Vitamin A Status in Premature Infants

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Abstract

Background : Premature infants are at risk of vitamin A deficiency due to inadequate transplacental transport, inadequate storage and increased tissue utilization. Previous studies reported a significant decrease in serum vitamin A levels in premature infants at birth compared to those of full term infants.

Objective : To determine serial changes of plasma vitamin A status during the first month of life in 19 healthy, very low birth weight premature infants.

Method : Subjects were fed with premature infant formula and received multivitamin supplementation. Plasma vitamin A concentrations were measured at 7, 14, and 30 days of age.

Results : Plasma vitamin A levels at 7,14 and 30 days of age were 24.63 $\pm$ 6.08, 30.97 $\pm$ 5.26 and 30.68 $\pm$ 7.14 μg/dl, respectively. Plasma vitamin A levels at age 7 days were significantly lower than those at 14 and 30 days of life ($p<0.001$). Three infants out of 19 (16%) had low plasma vitamin A (<20 μg/dl) at 7 days. At 14 and 30 days of age, all infants had normal plasma vitamin A levels.

Conclusion : The results suggested that healthy premature infants were prone to subclinical vitamin A deficiency during the first week of life which could be treated by adequate enteral feeding and routine multivitamin supplementation. A high dose of vitamin A supplementation was not necessary in healthy premature infants.

Key word : Vitamin A, Premature Infants

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Vitamin A is essential for vision, growth, epithelial cell integrity and immunity[1-3]. Vitamin A deficiency increases the risk of common childhood infection and may promote chronic lung disease in low-birth-weight infants by impairing lung healing, increasing the loss of cilia, increasing squamous cell metaplasia, increasing susceptibility to infection and decreasing the number of alveoli[2,4-6]. Supplementation of vitamin A in children has been shown to reduce morbidity and mortality[7]. A meta-analysis of vitamin A supplementation for premature infants without chronic lung disease revealed a 17 per cent increase in the survival rate[5,8-11]. Tyson et al indicated that one additional infant survived without chronic lung disease for every 14-15 infants who received 5,000 IU vitamin A supplementation[3]. Brandt et al reported that at birth serum vitamin A level was significantly lower in preterm infants than that of full term infants[1]. Many reports have stated that plasma retinol concentrations in premature infants are lower than those of term infants[12-14]. In addition, lower liver vitamin A concentrations were found in infants of ≤1,500 grams birth weight who died within 24 hours of birth[15].

Premature infants are dependent on daily supplies of vitamin A through breast milk or premature infant formula and multivitamin supplementation. Shenai et al observed that the effective and safe dose of vitamin A in premature infants was 2,000 IU/kg/day[5]. The purpose of this study was to determine changes in vitamin A status during the first month of life. This information is essential for considering the necessity and the optimal dosage of vitamin A supplementation in healthy premature infants.

SUBJECTS AND METHOD

The study group consisted of 19 preterm infants born at Ramathibodi Hospital and admitted to the Special Care Nursery. The inclusion criteria were premature infants, gestational age ≤36 weeks, birth weight ≤1,500 grams, APGAR score 10 at 5 minutes and without oxygen support. The exclusion criteria were hematocrit <40 per cent or hemoglobin <13 g/dl, major congenital anomalies, congenital infection and malabsorption. All subjects were fed with premature infant formula and supplemented with multivitamins. The initiation of enteral feeding ranged from the second to sixth day and multivitamin supplementation was given on the seventh day of life. Maternal disease was not considered in the selection of subjects and information on maternal nutritional status or vitamin supplementation was not obtained. Parental consent was obtained prior to the study after full explanation of the purpose.

A sample for vitamin A assay was collected from peripheral venous blood. All samples were protected from direct exposure to light by wrapping all test tubes with aluminum foil to prevent photodestruction of vitamin A. The plasma was separated by centrifugation, pipetted into foil covered plastic tubes and kept at -30°C. Plasma was extracted with hexane in the dark room using dyed dark brown glass test tube. Samples were analyzed in duplicate with retinyl acetate as internal standard and control sera were analyzed with every batch of samples. Plasma retinol (μg/dl) was analyzed by HPLC according to the procedure of International Vitamin A Consultative Group (IVACG)[16].

Statistical analysis

Values were expressed as mean ± SD and statistical differences were calculated by ANOVA with repeated measurement and multiple comparison by SNK test. Significant level was set at $p<0.05$.

RESULTS

The mean gestational age and birth weight of the subjects were 32.2 ± 1.9 weeks and 1,332.2 ± 156.4 grams, respectively. The age when enteral feeding was started ranged from 2 to 6 days. The premature infant formula and multivitamin supplementation provided 390 IU/100 kcal and 450 IU/day of vitamin A, respectively.

The mean values of intake of vitamin A, protein and energy are shown in Table 1. Within the first week of life, the mean values of vitamin A, protein and energy intake were low. By 14 and 30 days, these enteral intakes increased significantly to normal levels. The clinical characteristics of the subjects are shown in Table 2. The mean values of plasma retinol for 19 preterm infants were 24.63 ± 6.08, 30.62 ± 5.26 and 30.68 ± 7.14 μg/dl at age 7, 14 and 30 days respectively. Serum vitamin A level at 7 days of age was significantly lower ($p<0.001$) than those of 14 and 30 days of age. At the age of 7 days, three (16%) of the infants had plasma vitamin A levels less than the normal value of 20 μg/dl. At the age of 14 days, all infants had normal plasma

Table 1. Daily vitamin A, protein and energy intake from enteral feeding at each study age.

Age (days)	Vitamin A (IU/d)	Protein (g/kg/d)	Energy (kcal/kg/d)
7	253.6 ± 136.4	1.5 ± 0.7	49.2 ± 23.4
14	1164.2 ± 158.3[a]	3.7 ± 0.4[a]	124.5 ± 12.0[a]
30	1364.4 ± 168.9[a]	3.5 ± 0.4[a]	117.1 ± 14.9[a]

[a] Significantly different from age 7 days, $p<0.001$

Table 2. Clinical characteristics and plasma vitamin A levels at each study age.

Age (days)	Body weight (g)	Plasma vitamin A (μg/dl)
7	1,298.4 ± 170.8	24.6 ± 6.1
14	1,479.5 ± 222.7	31.0 ± 5.3[a]
30	2,097.6 ± 276.8	30.7 ± 7.1[a]

[a] Significantly different from age 7 days, $p<0.001$

vitamin A concentration which remained greater than 20 μg/dl at age 30 days. There was no significant difference between the levels at 14 and 30 days of age.

DISCUSSION

Previous studies have consistently reported that vitamin A status of preterm infants at birth is inadequate when compared to full term infants. Extremely-low-birth-weight infants are prone to vitamin A deficiency because they have low vitamin A storage at birth, poor intestinal absorption and inadequate vitamin A intake for several weeks or longer after birth[11,15,17]. Nutrient-enriched premature infant formula were provided as in-hospital nutritional management for premature neonates in order to achieve adequate nutrients. Vitamin A, protein and energy intake *via* enteral route were very low during the first week in the presented patients because the feeding was initiated on the second to sixth day. On the seventh day, multivitamin supplementation, providing 450 IU/day of vitamin A, was given. By 14 and 30 days of age, the enteral intake increased and the amount of vitamin A, protein and energy intake were adequate when compared to the recommended daily allowances for premature infants which are 1,400-3,300 IU/day, 3-3.5 g/kg/day and 80-100 kcal/kg/day respectively[18,19].

Shenai et al suggested that plasma vitamin A concentration equal to or in excess of 20 μg/dl in infants and children is considered to be adequate[20]. The present study revealed that at age 7 days plasma vitamin A level (24.63 ± 6.08 μg/dl) was significantly lower ($p<0.001$) than those at age 14 and 30 days. In this group, 3 infants out of 19 (16%) had vitamin A level <20 μg/dl and 8 infants (42%) had marginal level. It is most likely due to delayed enteral feeding in some infants and presumably owing to inadequate levels of vitamin A at birth. Vitamin A level at birth and retinol binding protein (RBP), which is a more specific test for vitamin A sufficiency, were not measured. Earlier studies reported that at birth vitamin A concentrations of premature infants were low (14.9 ± 0.98 μg/dl)[1]. The present study showed that, after 2 weeks of life, normal vitamin A status in healthy premature infants can be maintained through adequate enteral feeding of premature infant formula and routine multivitamin supplementation. A high dose of vitamin A is not necessary in healthy premature infants.

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REFERENCES

1. Brandt RB, Mueller DG, Schroeder JR, et al. Serum vitamin A in premature and term neonates. J Pediatr 1978; 92: 101-4.
2. Ross AC. Vitamin A status: Relationship to immunity and the antibody response. Proc Soc Exp Biol Med 1992; 200: 303-20.
3. Tyson JE, Wright LL, Oh W, et al. Vitamin A supplementation for extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. N Engl J Med 1999; 340: 1962-8.
4. Thurnham DI. Vitamin A deficiency and its role in infection. Trans R Soc Trop Med Hyg 1989; 83: 721-3.
5. Shenai JP, Kennedy KA, Chytil F, Stahlman MT. Clinical trial of vitamin A supplementation in infants susceptible to bronchopulmonary dysplasia. J Pediatr 1987; 111: 269-77.
6. Massaro GD, Massaro D. Postnatal treatment with retinoic acid increases the number of pulmonary alveoli in rats. Am J Physiol 1996; 270: L305-10.
7. West KP Jr, Howard GR, Sommer A. Vitamin A and infection: Public health implications. Annu Rev Nutr 1989; 9: 63-86.
8. Papagaroufalis C, Cairis M, Pantazatou E, Megreli C, Xanthou M. A trial of vitamin A supplementation for the prevention of bronchopulmonary dysplasia in very-low-birth-weight infants. Pediatr Res 1988; 23 (Suppl): 518A. (abstract)
9. Pearson E, Bose C, Snidow T, et al. Trial of vitamin A supplementation in very-low-birth-weight infants at risk for bronchopulmonary dysplasia. J Pediatr 1992; 121: 420-7.
10. Bental RY, Cooper PA, Cummins RR, Sandler DL, Wainer S, Rotschild A. Vitamin A therapy-effects on the incidence of bronchopulmonary dysplasia. South Afr J Food Sci Nutr 1994; 61: 141-5.
11. Kennedy KA, Stoll BJ, Ehrenkranz RA, et al. Vitamin A to prevent bronchopulmonary dysplasia in very-low-birth-weight infants: Has the dose been too low? The NICHD Neonatal Research Network. Early Hum Dev 1997; 49: 19-31.
12. Hustead VA, Gutcher GR, Anderson SA, Zachman RD. Relationship of vitamin A (retinol) status to lung disease in the preterm infant. J Pediatr 1984; 105: 610-5.
13. Zachman RD. Retinol (vitamin A) and the neonate: Special problems of the human premature infant. Am J Clin Nutr 1989; 50: 413-24.
14. Chytil F. The lungs and vitamin A. Am J Physiol 1992; 262: L517-27.
15. Shenai JP, Chytil F, Stahlman MT. Liver vitamin A reserves of very low birth weight neonates. Pediatr Res 1985; 19: 892-3.
16. International Vitamin A Consultative Group (IVACG). Biochemical methology for the assessment of vitamin A status. New York: The Nutrition Foundation, 1982.
17. Rush MG, Shenai JP, Parker RA, Chytil F. Intramuscular *versus* enteral vitamin A supplementation in very low birth weight neonates. J Pediatr 1994; 25: 458-62.
18. Nan Sen TL, Oswald AR. The vitamins. In: Goodhart RS, Shils MS, eds. Modern Nutrition in Health and Diseases. 6th ed. Philadelphia: Lea and Febiger, 1980: 142-59.
19. Schanler RJ. The low-birth-weight infant. In: Walker WA, Watkins JB, eds. Nutrition in Pediatrics Basic Science Clinical Applications. 2nd ed. Hamilton, London: BC Decker Inc., 1997: 392-412.
20. Shenai JP, Chytil F, Jhaveri A, Stahlman MT. Plasma vitamin A and retinol-binding protein in premature and term neonates. J Pediatr 1981; 99: 302-5.

ภาวะโภชนาการของวิตามินเอ ในทารกเกิดก่อนกำหนด

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ทารกเกิดก่อนกำหนดมีความเสี่ยงต่อการขาดวิตามินเอ เนื่องจากมีการสะสมในร่างกายน้อยและความต้องการมากกว่าทารกปกติ มีรายงานว่าทารกเกิดก่อนกำหนดมีระดับวิตามินเอในเลือดต่ำ การศึกษานี้มีวัตถุประสงค์เพื่อประเมินการเปลี่ยนแปลงของภาวะโภชนาการของวิตามินเอในช่วงอายุ 1 เดือน ในทารกเกิดก่อนกำหนด 19 ราย ซึ่งมีน้ำหนักแรกเกิดต่ำกว่า 1,500 กรัม และไม่ได้รับออกซิเจน ผู้ป่วยได้รับนมสูตรทารกเกิดก่อนกำหนดและวิตามินรวม ตรวจระดับวิตามินเอในพลาสมาเมื่ออายุ 7, 14 และ 30 วัน

ผลการศึกษาพบว่าระดับวิตามินเอในพลาสมาเมื่ออายุ 7, 14 และ 30 วัน เท่ากับ 24.63 $\pm$ 6.08, 30.97 $\pm$ 5.26 และ 30.60 $\pm$ 7.14 μg/dl ตามลำดับ ระดับวิตามิน เอ เมื่ออายุ 7 วัน ต่ำกว่าเมื่ออายุ 14 วัน และ 30 วัน ($p<0.001$) ทารก 3 คน จาก 19 คน (16%) มีระดับวิตามินเอในพลาสมาต่ำ (< 20 #g/dl) เมื่ออายุ 7 วัน แต่เมื่ออายุ 7 และ 14 วัน ทารกทุกรายมีระดับวิตามินเอปกติ การศึกษานี้แสดงว่าทารกเกิดก่อนกำหนดที่สุขภาพดีมีความเสี่ยงต่อการขาดวิตามินเอโดยไม่แสดงอาการในช่วง 7 วันแรกเกิด ระดับวิตามินเพิ่มขึ้นเป็นปกติเมื่อได้รับอาหารร่วมกับการเสริมวิตามินรวม จึงไม่มีความจำเป็นต้องเสริมวิตามินเอ ขนาดสูงในทารกเกิดก่อนกำหนดเหล่านี้

คำสำคัญ : วิตามินเอ, ทารกเกิดก่อนกำหนด

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