	68.4 (6.4)	-2.1 (7.9)	185 (39.3%)
	Tense (11)	75.2 (6.7)	68.6 (6.1)	-6.7 (8.7)	2 (18.2%)
Vitamin A	Normal (461)	70.3 (6.8)	68.2 (6.8)	-2.2 (8.1)	190 (41.2%)
	Tense (22)	72.7 (6.3)	71.1 (6.1)	-1.6 (7.3)	9 (40.9%)

[a] : value (ANOVA) = 0.30.

have been demonstrated to have very similar RI values compared to the anterior cerebral.[7,10] The quality of the wave forms graded acceptable in 98% of the baseline studies and in 97% of the 24-hour studies. The quality of the sonographic images obtained for ruling out hemorrhage was graded good in 97% of baseline and 24-hour studies. The absence of intracranial hemorrhage was confirmed in all studied. No ventricular dilatation was observed in any infant, including those with bulging fontanels. The reviewer agreed with all wave forms selected for calculation of the RI in all ultrasound studied from both groups at both examinations.

A bulging fontanel suggests an increase in intracranial fluid volume which is not necessarily associated with an increase in intracranial pressure (ICP).[11] To assess the relationship between the clinical findings of the fontanel and intracranial pressure, we compared RI values and rates of clinical signs and symptoms for infants who did and did not develop a bulging fontanel (Table 6). Resistive index data were available in 33 of the 74 infants with bulging fontanels at 24 hours. The mean reduction in RI during the 24 hours after dosing was slightly less (NS) among infants in the vitamin A group who developed a bulging fontanel compared to infants with normal fontanel examinations at 24 hours in the vitamin A and placebo groups. The proportion of infants who experienced an increase in RI during the 24 hours after dosing was not different among infants who developed a bulging fontanel 24 hours following vitamin A compared with infants who had normal fontanel examinations following vitamin A or placebo. Similarly, presence of a bulging fontanel was not associated with higher rates of any sign or symptom assessed at any time during the 48 hour period after dosing. Odds ratios were not different from 1.0 for developing irritability, vomiting, loose stools, or fever among infants who developed a bulging fontanel at 24 or 48 hours compared to infants whose fontanel examinations were normal (data not shown).

A total of 197 (97 and 100 in the control and vitamin A groups, respectively) low birth weight (< 2500 g) infants were included in the study and evaluated separately. Three infants (1 control, 2 vitamin A) had slightly bulging fontanels at 24 hours; at 48 hours 1 infant in the control group and not in the vitamin A group had a bulging fontanel. Within the sample size constraints there was no evidence that low birth weight or premature infants were at any greater risk of developing a bulging fontanel. Ultrasound data was available for only 18 low birth weight infants at baseline, and for 16 at 24 hours. Mean RI values did not differ between groups at baseline (73.1% vs. 70.8%, p=0.46) or at 24 hours (71.7% vs. 72.2%, p=0.92) for control and vitamin A groups, respectively. Compared to term infants, reported RI values for low birth weight infants were higher and more varied (i.e., 78%, range: 50-100%).[7,10]

Of the 234 infants in whom a home visit was attempted three weeks after dosing, 228 (97.4%) were successfully examined. Mean weight gain over the period did not differ between groups (22.3 g/day versus 23.8 g/day for control and

vitamin A groups, respectively, p=0.45). This approximates the 25th percentile rate of growth of a reference sample of American children.[12] All infants were alive at the time of the visit.

Discussion

Bulging of the anterior fontanel was the only side effect which occurred at a significantly higher rate following a 52 μmol oral dose of vitamin A compared to placebo. Bulging fontanels have been commonly reported in infants following large doses of vitamin A.[6,13-18] The mechanism is poorly understood. Ironically, in pigs,[17] vitamin A toxicity results in decreased ICP. Nonetheless, these animal models provide clues to the human process. Free vitamin A (not bound to RBP) can penetrate the central nervous system (CNS)[20] where it apparently alters capillary permeability of the arachnoid villi (the site of cerebral spinal fluid resorption).[19] Others have speculated that changes in the cellular integrity of the choroid plexus tissue (the site of CSF formation) may result in an over-production of CSF.[21] Interestingly, in humans, increased ICP can also result from vitamin A deficiency.[19]

While the details remain obscure, vitamin A apparently affects the integrity of the membranes responsible for resorption and/or formation of CSF, so that CSF volume increases in humans during both deficiency and toxicity of vitamin A. The human cranium can accommodate a range of CSF volumes without changing intracranial pressure.[23] In infants, perhaps because sutures and fontanels are open, even larger increases in volume can be accommodated in the cranium before pressure increases.[24] When CSF volume increases beyond the compliance of the cranium, intracranial pressure increases with concomitant neurologic symptoms such as vomiting and irritability.

In our study, bulging fontanel was not associated with increased rates of any morbidity assessed at any time throughout the period of follow-up. In addition, we used duplex Doppler cranial sonography as a non-invasive indicator of intracranial pressure. Several authors have shown a strong linear correlation between RI and increased intracranial pressure.[7,25-27] Mean RI values were remarkably similar for infants in the control and vitamin A groups and were consistent with reported values of normal infants. RI values over 100% represent back flow of arterial blood during diastole, of ten as a result of increased cerebrovascular resistance. No infant in our study had an RI value over 87%, even those who developed bulging fontanels and those with low birth weights. In addition, RI values normally fall quickly as infants mature.[28] We observed this fall in RI between the infants first and second days of life, and the mean decrease was nearly identical for the vitamin A and placebo groups. Even among infants who developed a bulging fontanel by 24 hours after dosing, the mean change in RI for the same time period was negative.

These findings suggest that while intracranial volume may have increased due to the vitamin A, the compliance of the neonatal cranium was sufficient to

prevent an increase in pressure. Furthermore, even the increased intracranial volume experienced by the infants following 52 μmol vitamin A was rare and modest.

All but one of the bulging fontanels were graded as "slight" and the proportion of infants with increases in head circumference of > 0.5 cm in a 24-hour period were similar following vitamin A or placebo.

The literature contains reports of at least 13 infants who were 4 months of age or less at the time of exposure to total doses of vitamin A ranging from 314 μmol (300 000 IU) to 750 000 IU administered over the periods of 1 day to 9 months.[6,13,15,16] All presented bulging fontanels and all but one[13] had concomittant neurologic and other toxic signs and symptoms including vomiting,[6,14,16] irritability,[14,16] skin and skeletal lesions.[14,15] In all infants symptoms resolved completely on cessation of the vitamin. Five of these infants were developmentally assessed at 3 1/2 to 5 years of age and found to be normal.[14,15] Two underwent psychological testing at 4 years of age and found to have above average intelligence with no evidence of organic brain disease.[15] Although not conclusive, the apparent absence of long term neurologic sequels in cases of severe vitamin A toxicity clearly accompanied by increased ICP is reassuring in interpreting the clinical significance of the cases of bulging fontanel in this study in which there was no evidence of increased ICP.

Neonatal dosing may offer several benefits. Infants normally accrue stores of vitamin A during lactation.[29] However, the milk of women living in areas where vitamin A deficiency is endemic, while sufficient in preventing xerophthalmia during lactation, may be insufficient to allow the infant to build necessary stores.[29] Infants who are not breast fed are at greatest risk of developing severe vitamin A deficiency.[30] Accordingly, supplementation of neonates consuming vitamin A-poor breast milk, or not breast fed at all, may promote accrual of vitamin A stores in preparation for weaning when an adequate vitamin A-rich diet is often lacking.

Thanangkul demonstrated that provision of a 52 μmol dose at birth maintained higher circulating retinol concentrations for 7 1/2 months compared to placebo controls.[31]

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