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ScienceDirect

Journal of the Chinese Medical Association xx (2017) 1−5

www.jcma-online.com

Original Article

Is there a potential link between vitamin D and pulmonary morbidities in preterm infants?

Yang Yang, Yun Feng, Xu Chen, Xiao-nan Mao, Jing-han Zhang, Li Zhao, You-yan Zhao, Rui Cheng*

Department of Neonates, Children's Hospital of Nanjing Medical University, Nanjing, China

Received May 29, 2017; accepted July 29, 2017

Abstract

Background: There hasn't been conclusive proof about the association between vitamin D and pulmonary morbidities of prematurity.
Methods: 106 preterm infants were retrospectively included into this study. Clinical data and blood samples of all the patients were collected within 24 h of admission.
Results: (1) Respiratory distress syndrome (RDS) patients were mainly concentrated in "≤30 weeks" stage when compared with other two gestational age groups. The only significant decrease of vitamin D concentration between RDS and non-RDS patients reflected in "≤30 weeks" stage (RDS *vs.* non-RDS: 29.48 ± 13.06 *vs.* 40.47 ± 20.52 nmol/l). (2) Bronchopulmonary dysplasia (BPD) patients were also concentrated in "≤30 weeks" stage. Vitamin D concentration showed significant difference both in "≤30 weeks" stage and "30−34 weeks" stage (≤30 weeks stage, BPD *vs.* non-BPD: 33.20 ± 16.51 *vs.* 39.21 ± 16.65 nmol/l; 30−34 weeks stage, BPD *vs.* non-BPD: 30.36 ± 15.50 *vs.* 41.21 ± 20.40 nmol/l). (3) Though vitamin D concentration in mechanical ventilation (MV) group was lower than non-MV group, there're no significant differences. (4) Vitamin D concentration in dead cases was significant lower than survival patients at discharge. (5) It showed a good correlation between vitamin D concentration and serum Ca, serum P, duration of MV and duration of oxygen support in "≤30 weeks" stage.
Conclusion: The significant decrease of vitamin D concentration between RDS and non-RDS patients only reflected in "≤30 weeks" stage. And significant decrease of vitamin D concentration in BPD patients was both showed in "≤30 weeks" stage and "30−34 weeks" stage, which is consistent with "duration of oxygen support". However, the overall effect did not show any difference in all preterm infants. It seems that the appropriate concentration of vitamin D is beneficial to lung maturation of human. Certainly, large sample, multi-center randomized controlled trials are necessary.

Keywords: BPD; Preterm infants; RDS; Vitamin D

1. Introduction

The importance of vitamin D in newborn and child health has been increasingly recognized in the last several years.[1,2] Furthermore, vitamin D seems to play a role in embryogenesis, cellular growth and differentiation, including the regulation of lung development and lung maturation in the fetus.[3−5] So, the impact of vitamin D on lung development and pulmonary diseases of early life has attracted more and more attention of neonatologists.

Respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) are major pulmonary complications to preterm infants. To date, the most dramatic improvement in treating RDS is intratracheal surfactant and mechanical ventilation, leading to decreased mortality and morbidity.[6]

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Professor Rui Cheng, Department of Neonates, Children's Hospital of Nanjing Medical University, 72, Guangzhou Road, Nanjing, Jiangsu 210008, China.
E-mail addresses: chengrui@163.com, yy860507@126.com (R. Cheng).

http://dx.doi.org/10.1016/j.jcma.2017.07.011

However, despite improved treatment techniques, RDS is still a severe, high-mortality disease in the extremely premature infant. In survivors, a considerable part of preterm infants may be accompanied by BPD, a chronic lung disease characterized by impaired alveolar development and inflammation response.[7] In fact, many preterm infants, especially extremely low birth weight babies need oxygen support for a long time after birth in routine clinical practice.

Vitamin D deficiency is common among infants, and pregnant and lactating mothers in the worldwide.[8,9] Among the population of newborns, preterm babies often have less vitamin D stores due to less sunlight exposure and decreased trans-placental transfer from deficient mothers, and consequently have a higher requirement.[10,11] Animal and laboratory studies have showed substantial positive effects of vitamin D on the alveolar type II cell (ATII), fibroblast proliferation, surfactant synthesis, and alveolarization.[3,12,13] These data support the hypothesis of hypovitaminosis D as a frequent, modifiable risk factor of RDS and BPD. However, the evidence of an impact of vitamin D on human fetal and neonatal pulmonary diseases has still been sparse.[14] KE Joung et al.[15] once found that low 25(OH)D level is frequent and modifiable among preterm infants at birth. However, they didn't detect any association between vitamin D status and pulmonary or other morbidities of prematurity.

In view of such an uncertain situation, clinical data of 106 preterm infants from our center were analyzed retrospectively. And we hope that this paper could add some persuasive evidences to clinical application of vitamin D in preterm infants.

2. Methods

2.1. Preterm infants

(1) Inclusion criteria: from January 2015 to January 2016, we retrospectively selected (By random number table method to avoid selection bias) 106 preterm infants (Gestational age <37 weeks) admitted to Children's Hospital of Nanjing Medical University, a representative level III NICU in East China. (2) Exclusion criteria: infants with severe congenital malformations, severe infection, inherited metabolic diseases, give up treatment within 24-h after birth. (3) Diagnostic criteria of BPD: BPD is defined as a requirement for oxygen at 36 weeks' corrected gestational age.[16,17] Diagnostic criteria of RDS: RDS is defined according to the latest guideline – 2016 European Consensus Guidelines on the Management of Respiratory Distress Syndrome.[18] (4) Ethics: This retrospective observational study was approved by the hospital ethics committee (Number: NJCH2016003) and informed consent was obtained from the patient's guardians.

2.2. Collecting methods

(1) All enrolled infants were admitted to hospital within 24 h after birth to collect the routine clinical data and blood samples. Clinical data contain: mother's age, birth weight, gestational age, admission age, gender, Apgar score, clinical diseases and respiratory support. Blood samples were collected, comprising: vitamin D concentration, serum calcium and serum phosphorus. (2) Blood samples collection method: Take fasting peripheral venous blood 2 ml within the age of 24 h, saved in procoagulant tube. 25(OH)D (Represented as vitamin D) level was measured by automatic biochemical analyzer (Type 1024, Tokyo), showing as nmol/l.

2.3. Statistical methods

Statistical analysis was performed using SPSS 13.0 software. Quantitative data were showed as mean ± standard deviation. Between the two groups were compared using *t* test, and among more than two groups were compared using analysis of variance. Pearson correlation coefficients between the variables were calculated. For qualitative data, Pearson chi-square test (or fisher exact probability method) were performed. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Analysis of baseline data

This study finally included 106 preterm infants, and newborns between 30 and 34 weeks occupy the majority of the proportion. Mothers' age gradually decreased with gestational age increasing ($P < 0.05$), while vitamin D concentration increased gradually with gestational age. But there're no significant differences in gender, admission age, Apgar score, serum Ca and serum P among different gestational age groups (Shown in Table 1).

3.2. Comparison of vitamin D concentration between RDS and non-RDS, BPD and non-BPD, mechanical ventilation (MV) and non-MV, death and survival

(1) RDS patients were mainly concentrated in "≤30 weeks" stage (11/15, 73.3%) compared with other two gestational age stages (Shown in Table 1). The only significant decrease of vitamin D concentration between RDS and non-RDS patients reflected in "≤30 weeks" stage (RDS *vs.* non-RDS: 29.48 ± 13.06 *vs.* 40.47 ± 20.52 nmol/l) ($P < 0.05$) (Shown in Table 2).

(2) BPD patients were also concentrated in "≤30 weeks" stage (3/15, 20.0%) compared with other two gestational stages (Shown in Table 1). Vitamin D concentration showed significant difference between BPD and non-BPD patients both in "≤30 weeks" and "30–34 weeks" stages (≤30 weeks, BPD *vs.* non-BPD: 33.20 ± 16.51 *vs.* 39.21 ± 16.65 nmol/l; 30–34 weeks, BPD *vs.* non-BPD: 30.36 ± 15.50 *vs.* 41.21 ± 20.40 nmol/l) ($P < 0.05$) (Shown in Table 2).

(3) Though vitamin D concentration in MV group was lower than non-MV group, there're no significant differences ($P > 0.05$) (Shown in Table 2).

(4) It has a higher mortality in the "≤30 weeks" group ($P < 0.01$) (Shown in Table 1). And vitamin D concentration

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Table 1
Baseline data of preterm infants.

	Gestational age			Statistics	*P*
	≤30 weeks (15)	30–34 weeks (59)	≥34 weeks (32)		
Mother's age (Y)	30.5 ± 14.8	29.6 ± 13.5	27.4 ± 13.1	F = 12.7	P < 0.05
Birth weight (g)	1283.0 ± 229.3	1784.5 ± 335.8	2327.7 ± 432.4	F = 50.30	P < 0.0001
Gender (M/F)	8/7	32/27	17/15	$\chi^2 = 3.89$	P = 0.57
Age (hour)	12.5 ± 7.0	15.9 ± 8.8	16.7 ± 9.2	F = 0.53	P = 0.59
Apgar score (n/N)					
1min < 8	3/15	5/59	2/32	FET = 2.02	P = 0.36
5min < 8	1/15	1/59	1/32	FET = 0.92	P = 0.63
Mechanical Ventilation	7/15	15/59	6/32	$\chi^2 = 4.16$	P = 0.13
RDS	11/15	15/59	8/32	$\chi^2 = 10.13$	P < 0.05
Days with oxygen	14.8 ± 7.6	11.2 ± 6.8	5.2 ± 2.3	F = 14.8	P < 0.05
BPD	3/15	3/59	1/32	FET = 3.94	P = 0.14
Death	3/15	1/59	0/32	FET = 8.92	P = 0.01
Vitamin D concentration (nmol/l)	35.0 ± 12.9	37.5 ± 22.6	40.8 ± 23.9	F = 0.48	P = 0.62
Serum Ca (mmol/l)	2.2 ± 0.2	2.3 ± 0.3	2.2 ± 0.2	F = 2.31	P = 0.11
Serum P (mmol/l)	3.0 ± 1.3	3.3 ± 1.4	2.7 ± 1.0	F = 0.95	P = 0.39

FET: Fisher Exact Test.

Table 2
Comparison of vitamin D concentration between RDS and non-RDS, BPD and non-BPD, MV and non-MV, death and survival.

Group	Concentration (nmol/l)		Statistics	*P*
Total				
Vitamin D (RDS *vs.* non-RDS)	36.43 ± 17.27	39.36 ± 19.06	*t* = 0.41	0.89
Vitamin D (BPD *vs.* non-BPD)	33.16 ± 16.33	38.90 ± 16.78	*t* = 2.14	0.08
Vitamin D (MV *vs.* non-MV)	36.48 ± 14.29	41.91 ± 15.32	*t* = 2.27	0.07
Vitamin D (Death *vs.* Survival)	38.22 ± 16.87	51.12 ± 23.94	*t* = 8.35	<0.001
≤30 weeks				
Vitamin D (RDS *vs.* non-RDS)	29.48 ± 13.06	40.47 ± 20.52	*t* = 4.83	<0.05
Vitamin D (BPD *vs.* non-BPD)	33.20 ± 16.51	39.21 ± 16.65	*t* = 7.33	<0.001
Vitamin D (MV *vs.* non-MV)	34.18 ± 14.45	42.58 ± 21.30	*t* = 3.15	0.06
Vitamin D (Death *vs.* Survival)	32.60 ± 17.05	57.32 ± 16.17	*t* = 4.09	<0.05
30–34 weeks				
Vitamin D (RDS *vs.* non-RDS)	40.32 ± 18.05	41.09 ± 17.92	*t* = 0.45	0.86
Vitamin D (BPD *vs.* non-BPD)	30.36 ± 15.50	41.21 ± 20.40	*t* = 6.41	<0.001
Vitamin D (MV *vs.* non-MV)	38.98 ± 15.91	45.41 ± 22.38	*t* = 1.89	0.08
Vitamin D (Death *vs.* Survival)	43.84	40.68 ± 14.58	/	/
≥34 weeks				
Vitamin D (RDS *vs.* non-RDS)	39.49 ± 15.03	36.52 ± 12.14	*t* = 0.67	0.80
Vitamin D (BPD *vs.* non-BPD)	35.92	36.28 ± 14.35	/	/
Vitamin D (MV *vs.* non-MV)	34.19 ± 14.07	37.92 ± 17.75	*t* = 0.81	0.49
Vitamin D (Death *vs.* Survival)	/	/	/	/

in dead patients was significant lower than survival infants at discharge ($P < 0.001$) (Shown in Table 2).

3.3. Correlation between vitamin D concentration and serum Ca, serum P, duration of MV, duration of oxygen support

It showed a good correlation between vitamin D concentration and serum Ca, serum P, duration of MV and duration of oxygen support in "≤30 weeks" group ($P < 0.05$). In "30–34 weeks" stage, there're significant correlations between vitamin D concentration and serum Ca, duration of oxygen support. The only significant difference in "≥34 weeks" stage was reflected in the correlation between vitamin D concentration and serum Ca ($P < 0.05$) (Shown in Table 3).

4. Discussion

With the development of perinatal medicine and technology in neonatal intensive care, a greater proportion of very and extremely low birth weight babies survive. But it also induces the incidences of RDS and BPD potentially increases in preterm infants. Although their pathogenesis has not yet been studied completely, immature lung development has been demonstrated to play an important role in the development of these diseases.

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Table 3
Correlation between vitamin D concentration and serum Ca, serum P, duration of MV, duration of oxygen support.

Group		P
≤30 weeks		
Vitamin D *vs.* serum Ca	$r = 0.45$	$P < 0.0001$
Vitamin D *vs.* serum P	$r = 0.55$	$P < 0.0001$
Vitamin D *vs.* duration of MV	$r = -0.24$	$P = 0.01$
Vitamin D *vs.* duration of oxygen support	$r = -0.81$	$P < 0.0001$
30–34 weeks		
Vitamin D *vs.* serum Ca	$r = 0.40$	$P < 0.05$
Vitamin D *vs.* serum P	$r = 0.01$	$P = 0.96$
Vitamin D *vs.* duration of MV	$r = -0.10$	$P = 0.63$
Vitamin D *vs.* duration of oxygen support	$r = -0.57$	$P < 0.0001$
≥34 weeks		
Vitamin D *vs.* serum Ca	$r = 0.42$	$P = 0.02$
Vitamin D *vs.* serum P	$r = 0.03$	$P = 0.86$
Vitamin D *vs.* duration of MV	$r = -0.03$	$P = 0.89$
Vitamin D *vs.* duration of oxygen support	$r = -0.16$	$P = 0.60$

Regarding lung development and maturation, several studies in rodents have shown a positive effect of vitamin D on the proliferation of ATII cells and fibroblasts, surfactant synthesis, and up-regulation of vitamin D receptor (VDR) in the lungs.[3,19–21] Rehan et al.[22] once demonstrated the ability of vitamin D to stimulate the production and secretion of surfactant-related phospholipids in human ATII cells. Phokela et al.[23] studied how $1,25(OH)_2D_3$ increases surfactant protein-B mRNA expression in human ATII cells and reduces the expression of surfactant protein-A mRNA in human fetal lung tissue and isolated ATII cells. They also demonstrated how $1,25(OH)_2D_3$ up-regulates VDR expression in human fetal lung tissue and human isolated ATII cells, confirming the findings of Nguyen et al. in human ATII cells.[5] In summary, vitamin D may be an important breakthrough direction to the study of pulmonary morbidities in the absence of sufficient clinical evidence.

4.1. RDS

In 1996, Nguyen et al. found that ATII cells, but not fibroblasts, express VDR.[14,24] To study the release of phospholipids, the cultured ATII cells were incubated with $1,25(OH)_2D_3$ (10^{*-9} M) or EB-1213 (10^{*-9} M) and prepared for thin-layer chromatography. Compared with controls, $1,25(OH)_2D_3$ stimulated the synthesis and secretion of phospholipids by ATII cells significantly. The authors suggested on that basis that $1,25(OH)_2D_3$ might be useful in the prevention or treatment of RDS. In a study from 2014, Mandell et al.[12] demonstrated that vitamin D has a proliferative and protective effect on fetal ATII cells and speculated that early vitamin D therapy might be a potential strategy for reducing the risk of acute respiratory distress.

Only one identified human study on RDS was reported by Ataseven F et al.[25] An increased risk of RDS was found for 25(OH)D below 25 nmol/l in univariate analysis. However, Our study showed that the significant difference between RDS and non-RDS patients on vitamin D concentration only reflected in "≤30 weeks" stage ($P < 0.05$), while the overall effect didn't show any statistical difference. Similar result was also found in the correlation between vitamin D concentration and duration of MV. Gestational week <30 is an important stage of fetal lung development, including alveolar surfactant. During this phase, synthesis and secretion of pulmonary surfactant has not completely started yet. In the context of low vitamin D concentration, this may be the cause of the high incidence of pulmonary diseases in this stage.

Gestational age is a criterion for judging fetal maturity. According to our data, vitamin D concentration gradually increased with gestational age (≤30 weeks, 30–34 weeks, ≥34 weeks) though there's no significant difference (Table 1). In the "≤30 weeks" stage, RDS and BPD patients (Including dead cases) all showed lower vitamin D concentration. Compared with that, in ≥34 weeks group, with vitamin D concentration increasing, incidence of RDS showed no difference between groups, and no dead cases appeared. It suggests that vitamin D concentration may be relevant to lung development of premature infants. And the appropriate concentration of vitamin D is beneficial to normal lung maturation of humans.

4.2. BPD

Hypovitaminosis D is frequent, not only during pregnancy, but also in preterm neonates. In Ireland, 78% of very preterm neonates born had a serum $25(OH)D_3$ below 50 nmol/l at 18 days of age despite vitamin D supplementation.[2] Similar results also could be found in Tianyue's paper, which reported abnormal rate of $25(OH)D_3$ reaches 26.7% in very low birth weight infants in China.[26] Other studies have reported a mean cord blood $25(OH)D_3$ concentration in preterm infants between 14.5 and 29.2 nmol/l.[1,27]

Onwuneme et al.[28] once found an association between vitamin D status and acute respiratory morbidity (As defined by differences in duration of positive pressure ventilation and highest oxygen concentration required in the delivery room). Backstrom et al.[29] conducted a randomized trial of 39 preterm infants to 200 *vs.* 960 IU of vitamin D per day for 3 months and observed a reduced need for assisted ventilation in the high-dose group. Although human studies of high evidence level and high quality on vitamin D and BPD are still missing, a meta-analysis of nine human vitamin A supplementation randomized controlled trial (RCT) showed a reduced risk for oxygen requirement at 1 month of age, or the combined outcome death at 1 month or oxygen requirement at 36 week postmenstrual age, in preterm neonates with birthweight 1500 g or gestational age 32 week gestation.[30] Because vitamin D acts through the VDR on the same vitamin D response elements as the retinoid X receptor of vitamin A, a similar effect of vitamin D could be plausible although yet not proven in humans.

In fact, a variety of host factors may confer altered susceptibility to BPD in preterm infants and some of these may be genetic and related to vitamin D bioavailability that is not only reflected in $25(OH)D_3$ levels. For example, common vitamin

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D-related polymorphisms, in vitamin D-binding protein or VDR likely alter the bioavailable levels of 25(OH)D_3. Koroglu OA et al.[19] concluded that the VDR Fok I polymorphism was associated with an increased adjusted risk of BPD. By contrast, KE Joung et al.[15] found there isn't any association between vitamin D status and pulmonary or other morbidities of prematurity. While our study found that BPD patients mainly focused on ≤30 weeks stage (3/15, 20.0%) compared with other two gestational age groups (Shown in Table 1). It showed a good correlation between vitamin D concentration and duration of oxygen support in "≤30 weeks" and "30−34 weeks" stages ($P < 0.05$). Besides, vitamin D concentration in dead patients was significant lower than survival infants at discharge ($P < 0.001$) (Shown in Table 2). Theses data may suggest that at least vitamin D is beneficial to infants with gestational age "≤30 weeks".

In conclusion, we found the significant decrease of vitamin D concentration between RDS and non-RDS patients only reflected in "≤30 weeks" stage. Significant decrease of vitamin D concentration in BPD patients was both showed in "≤30 weeks" stage and "30−34 weeks" stage, which is consistent with "duration of oxygen support". However, the overall effect did not show any difference in all preterm infants. Besides, as two of the limitations, our sample size is not large enough for single center study, and we didn't analyze the dynamic changes in vitamin D concentration during hospitalization. We didn't perform multivariate analysis to adjust the confounding variables. But, the present knowledge from animal and laboratory data should encourage researchers to perform large sample, multi-center RCT on the effect of vitamin D in the prevention and treatment of RDS and BPD.

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