Journal of the Formosan Medical Association (2017) 116, 626–633

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

ORIGINAL ARTICLE

Serum retinol levels and neonatal outcomes in preterm infants

Hsing-Jin Chen [a], Chyong-Hsin Hsu [b], Bor-Luen Chiang [c,*]

[a] *Graduate Institute of Clinical Medicine College of Medicine of National Taiwan University, Taipei, Taiwan*
[b] *Department of Pediatrics, Division of Neonatology, Mackay Memorial Hospital, Taipei, Taiwan*
[c] *Graduate Institute of Immunology, National Taiwan University, Taipei, Taiwan*

Received 18 August 2016; received in revised form 11 January 2017; accepted 26 April 2017

KEYWORDS
Bronchopulmonary dysplasia;
Glucocorticoids;
Preterm infant;
Retinopathy of prematurity;
Retinol

Background/Purpose: Glucocorticoids are frequently administered to preterm infants, both antenatally and postnatally; however, the effect on serum retinol levels has not been determined. The risk of bronchopulmonary dysplasia is increased in premature infants with low retinol concentrations.
Objectives: Our purpose was to determine the effect of glucocorticoid administration on serum retinol levels in preterm infants.
Methods: All infants <1250 g or <29 weeks' gestation admitted to the neonatal intensive care unit within 48 h of birth were eligible for inclusion. A retinol concentration <20 μg/dL during the first 48 h of birth was defined as low serum retinol, and a level <10 μg/dL as retinol deficiency.
Results: Data from 115 premature infants were collected during a 7-year period, from 2005 to 2012. Neither antenatal nor postnatal steroid administration affected retinol concentrations. Retinol deficiency was associated with an increased risk for severe respiratory distress syndrome and adverse pulmonary outcome (death during the first 28 days of life and long-term oxygen dependence >90 days); low retinol levels conferred an increased risk for bronchopulmonary dysplasia. Prolonged duration of total parenteral nutrition (>21 days) was associated with serum retinol deficiency during hospitalization ($P < 0.05$). Retinol deficiency was associated with an increased risk for delayed neurological development in 1-year-old and 2-year-old children.
Conclusion: Glucocorticoids do not affect retinol levels in premature infants, but retinol concentrations are correlated with respiratory and neurological outcomes.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

* Corresponding author. Graduate Institute of Immunology, National Taiwan University, No. 1, Sec. 1, Ren-ai Rd, Jhongjheng District, Taipei 100, Taiwan.
E-mail address: gicmbor@ntu.edu.tw (B.-L. Chiang).

http://dx.doi.org/10.1016/j.jfma.2017.04.019

Introduction

Bronchopulmonary dysplasia (BPD) is the most common chronic lung disease occurring in premature infants treated with oxygen and mechanical ventilation. The pathogenesis of BPD is complex and poorly understood. Briefly, various factors can result in injury to small airways and interfere with alveolarization (alveolar septation), resulting in alveolar simplification and an overall reduction in the surface area available for gas exchange.[1,2] Nutrient deficiency, particularly of retinol, is a main cause of chronic lung disease in premature infants.[3] The retinol concentration in the blood of premature infants is reportedly lower than that seen in full-term infants,[4–6] and the risk for BPD and other chronic lung diseases is increased in premature infants with low retinol concentrations.[6–9] Findings, such as alveolar collapse, loss of ciliated cells, abnormalities of keratinization, and necrotizing bronchiolitis, seen on pathological sections of human lungs with diseases caused by retinol deficiency are similar to the pathological findings in patients with BPD.[10–12]

The main storage organ for retinol is the liver, and retinol stores are known to be lower in premature infants than in full-term infants.[13,14] Furthermore, the retinol carrier protein is lower in premature infants than in term infants, which affects delivery of retinol to the liver for storage.[6] Some studies have shown that BPD and chronic lung disease in premature infants cannot be prevented by the intramuscular administration of retinol[15,16]; these studies vary, however, in their methods and timing of retinol-concentration measurement. In addition, there are various and complicated factors that affect the development of BPD and chronic lung disease and that affect retinol levels in premature infants. These include the use of antenatal steroids, the presence of inflammatory disease, and malnutrition status.[6,17–21]

In addition to BPD, premature infants are at risk for intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), and delayed neurological development.[22–24] One study showed that the severity of IVH might be reduced with postnatal retinol administration.[22] Experiments using a rat model showed that postnatal retinol supplementation could regulate the performance of vascular endothelial growth factor (VEGF) and reduce the severity of retinopathy caused by oxygen administration.[25] Reduction of blood retinol concentration has been correlated with ROP in one study,[26] but another study showed that retinol concentration is irrelevant after controlling for other factors.[27] Zhang et al.[24] reported that the concentration of retinol in the umbilical-cord blood is positively correlated with future language- and social cognitive development.

The objectives of the present study were to determine the effect of glucocorticoid administration on serum retinol levels in preterm infants and to determine the relation between retinol levels and BPD, chronic lung disease, sepsis, IVH, ROP, and neurological outcomes.

Methods

Subjects

All infants with a birth weight <1250 g or gestational age (GA) <29 weeks admitted within 48 h of birth to the neonatal intensive care unit of Mackay Memorial Hospital in Taiwan were eligible for study inclusion after their parents provided written informed consent. This study was approved by the ethics committees of Mackay Memorial Hospital.

Nutrition, feeding, and retinol intake

All infants received intravenous parenteral nutrition with supplemental vitamins (MVI-Paediatric; U-LIANG Pharmaceutical Co, Ltd., Jungli City, Taiwan). Infants received 1.0 mL/day of the vitamin solution, which provided 2000 IU/day of retinol; infusion began within 24–48 h of birth. Enteral feedings began as soon as possible, with human milk given in nonnutritive volumes (1 mL/2–4 h), and advanced as tolerated. We used continuous or bolus feeding of either human milk with fortifier, preterm formula, or term formula at 150–180 mL/kg/day, with the average estimated enteral intake of retinol from milk ranging from 100 to 400 μg/kg/day. Oral vitamin supplementation, using infantile multivitamin drops (Poly Baby; Root Chemical & Pharmaceutical Co., Ltd, Taiwan) commenced when the infant was tolerating full oral feeding. The dose, 1 mL/day, contained 1500 IU/day of retinol, 400 IU/day of vitamin D, and 35 mg/day of vitamin C.

Steroid administration

Our standard hospital policy was to administer antenatal glucocorticoids to women in preterm labor at <34 weeks' gestation. Either dexamethasone, 3 doses of 8 mg every 8 h, or betamethasone, 2 doses of 12 mg every 24 h, was given. Patients had the right to accept or decline steroid administration. Patients who received a single dose, with birth occurring within 6 h of administration, were not considered to have received steroids.

Postnatal parenteral steroid therapy was administered at the discretion of the attending neonatologist. Eligible infants were >4 days of age with a fraction of inspired oxygen (FiO_2) >30%, a high mean airway-pressure (MAP ≧ 7 cm), and chest radiography showing the classic changes of BPD. Postnatal inhalation steroids were also administered at the discretion of the neonatologist to infants dependent on mechanical ventilatory support for >14 days in whom chest radiography showed development of classical BPD changes. Budesonide, 200 μg/puff, was administered as 1 puff twice daily until infants were weaned from continuous positive airway-pressure (CPAP) ventilatory support; the average duration of administration was 3–4 weeks.

Retinol concentration

A 1.0-mL sample of venous blood was obtained from infants at 48 h of life and again at 7, 14, and 28 days of age. A sample was also obtained at 36 weeks' postconceptional age (PCA). Samples were collected in amber microcontainers, separated, and stored in the dark at −80 °C until analysis. Serum retinol levels were determined using high-performance liquid chromatography.[23] A retinol concentration <20 μg/dL during the first 48 h after birth was defined as a low serum retinol level at birth. Infants with 1 or more measurements <20 μg/dL between day 7 of life and 36 weeks' PCA were classified as having persistent low