Vitamin A Supplementation for Prevention of Bronchopulmonary Dysplasia in Very-Low-Birth-Weight Premature Thai Infants: A Randomized Trial

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Background: *Bronchopulmonary dysplasia (BPD) is one of the most significant complications among very-low-birth-weight (VLBW) premature infants. Vitamin A deficiency increases the risk of BPD in VLBW infants.*
Objective: *To assess the effect of vitamin A supplementation for prevention of bronchopulmonary dysplasia in VLBW premature Thai infants.*
Study design: *Randomized control trial.*
Material and Method: *Eighty premature infants weighing <1,500 g who received mechanical ventilation or oxygen supplementation at 24 hours of age-admitted to Neonatal units of Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand-were assigned to receive either intramuscular vitaminA 5,000 IU 3 times/week (treatment group) or sham procedure (control group) for four weeks. Serum vitamin A levels were measured before and after administration of the vitamin A.*
Results: *The baseline of mean serum vitamin A levels were similar in both groups. The mean serum level of vitamin A was significantly higher in the vitamin A supplemented infants than in the control infants on day 7 (1.41±0.48 vs. 0.92±0.38 μmol/L, p<0.001), day 14 (1.48±0.90 vs. 0.96±0.36 μmol/L, p = 0.001) and day 28 (1.42±0.63 vs. 0.76±0.30 μmol/L, p<0.001) after vitamin A supplementation. None of the infants in the vitamin A supplemented group, compared to 5% of the infants in the control group, had vitamin A level <0.35 μmol/L, (indicating severe vitamin A deficiency) at 28 days. Fewer of the premature infants in the vitamin A supplemented group required oxygen supplementation at 36 weeks postmenstrual age than in the control group albeit not statistically significant (22.5 vs. 35% relative risk 0.71; 95% CI 0.40-1.26; p = 0.21). Supplementation with vitamin A was also associated with a significant reduction in the duration of intubation (10.8±3.1 days vitamin A supplemented group vs. 26.1±6.4 days control group, p = 0.03), days on oxygen therapy (29.8±5.1 days vitamin A supplemented group vs. 58.2±9.1 days control group, p = 0.01) and length of hospital stay (61.9±4.2 days vitamin A supplemented group vs. 88.3±7.2 days control group, p = 0.002).*
Conclusion: *The dose of vitamin A used in this study reduced biochemical evidence of vitamin A deficiency and, without complications, resulted in reducing duration of intubation, days of oxygen therapy, and length of hospital stay in premature infants suffering VLBW.*

Keywords: *Bronchopulmonary dysplasia, Premature infants, Vitamin A*

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Bronchopulmonary dysplasia (BPD) remains one of the most significant complications in very-low-birth-weight (VLBW) premature infants. Although some of the risk factors for BPD can be modified after birth, other risk factors such as lung immaturity and impaired lung repairing process are less well understood. Vitamin A is a group of retinal compounds required for regulation and promotion of growth and differentiation of cells including cells in the retina of the eyes and cells in the lungs[1,2]. Several studies suggest that vitamin A deficiency increases the risk of BPD in VLBW infants[3-5]. It has, therefore, been hypothesized that treatment with vitamin A to correct the deficiency state in the infants at risk can reduce incidence of BPD.

Compared to term infants, the majority of premature infants have a generalized deficiency of vitamin A and a specific carrier protein called plasma retinol-binding protein[6-8]. These high-risk infants are

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born with inadequate body stores of vitamin A; moreover, they are often unable to tolerate routine oral supplementation and the deficiency of vitamin A cannot be restored by the use of commercially-available, parenteral vitamin preparations[9]. Importantly, vitamin A irreversibly oxidizes and loses its biological activity when exposed to light, and is significantly adsorbed to the tubing making administration via intravenous alimentation solutions unreliable[10].

Vitamin A supplementation for premature infants began with the observation that the histological appearance of the lungs of vitamin A-deficient rodents resembled that of premature infants who had BPD. Subsequent studies demonstrated that these lung lesions could be reversed by vitamin A supplementation to deficient animals and that plasma retinol levels could be increased[11]. Owing to poor gastrointestinal tract absorption and unreliable absorption of vitamin A from parenteral nutrition, intramuscular vitamin A injection is the preferred route for achieving normal serum levels[12-15].

The aim of the present study was to assess the effect of intramuscularly delivered vitamin A supplementation in prevention of bronchopulmonary dysplasia at 36 weeks postmenstrual age in very-low-birth-weight premature infants.

Material and Method

The present study was reviewed and approved by the Khon Kaen University Ethics Committee for human research, and written informed consent was obtained from the parents of each infant.

Subjects

The statistical formula below was used to calculate sample size.

$$n = \frac{2 (Z_{alpha} + Z_{beta})^2 P (1-P)}{(\Delta P)^2}$$

$P = (P_{treatment} + P_{control})/2$

BPD in control group =0.62, BPD in treatment group is 0.34[12]

Alpha = 0.05

Beta = 0.84

$Z_{alpha} = 1.65$

$Z_{beta} = 0.84$

$$n = \frac{2 (1.65 + 0.84)^2 0.48 (1-0.48)}{(0.28)^2} = 39.5/group$$

The authors enrolled 80 premature infants-admitted to the Neonatal Unit of Srinagarind Hospital, Khon Kaen University between July 2004 and July 2007-weighing <1,500 g who had received mechanical ventilation or oxygen supplementation at 24 hours of age. To reduce the likelihood of early death unrelated to vitamin A status and to facilitate enrollment, the authors enrolled infants at 24 to 96 hours after birth. Exclusion criteria were infants with major congenital anomalies, congenital non-bacterial infection, terminal stage of illness (as indicated by a pH below 6.80 or hypoxia with bradycardia for >2 hours).

The infants were assigned to a vitamin A or control group by a research nurse using a randomization list (with sealed envelopes containing the treatment assignments randomized by blocks of 4). A dose of vitamin A (5,000 IU; 0.1 mL) was given on Mondays, Wednesdays and Fridays for 4 weeks via a 1-mL syringe with a 26-gauge needle. The same dose was used regardless of birth-weight, because the smallest infants have (a) the highest incidence of bronchopulmonary dysplasia, (b) the lowest vitamin A stores at birth, and (c) the lowest enteral intakes. The vitamin A preparation (Chochola A, Esai Co., Ltd, Japan) was refrigerated and shielded at all times from direct light.

To avoid pain and potential side effects, the control infants received a sham procedure rather than a placebo injection. For each treatment, a screen was placed around the bed, a pacifier was used for non-pharmacological pain management, and the injection site was covered with cotton and tape. The same covering was placed on the control infants. The research nurse removed the covering at the next treatment. (Owing to the small needle, the injection site was not visible to the nurse).

To assess vitamin A supplementation under usual clinical circumstances, the attending neonatologist from the Neonatal Intensive Care Unit retained responsibility for decision-making regarding the use of (a) enteral feeding, (b) parenteral nutrition, (c) mechanical ventilation and (d) oxygen therapy.

Evaluation

All vitamins and enteral feedings provided were recorded. Experienced personnel involved in the care of the infants evaluated the infants for signs of potential vitamin A toxicity by assessment of the anterior fontanelle, head circumference, liver size, sign of edema, cutaneous abnormalities, lethargy, and irritability. If vitamin A toxicity were suspected, the neonatologist had to decide whether to continue treatment based on physical findings without

knowledge of the treatment assignment.

Study outcomes

Bronchopulmonary dysplasia was defined as the need for oxygen therapy at 36 weeks postmenstrual age (Gestational age was defined by using the accurate last menstrual period or physical assessment by Ballard scores). Sepsis was defined on the basis of a positive blood culture and treatment with antibiotics for at least five days. Other outcomes measured included: (a) necrotizing enterocolitis (NEC) ≥stage 2 according to Bell's criteria; (b) patent ductus arteriosus (PDA) diagnosed by cardiologists using echocardiography; (c) retinopathy of prematurity (ROP) evaluated by Pediatric ophthalmologists; and, (d) severe intraventricular hemorrhage (IVH) grade 3 or 4 diagnosed by radiologists using cranial ultrasonography.

Collection of serum samples

Blood samples (500 µL) were obtained from peripheral venous blood or drawn from an indwelling arterial catheter on day 1 before and on day 7, 14 and 28 after vitamin A supplementation. All blood samples were wrapped with aluminum foil to prevent any photodegradation of vitamin A by exposure to light.

Serum samples were obtained from the spontaneous coagulation of blood. The blood was then centrifuged at 2,500 rpm at 4°C for 10 min to obtain serum. Hemolyzed samples were excluded. The serum was stored at -80°C until analysis.

Determination of vitamin A

Vitamin A levels were measured in a laboratory of biochemistry department by reverse-phase high performance liquid chromatography (HPLC) system with a dual wave length spectrophotometric detector as per Thurnham et al[16].

Statistical analysis

Data were analyzed with STATA software and the two groups compared using the Student's t-test, Chi-square test, and the Fisher's exact test, where appropriate. A *p*-value of <0.05 was considered statistically significant. Relative risks with the respective 95% confidence interval were presented.

Safety of vitamin A supplementation

None of the signs of potential vitamin A toxicity that could not be explained by other factors (e.g. intraventricular hemorrhage, post-hemorrhagic hydrocephalus causing a full fontanelle) was identified in any of the premature infants enrolled in the present study.

Results

The baseline characteristics of the infants in vitamin A supplemented and control groups were similar (Table 1). The respective mean birth-weight of infants in the vitamin A and control group was 1,152.8±203.6 g (680-1,460 g) and 1,123.1±218.1 g (670-1,490 g). The respective mean gestational age of infants in the vitamin A and control group was 29.0±1.7 week (24-32 week) and 28.9±1.9 week (24-32 week).

The mean serum vitamin A levels before administration of the vitamin A were similar in both groups (Fig. 1). The mean serum level of vitamin A was higher in the vitamin A supplemented infants than in the control infants on day 7 (1.41±0.48 vs. 0.92±0.38 µmol/L, $p<0.001$), day 14 (1.48±0.90 vs. 0.96±0.36 µmol/L, $p = 0.001$) and day 28 (1.42±0.63 vs. 0.76±0.30 µmol/L, $p<0.001$) after vitamin A supplementation. Fewer infants in the vitamin A group had serum vitamin A

Table 1. Baseline characteristics of the premature infants

Characteristics	Vitamin A group (n = 40)	Control group (n = 40)
Birth weight (g): mean ± SD	1,152.8±203.6 (680-1,460 g)	1,123.1±218.1 (670-1,490 g)
Gestational age (week): mean ± SD	29.0±1.7 (24-32 week)	28.9±1.9 (24-32 week)
Small for gestational age: No. (%)	8 (20)	7 (17.5)
Male sex: No. (%)	20 (50)	21 (52.5)
Antenatal corticosteroid: No. (%)	29 (72.5)	29 (72.5)
Apgar scores at 1, 5 min (median)	2, 6	2, 6
Respiratory status at 24 hour		
Mechanical ventilation: No. (%)	27 (67.5)	28 (70)
Mean airway pressure (cmH_2O): mean ± SD	7.0±1.7	7.1±1.7
Time from birth to first treatment (hour): mean ± SD	49.1±27.2	49.3±17.4

levels less than 0.7 µmol/L on day 28 compared to the control group (10 vs. 45%). None of the infants in the vitamin A group compared to 5% of those in the control group had a level <0.35 µmol/L at 28 days.

Supplementation with vitamin A was associated with a significant reduction in duration of intubation (10.8±3.1 days vitamin A supplemented group vs. 26.1±6.4 days in the control group, $p = 0.03$), days on oxygen therapy (29.8±5.1 days vitamin A supplemented group vs. 58.2±9. 1 days control group, $p = 0.01$) and length of hospital stay (61.9±4.2 days vitamin A supplemented group vs. 88.3±7.2 days control group, $p = 0.002$).

Bronchpulmonary dysplasia at 36 weeks postmenstrual age was lower in the vitamin A supplemented infants than in the control infants albeit the difference was not statistically significant (22.5 vs. 35% relative risk 0.71; 95% CI 0.40-1.26; $p = 0.21$). There were also non-significant trends toward reduction in:

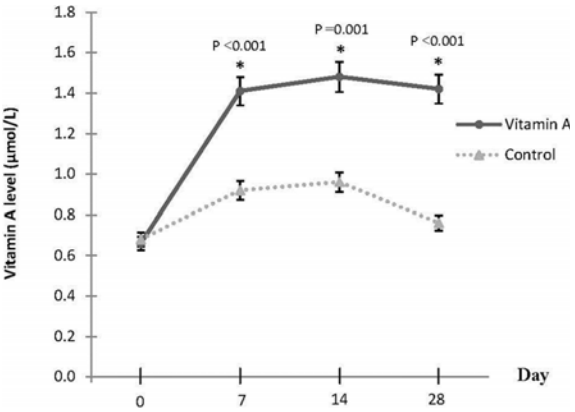

Fig. 1 Serum vitamin A level of the premature infants before and after supplementation.

(a) risk of retinopathy of prematurity (7.5% vitamin A supplemented vs. 17.5% control group, relative risk 0.41; 95% CI 0.11-1.43; $p = 0.07$); (b) nosocomial sepsis (35% vitamin A supplemented group vs. 42.5% control group, relative risk 0.83; 95% CI, 0.52-1.3; $p = 0.43$); (c) patent ductus arteriosus (47.5% vitamin A supplemented group vs. 57.5% control group, relative risk 0.81; 95% CI, 0.52-1.26; $p = 0.37$); (d) necrotizing enterocolitis (17.5% vitamin A supplemented group vs. 20% control group, relative risk 0.84; 95% CI, 0.46-1.55; $p = 0.57$); and, (e) severe intraventricular hemorrhage grade 3 or 4 (0 vitamin A supplemented group vs. 5% control group; $p = 0.15$) (Table 2).

Discussion

Very-low-birth-weight premature infants are prone to vitamin A deficiency because of (a) less transplacental transport from mothers (b) inadequate intake from enteral feeding for several weeks after birth and (c) poor gastrointestinal absorption. Inadequate provision and unreliable delivery of parenteral vitamin A may exacerbate the problem of vitamin A deficiency. The present study attempted to define serum vitamin A levels and the role of vitamin A supplementation for prevention of bronchopulmonary dysplasia in very-low-birth-weight premature Thai infants and confirmed that intramuscular vitamin A supplementation can increase the serum level of vitamin A in this susceptible population. Forty-five percent of premature infants in the control group had vitamin A levels <0.7 µmol/L-which is considered vitamin A deficient-compared to 10% in the supplemented group. None of the infants in the vitamin A group, moreover, had a level <0.35 µmol/L, which is suggestive of severe vitamin A deficiency and depleted liver stores compared to 5% of infants in the control group. The dose of vitamin A

Table 2. Bronchopulmonary dysplasia (BPD) and other outcomes of the premature infants

Outcomes	Vitamin A group (n = 40)	Control group (n = 40)	*p*-value
BPD at 36 week post menstrual age: No. (%)	9 (22.5)	14 (35)	0.21
Death before discharge: No. (%)	2 (5)	1 (2.5)	0.56
Retinopathy of prematurity: No. (%)	3 (7.5)	7 (17.5)	0.07
Hospital acquired sepsis: No. (%)	14 (35)	17 (42.5)	0.43
Necrotizing enterocolitis: No. (%)	7 (17.5)	8 (20)	0.57
Patent ductus arteriosus: No. (%)	19 (47.5)	23 (57.5)	0.37
Intraventricular hemorrhage grade 3 or 4: No. (%)	0 (0)	2 (5)	0.15
Days on endotracheal tube (days): mean ± SD	10.8±3.1	26.1±6.4	0.03
Days on oxygen therapy (days): mean ± SD	29.8±5.1	58.2±9.1	0.01
Length of hospitalization (days): mean ± SD	61.9±4.2	88.3±7.2	0.002

supplementation in this study was similar to previous studies and there was no clinical evidence of vitamin A toxicity[17].

The results of a large multicenter trial and meta-analysis found that vitamin A supplementation to VLBW infants was associated with a reduction in mortality and oxygen requirement at one month of age and oxygen requirement at postmenstrual age 36 weeks[17,18]. There is, however, no data on vitamin A supplementation in VLBW infants in Thailand. The present study demonstrated that fewer infants in the vitamin A supplementation group required oxygen at 36 weeks postmenstrual age albeit the difference was not statistically significant (22.5 vs. 35% relative risk 0.71; 95% CI 0.40-1.26; $p = 0.21$) Additionally, the duration of intubation, oxygen therapy and length of hospital stay were significantly shorter among the vitamin A supplemented infants.

Low plasma vitamin A levels are associated with development of retinopathy of prematurity in some studies[12,19]. Pooled data show a trend towards a reduction in retinopathy of prematurity, culture positive nosocomial sepsis in infants supplemented with vitamin A (albeit not a statistically significant difference)[18]. The incidence and severity of intraventricular hemorrhage is higher among infants with low hepatic storage of vitamin A[4]; however, supplementation has not been shown to reduce significantly the incidence of intraventricular hemorrhage[17].

Vitamin A was observed to accelerate the development of oxygen induced constriction of the ductus arteriosus postnatally in a rat model[20]. By comparison, in a small group of ventilator-dependent preterm infants weighing between 500 and 1,500 g, intramuscular vitamin A did not affect spontaneous closure of PDA[21]. Supplementation with vitamin A in very-low-birth-weight premature infants in the present study was associated with trends (not statistically significant) toward a reduction in risk of retinopathy of prematurity, nosocomial sepsis, patent ductus arteriosus, necrotizing enterocolitis and severe intraventricular hemorrhage.

Conclusion

The dose of vitamin A used in the present study reduced biochemical evidence of vitamin A deficiency and resulted in a reduction in the duration of intubation, days of oxygen therapy, length of hospital stay (without adverse effect). The authors conclude that vitamin A supplementation should be given to very low birth weight, premature infants requiring respiratory support or oxygen therapy at risk of developing bronchopulmonary dysplasia. Additional benefits of vitamin A supplementation may, moreover, be obtained in this high-risk population.

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Potential conflicts of interest

None.

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การให้วิตามิน เอ ในการป้องกันภาวะโรคปอดเรื้อรังในทารกเกิดก่อนกำหนดน้ำหนักตัวน้อยมาก

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ภูมิหลัง: โรคปอดเรื้อรังเป็นภาวะแทรกซ้อนที่พบบ่อยในทารกเกิดก่อนกำหนดน้ำหนักตัวน้อยมาก ทารกที่มีภาวะขาดวิตามิน เอ มีความเสี่ยงสูงต่อการเกิดโรคปอดเรื้อรัง

วัตถุประสงค์: เพื่อประเมินผลของการให้วิตามิน เอ ชนิดฉีดเข้ากล้ามในการป้องกันภาวะโรคปอดเรื้อรังในทารกเกิดก่อนกำหนดน้ำหนักตัวน้อยมาก

วัสดุและวิธีการ: ทารกเกิดก่อนกำหนดน้ำหนักตัวน้อยกว่าหรือเท่ากับ 1,500 กรัมที่ได้รับการช่วยหายใจ หรือได้รับออกซิเจนใน 24 ชั่วโมงแรกของชีวิตที่เข้ารับการรักษาในหอผู้ป่วยทารกแรกเกิดโรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น จำนวน 80 ราย โดยเป็นทารกที่ได้รับวิตามิน เอ ชนิดฉีดเข้ากล้าม 5,000 IU สัปดาห์ละ 3 ครั้ง เป็นเวลา 4 สัปดาห์ 40 ราย เปรียบเทียบกับกลุ่มควบคุม 40 ราย และมีการวัดระดับวิตามิน เอ ในเลือดก่อนและหลังให้วิตามินเอ

ผลการศึกษา: ระดับวิตามิน เอ ในเลือดก่อนการให้วิตามินเอไม่แตกต่างกันในทารกทั้งสองกลุ่ม ระดับวิตามินในทารก ที่ได้รับวิตามิน เอ สูงกว่าในทารกกลุ่มควบคุมหลังการให้ยาวันที่ 7, 14 และ 28 อย่างมีนัยสำคัญ ทารกกลุ่มควบคุมมีระดับวิตามินเอในเลือดที่น้อยกว่า 0.35 μmol/L ซึ่งเป็นระดับที่บ่งชี้ภาวะขาดวิตามินเอรุนแรงได้ร้อยละ 5 ในขณะที่ไม่พบในทารกที่ได้รับวิตามินเอ พบภาวะโรคปอดเรื้อรังในทารกที่ได้รับวิตามินเอน้อยกว่าทารกกลุ่มควบคุม แต่ไม่มีนัยสำคัญทางสถิติ นอกจากนั้นระยะเวลาการใส่ท่อช่วยหายใจ ระยะเวลาการได้รับออกซิเจน และระยะเวลาการอยู่โรงพยาบาลในทารกที่ได้รับวิตามินเอสั้นกว่ากลุ่มควบคุมอย่างมีนัยสำคัญโดยไม่พบผลข้างเคียงจากการให้วิตามินเอ

สรุป: วิตามิน เอ ขนาดที่ให้ในการศึกษานี้สามารถลดภาวะขาดวิตามิน เอ ได้โดยไม่มีภาวะแทรกซ้อนนอกจากนั้น ยังลดระยะเวลาการใส่ท่อช่วยหายใจ ระยะเวลาการได้รับออกซิเจนและระยะเวลาการอยู่โรงพยาบาลในทารกเกิดก่อนกำหนดน้ำหนักตัวน้อยมาก