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Vitamin D deficiency and respiratory morbidity among African American very low birth weight infants

S. Nadya J. Kazzi*, Sreenivas Karnati[1], Subhash Puthuraya[1], Ronald Thomas

Department of Pediatrics, Wayne State University, Detroit, MI, United States

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ABSTRACT

Background: Very low birth weight infants (VLBWI) have unexplained variation in respiratory morbidity, including respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD). We examined a potential association to serum 25-hydroxyvitamin D (s-25OHD) on day one.

Study design: Prospective, observational study on 89 VLBWI (≤1250 g). S-25OHD (day one and 21) and respiratory severity score (RSS) (day one) were examined. Other respiratory morbidities including BPD were compared between infants with s-25OHD ≤ 10 ng/ml (deficient) versus > 10 ng/ml (adequate).

Results: Eighty one neonates (91%) were African Americans. The mean (SD) birthweight was 868 (229) g, gestational age 27 (2) weeks. On day one, mean (SD) s-25OHD was 15.48 (8.31) ng/ml, with 32 (37%) being vitamin D deficient. The deficiency and adequate VLBWI groups had similar birthweight; 860 (262) vs 873 (210) g, and gestational age; 27 (2) vs 27 (2) weeks. In 78 survivors, s-25OHD rose from 15.48 (8.31) ng/ml day one to 52.36 (22.49) ng/ml day 21 after supplementation, $p < 0.001$. On day one, increasing RSS was inversely related to s-25OHD, trend $p = 0.054$. Compared to the adequate group, the deficiency group had higher RSS (5.0 ± 2.7 vs 3.6 ± 1.9), required surfactant therapy more frequently (91% vs 72%), and needed home oxygen therapy more often (48% vs 26%), $p \leq 0.05$ for all. Among infants with BPD, the severity of disease was inversely related to s-25OHD, trend $p < 0.09$.

Conclusion: Lower levels of s-25OHD were associated with increased severity of RDS and BPD among a cohort of mostly African American VLBWI.

1. Introduction

Recent advances in obstetrical and neonatal care have improved survival among very low birth weight infants (VLBWI). However, respiratory morbidity, with its attendant complications, bronchopulmonary dysplasia in particular, continues to adversely affect the short and long-term outcomes of very low birth weight infants (VLBWI) [1,2]. Bronchopulmonary dysplasia (BPD), a chronic lung disease of prematurity, inflicts significant long term morbidities upon surviving VLBWI including a need for prolonged home oxygen and at times ventilator support [3], frequent re-hospitalizations due to respiratory infections and/or bouts of wheezing [4], relentless pulmonary hypertension [5], abnormalities in lung function with limited exercise tolerance that persist into adulthood [6], poor somatic growth [7] and late neurodevelopmental sequelae [8]. The “new BPD”, as the disease is referred to and as contrasted to the original “classical” form of the disease [9], is characterized by features consistent with impaired lung development mainly reduced alveoli, paucity of alveolar crests, larger and fewer air spaces, dysmorphic capillary bed with excessive inflammation and minimal fibrotic changes [10]. Studies in experimental animals and preterm infants suggest several antenatal and postnatal mechanisms that disrupt alveolar growth and angiogenesis [11].

Vitamin D has long been recognized for its traditional role in calcium and bone homeostasis [12]. Epidemiological studies have highlighted its non-skeletal effects particularly the association of deficient levels of the vitamin with early childhood respiratory infections, wheezing and asthma [13–16]. Studies in experimental animals have demonstrated an important role for vitamin D in modulating lung growth and development [17–19]. Other investigators demonstrated an association between vitamin D deficiency and acute respiratory morbidity among preterm infants [20,21]. Recent investigations aimed at clarifying the relationship between deficient levels of vitamin D and respiratory morbidity including BPD among preterm infants yielded conflicting results [22–26]. Our hypothesis was that fetal exposure to deficient levels of s-25OHD may interfere with proper lung growth resulting in increased respiratory morbidity among VLBWI. The purpose

* Corresponding author at: Department of Pediatrics, Hutzel Women Hospital, 3980 John R, Detroit, MI 48201, United States.
E-mail addresses: nkazzi@med.wayne.edu (S.N.J. Kazzi), rthomas@med.wayne.edu (R. Thomas).
[1] Current address: Cleveland Clinic, Department of Pediatrics, 9500 Euclid Avenue, Cleveland, OH 44195.

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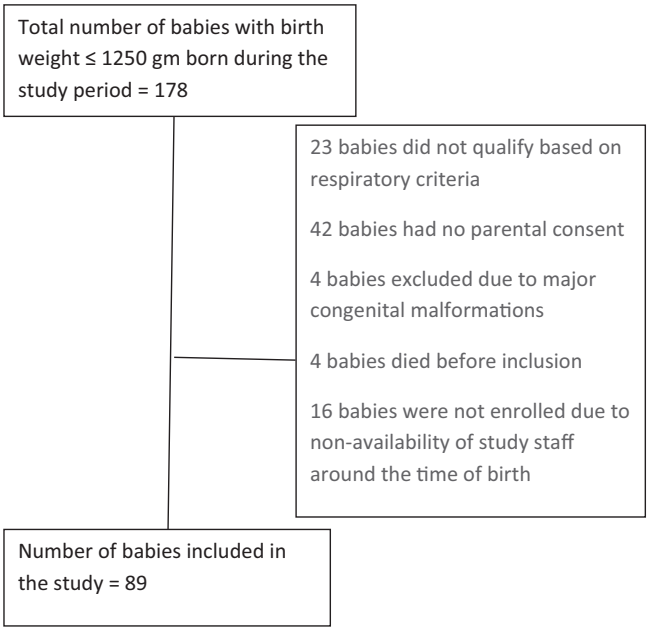

Fig. 1. Flow chart of patients included in study.

of our study was to examine the association between deficient s-25OHD levels at birth and respiratory morbidity that evolved during hospitalization among VLBWI. Moreover, we evaluated the adequacy of our current protocol of vitamin D supplementation among VLBWI by measuring s-25OHD levels at 21 days of age among surviving infants.

2. Materials and methods

This prospective study was conducted in the Neonatal Intensive Care Units at Hutzel Women Hospital and Children Hospital of Michigan, in Detroit, MI between January 2012 and April 2014.

2.1. Study population

Preterm infants with birthweight (BW) ≤ 1250 g who required mechanical ventilation, nasal CPAP or oxygen supplementation within the first 24 h of life were recruited. Infants were excluded if they did not have a prolonged need (> 12 h) for respiratory support on day one of life, had major congenital anomalies, or consent for study participation could not be obtained from their parents/guardian within the first 24 h of life (Fig. 1). The study protocol was approved by the Institutional Review Boards at Wayne State University and Detroit Medical Center. An informed consent was obtained from a parent or a guardian before enrollment into the study. Blood samples (0.5 ml) were collected from all infants within the first 24 h of life before the initiation of vitamin D supplementation through total parenteral nutrition and from surviving infants at 21 days of age. We assumed that infant's s-25OHD levels obtained within the first day of life, before the administration of any vitamin D supplement, were reflective of fetal vitamin D status. The timing of blood sampling at 21 day of life was selected arbitrarily to antecede the 28 days cut off for the definition of BPD [27] while allowing time for s-25OHD levels to stabilize with postnatal vitamin D supplementation. Blood samples were centrifuged within a half hour of collection and sera were separated and stored at −80 °C until final analyses. Levels of total s-25OHD (s-25OHD3 and s-25OHD2) were determined using liquid chromatography-tandem mass spectrometry (LC-MS/MS method) (NMS Labs, Willow Grove, PA). The intra-assay and inter-assay coefficients of variation (CVs) and accuracy for s-25OHD3 were: 2.41%, 3.21% and 105.41% at a concentration of 3.7 ng/ml; for s-25OHD2, the corresponding values were as follows: 6.02%, 6.76% and 105.48% at a concentration of 2.8 ng/ml, respectively. Total levels of s-25OHD are reported in this study. To convert levels of s-25OHD from ng/ml to nmol/l multiply by 2.496.

Maternal and infants' demographic and clinical data were collected prospectively including need for delivery room resuscitation (positive pressure ventilation and or oxygen supplementation), respiratory distress syndrome, surfactant therapy, any respiratory complication (air leak, pulmonary hemorrhage, and ventilator-associated pneumonia), hemodynamically significant PDA requiring medical therapy or surgical ligation, episodes of suspected or proven (positive culture) clinical sepsis treated with intravenous antibiotics for 7–10 days, duration of ventilation, oxygen supplementation and length of hospitalization. Ventilator associated pneumonia was diagnosed in the presence of increased ventilator support, worsening findings on chest x-ray and a positive respiratory bacterial culture necessitating treatment with intravenous antibiotics for 7–10 days. All infants were started on total parenteral nutrition (TPN) after the first day of life. Vitamin D3 (cholecalciferol) from the pediatric multivitamin for injection product was used for daily vitamin D supplement in TPN. The product contains all of the essential fat and water soluble vitamins and each 5 ml provides 400 IU of vitamin D. Dosing in infants was weight based with infants weighing < 1000 g receiving 2 ml daily and infants between 1000 and 3000 g receiving 3.5 ml per day. The addition of pediatric multivitamin during compounding included the best estimate for parenteral nutrition intake in order to ensure maximum allowable vitamin D supplementation. As such, this corresponds to a supplementation range of 160–280 IU of parenteral vitamin D per day. Additional oral vitamin D supplementation was introduced with the initiation of enteral feeding in the form of breastmilk or milk formula. This was further optimized through the fortification of enteral feeding using human milk fortifiers and increasing the caloric density. Oral multivitamin supplements were initiated for all preterm infants once full enteral feeding volume was achieved and this ensured the recommended daily allowance of 400 IU of vitamin D. Severity of respiratory illness among ventilated infants was determined on day one by respiratory severity score (RSS = FiO2 × MAP). Bronchopulmonary dysplasia was defined and its severity determined according to Jobe and Bancalari's classification [27]. All infants with moderate or severe BPD underwent room air challenge [28] at 36 weeks postmenstrual age or discharge whichever occurred earlier and their BPD's classification adjusted according to test result. Supplemental home oxygen therapy administered via nasal cannula was provided to infants unable to maintain a SaO2 ≥ 92% in room air and who, otherwise, were medically ready to be discharged home (able to maintain temperature in crib, tolerating full oral feedings and gaining weight, and has stable cardiorespiratory status for five to seven days prior to home discharge).

2.2. Statistical analysis

This study was an observational, exploratory-pilot study. At the time of study conception, we did not have an estimate of the frequency of s-25OHD deficiency in our patient population. Variance exists in the literature with regards to the frequency of vitamin D deficiency given differing geographic locations, racial distribution and perhaps religious observances which may impact sun exposure and vitamin D synthesis. Therefore, calculating a sample size a priori based on existing literature would arguably be unreliable, making the study results difficult to replicate. Our contribution is offering an effect size specific to our demographics for other investigators to pursue.

Our primary outcome was to examine the relationship between levels of s-25OHD and severity of respiratory distress syndrome (RDS) as represented by RSS on day one. Our secondary outcomes included other respiratory parameters or diagnoses such as need for and frequency of surfactant therapy, need for mechanical ventilation, occurrence of air leaks, ventilator- associated pneumonia, BPD and need for supplemental oxygen therapy. For the primary association, day one s-25OHD