ORIGINAL ARTICLE

Bronchopulmonary Dysplasia: A Hazard Factor in Preterms due to Maternal / Neonatal Vitamin D Inadequacy

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ABSTRACT

Aim: To explore the conceivable relationship between maternal/neonatal 25-hydroxy vitamin-D (25-OHD) levels and advancement of bronchopulmonary dysplasia (BPD).

Methods: This prospective study was conducted at Ch. Rehmat Ali Trust Hospital Lahore from 1st July 2017 to 31st December 2017. Two hundred preterms newborn children less than or equal to 32-weeks of gestation, who were determined to have respiratory trouble disorder were enlisted. 25-hydroxy vitamin-D levels were resolved in maternal/neonatal blood tests that were acquired at the time of admission to neonatal emergency unit. Congenital and chromosomal anomalies and infants who died before 36-weeks of gestation were not included in the study.

Results: Bronchopulmonary dysplasia was developed in 62 (31%). In bronchopulmonary dysplasia group, both maternal and neonatal 25-hydroxy vitamin D levels were essentially lower contrasted with those in no bronchopulmonary dysplasia group (P<0.0001). A positive relationship was identified amongst maternal and neonatal 25-hydroxy vitamin-D levels. All of bronchopulmonary dysplasia infants had 25-hydroxy vitamin-D level <10ng ml-1, which shows sever inadequacy. Univariate logistic regression investigation uncovered that maternal/neonatal vitamin-D levels were critical indicator of bronchopulmonary dysplasia. Odd ratio was 0.76 and 0.61 respectively, p<0.001.

Conclusion: We exhibited out of the blue that lower maternal and neonatal vitamin 25-hydroxy vitamin-D levels were related with bronchopulmonary dysplasia advancement in preterm babies. However, additionally thinks about bigger example sizes are expected to depict the conceivable connection between vitamin-D deficiency and bronchopulmonary dysplasia.

Keywords: Neonatal Vitamin-D Deficiency, Bronchopulmonary Dysplasia, 25-Hydroxy Vitamin-D Levels.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a chronic lung illness which is most common complication in premature babies, with huge risk happening in those at ≤26-weeks of gestation[1]. Thirty to forty percent infants, who have extremely low birth weight, may affects from bronchopulmonary dysplasia[2,3]. The new bronchopulmonary dysplasia is characterized by the drawn out requirements for supplemental oxygen or mechanical ventilation beyond thirty six weeks post-menstrual age.[4] The histologic characteristics of new bronchopulmonary dysplasia are described by formative arrest and disabled alveolar improvement joined by a capture of pulmonary microvasculature advancement, all of which mirror the formative adolescence of these high hazard preterms conceived at the intersection of canalicular and saccular period of lung development[1,5,6].

Bronchopulmonary dysplasia has a multifactorial etiology. However, regardless to forerunner occasion, infant lungs that have died of bronchopulmonary dysplasia show variations in mesenchyme which influences early lung development and furthermore late lung remodeling. Therefore, disrupted mesenchyme could potentially disrupt normal lung morphogenesis[7-9]. Lung morphogenesis is featured by a complex order of endodermal & mesodermal cell to cell interactions that outcome in the advancement of develop airways and alveolar structure[10,11]. Mechanisms that intervene these connections can influenced by an assortment of inherent and external factors, including vitamin-D[12].

In utero influencing alveolar epithelial mesenchymal interactions, vitamin-D has been reported as an important regulator of lung growth[13,14]. Although, existing data recommend a relationship of maternal intake vitamin-D during pregnancy and flowing 25-hydroxy vitamin-D levels with immaturity asthma and wheezing[15-17]. So far, prospectively there has been no examination which tentatively exploring the relationship of maternal and neonatal levels of vitamin-D with early respiratory morbidities of neonatal, for example, respiratory pain disorder and bronchopulmonary dysplasia.[18] The point of our examination was to explore the conceivable relationship between maternal/neonatal 25-hydroxy vitamin-D levels and bronchopulmonary dysplasia development in preterm newborn children.

MATERIALS AND METHODS

This prospective study was conducted at Ch. Rehmat Ali Trust Hospital Lahore from 1st July 2017 to 31st December 2017. Two hundred pre-term newborn children less than or equal to 32-weeks of gestation who were determined to have respiratory trouble disorders were included. The infants were excluded from this study who have congenital and chromosomal anomalies and infants who died before 36-weeks of gestation. Early surfactant treatment was given to all infants. Synchronized intermittent mandatory ventilation (SMIV) with 40 to 60 breaths min^{-1} rate, 0.35s to 0.38s inspiratory time, positive and expiratory pressure

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(PEEP) of 5cmH_2O to 6cmH_2O and peak inspiratory pressure (PIP) giving best chest wall rise and tidal volume was the essential method of ventilation in newborn children who could not be extubated promptly. Patients were extubated to nasal CPAP (continuous positive airways pressure) when positive end expiratory pressure equal to 4 to 5cmH_2O, peak inspiratory pressure=15cmH_2O, per minute rate=15 and FiO_2 ≤ 30% were attained. At 3rd day of life, all of enlisted infants were assessed through echocardiography for the presence of patent ducts arteriosus (PDA). If hemodynamically a significant patent ducts arteriosus was diagnosed, pharmacologic treatment with ibuprofen was given. Patients on supplemental oxygen or mechanical ventilation at or beyond 36-weeks of gestation were characterized as having bronchopulmonary dysplasia.

In the presence of maternal fever, tachycardia, uterine tenderness, foul smelling amniotic fluid and leukocytosis, chorioamnionitis (intra-amniotic infection) was clinically diagnosed. Demographic features at maternal were recorded including age, socio-economic status, mother's head cover status, presence of disease and educational level. Season of birth and APGAR scores of all newborns were recorded. During study period, birth season was classified in three groups; spring, summer and fall. According to usage of maternal vitamin-D supplementation, it was classified; insufficient usage (usage less than three months), no usage, >3-months regular usage.[18]

At the time of admission to neonatal intensive care unit, samples of blood were obtained from enrolled infants during routine blood sampling. After delivery maternal blood was obtained for routine laboratory analysis. Both maternal and neonatal plasmas were separated from blood samples and store it on -80^{0}C. 25-hydroxy vitamin-D levels were determined by using Shimadzu LC20AT model HPLC (high performance liquid chromatography system). SPSS was used to evaluate the data. In count and percentage the categorical factors are summarize, while continuous ones are summarize as median, mean, standard deviation, maximum, minimum and interquartile range. In terms of normal pattern the continuous factor/variables were assessed and as all continuous variables/factors which meet the normal distribution criteria, were compared through *t*-test, whereas x^2 tests were used to compare the categorical ones. At *p* value <0.05, statistical significance was considered.

RESULTS

Sixty two infants developed bronchopulmonary dysplasia and remaining 138 infants did not developed bronchopulmonary dysplasia out of these 200 infants. In table-I, demographic characteristics are summarized for both groups with and without bronchopulmonary dysplasia. In the group of bronchopulmonary dysplasia, APGAR score (1st & 5th minute), birth weight and gestational week were found significantly lower as shown in Table 1. Mechanical ventilation duration, continuous positive airway pressure (CPAP) and supplemental oxygen treatment duration, hospitalization and number of patients with diagnose of patent ductus arteriosus (PDA) were higher significantly in the group of bronchopulmonary dysplasia (Table 2). No difference was observed among groups with respect to maternal morbidities, maternal education status and maternal age. However, the mothers were less likely regular use of vitamin-D in the group of bronchopulmonary dysplasia, which was significant statistically (*p* value = 0.001) and the mothers who were not use the vitamin-D supplementation was higher significantly in the group of bronchopulmonary dysplasia as compared to that group without bronchopulmonary dysplasia, *p* value 0.03 (Table 3). 25-hydroxy vitamin-D (25-OHD) level of maternal/neonatal were lower significantly in the group of bronchopulmonary dysplasia (BPD) as compared to the group with no bronchopulmonary dysplasia, *p* value 0.001 (Table 4). Between groups, this difference was significant when compare with respect to status of mothers regarding usage of vitamin-D (regular, irregular and no use).

25-hydroxy vitamin-D levels were in the sever deficiency range <10ng ml-1 in all infants (100%) under the group of bronchopulmonary dysplasia, while only 42 (30.4%) infants have the same deficiency range <10ng ml-1 of 25-OHD levels in the group of no-BPD. In the group of BPD findings of high proportion of newborns with 25-hydroxy vitamin-D levels (<10ng ml-1) compared with those newborns without BPD group was significant statistically, *p*=0.0001. In the group of no bronchopulmonary dysplasia most infants 69.6% had insufficient range of vitamin-D levels, 11ng ml-1 to 32ng ml-1. There were no infants who have sufficient level of 25-hydroxy vitamin-D. 96.8% bronchopulmonary dysplasia patients had level ≤10ng ml-1 of vitamin-D, while in 26.1% patients of control group had level ≤10ng ml-1 of vitamin-D. For prediction of bronchopulmonary dysplasia, sensitivity, specificity, positive predictive value and negative predictive value of neonatal 25-OHD level <10ng ml-1 were observed to 96.8, 73.9%, 62.5% and 98.1% respectively. A positive association was observed among maternal and neonatal 25-OHD levels in both BPD group *r=0.727* and *p* value 0.0001 and in the group of no-BPD *r=0.938* and *p* value 0.001. Every 1ng ml-1 increase the level of vitamin-D in mother and decrease the bronchopulmonary dysplasia probability in newborn by 24% (0.76 odd ratio, confidence interval 95%, 68-86; *p* value <0.001) and 39% (0.61 odd ratio, confidence interval 95%; 48-76; *p* value <0.001) respectively.

Table 1: Demographic characteristics of groups

Variable	**BPD (N=62)**	**No BPD (N=138)**	***p***
Birth weeks	27.2±2.4	28.9±2.4	0.001
Birth weight(g)	875.6±247.3	1063.8±251.1	0.001
C-Section N (%)	38 (61.3%)	86 (62.3%)	0.48
Sex			
Female	30 (48.4%)	72 (52.2%)	0.726
Male	32 (51.6%)	66 (47.8%)	0.44
Usage of antenatal steroid	16(25.80%)	50 (36.2%)	0.305
At 1 min APGAR score	0.7±0.9	3.1±2.2	0.001
APGAR score (5 min)	3.5±1.5	5.7±1.8	0.001
Birth season, N (%)			
Spring	14 (22.6%)	32 (23.2%)	0.778
Summer	16 (25.8%)	26 (18.8%)	
Autumn	16 (25.8%)	48 (34.8%)	
Winter	16 (25.8%)	32 (23.2%)	

Table 2: Comparison of risk factors among bronchopulmonary dysplasia

Risk Factors	**BPD (N=62)**	**No-BPD (N=138)**	***P***
Maternal Preeclampsia	6 (9.7%)	20 (14.5%)	0.508
Chorioamnionitis	10 (16.1%)	34 (24.6%)	0.342
PDA (Patent Ductus Arteriosus)	22 (35.5%)	10 (7.2%)	<0.001
Mechanical Ventilation (days)	28.5±20.0	9.1±5.5	<0.001
Nasal continuous positive airways pressure (CPAP) (days)	8.7±5.5	4.1±2.0	<0.001
Oxygen usage duration (days)	73.7±25.0	27.1±11.2	<0.001
Hospitalization Duration (days)	81.5±25.6	49.9±13.5	<0.001

Table 3: Maternal characteristics

Variable	**BPD (N=62)**	**No-BPD (N=138)**	***P***
Age of Mother	25.5±3.9	26.6±4.4	0.204
Headscarf Usage	32 (51.6%)	40 (29%)	0.029
Mothers Educational Level N(%)			
Illiterate/Unschooled	18 (29%)	52 (37.7%)	0.667
Elementary Level	36 (58.1%)	62 (44.9%)	
Secondary Level	6 (9.7%)	16 (11.6%)	
University or High Level	2 (3.2%)	8 (5.8%)	
Mother Usage of Vitamin-D: N(%)			
Regular usage	8 (12.9%)	60 (43.6%)	0.008
Irregular usage	40 (64.5%)	64 (46.4%)	
No usage	14 (22.6%)	14 (10.1%)	
Pre-eclampsia: N(%)	6 (9.7%)	20 (14.5%)	0.508
Membrane Premature Rupture: N (%)	26 (41.9%)	62 (44.9%)	0.780
Chorioamnionitis: N(%)	10 (16.1%)	34 (24.6%)	0.342
Gestational Diabetes Mellitus: N (%)	4 (6.5%)	6 (4.3%)	0.655

Table 4: 25-Hydroxy Vitamin-D Levels of Maternal and Neonatal

Level of 25-Hydroxy Vitamin-D	**BPD (N=62)**	**No-BPD (N=138)**	***p***
Mother ng ml-1	19.0±2.3	28.8±7.7	<0.001
Infant ng ml-1	7.2±1.6	14.9±4.7	<0.001

DISCUSSION

Although association was reported in recent years between deficiency of vitamin-D and several lung diseases, no study investigate the relationship among neonatal deficiency of vitamin-D and bronchopulmonary dysplasia development in preterm newborns. In this study possible relationship among maternal/neonatal 25-OHD levels and subsequent growth of bronchopulmonary dysplasia in premature infants was proposed. 25-hydroxy vitamin-D levels of neonate were definitely associated with maternal 25-hydroxy vitamin-D levels. Recently two randomized control trials suggest that during pregnancy supplementation of 4000IU/day vitamin-D started at 12-week to 16-week of gestation in pregnant females was protected and most effectively appeared in improving serum 25-OHD concentration in mothers and neonates.[19-21]

Vitamin-D may have a part in development of lung as suggested by data from human and animal studies. The natural effects, 1, 25OH2, D3 are intervened by the vitamin-D receptor (VDR), a nuclear receptor. With the bond of 1, $25(OH)_2$ D3 vitamin-D receptor subsequent to translocating to the core ties to vitamin-D reaction components and adjusts the outflow of vitamin-D target qualities. It has been accounted for that more than three thousand qualities have vitamin-D genes[11,22],a large number of which are engaged with lung development.[23,24] Pathway genes of vitamin-D have been accounted for to be up-regulated aimed the pseudo glandular and secular phases of lung advancement where proximal and distal aviation routes are framed, respectively.

Alveolar epithelial mesenchymal interactions influenced by vitamin-D. Some studies shows that there is specific binding sites in alveolar type-II cell for vitamin-D as well as $1,25(OH)_2$ D3 invigorates both surfactant phospholipids and protein amalgamation[13,25,26] as well as differentiation of fibroblast and alveolar type-II cell and growth in vivo and vitro.[27] In a current investigational study, *in utero* vitamin-D inadequacy was found to adjust lung structure and work and furthermore increase inflammation, which is one of hallmark in pathogenesis of bronchopulmonary dysplasia in preterm newborn children.[28] So, it can be hypothesized that vitamin-D influences developing lung through numerous mechanisms. Preterm newborn, <32-weeks of gestational age especially were recommended to have an increase hazard of vitamin-D deficiency due to short gestation duration, insufficient stores and supplementation insufficiency through gut during postnatal early days.[11,29] In this study, all of the preterm infants had 25-hydroxy vitamin-D levels in acute deficiency range who developed bronchopulmonary dysplasia. Preterms mothers were found to have lower 25-hydroxy vitamin-D levels significantly as compared to preterms, with no-BPD, mothers. We observed a positive association among maternal and neonatal serum 25-OHD levels, this finding in accordance to three studies[30,31]. However, insufficiency of vitamin-D was present in all of the patients, it may be reasonable to assess the vitamin-D deficiency effects on development of other prematurity morbidities to clarify the facts that deficiency of vitamin-D in correlated with prematurity or only specific to bronchopulmonary dysplasia. In our study, patient group with no-bronchopulmonary dysplasia 30% had the lowest vitamin-D levels, this may possible represent the fact that deficiency of vitamin-D might reproduce being more sick at birth. Many studies showing a correlation among lower maternal level of vitamin-D during pregnancy and ensuing childhood asthma or wheezing and atopy increased risk. While high level of vitamin-D demonstrated reduced asthma or wheezing rates[15-17,32,33].

Vitamin-D lower levels have been associated to lung function lower levels.[34] Deficiency of vitamin-D and lower respiratory tract infections association has been demonstrated in infants and children.[18,35,36] This recent study showed that lower neonatal and maternal levels of 25-OHD correlated with early onset sepsis in term newborns.[37] Our study demonstrated a possible correlation among maternal/neonatal levels of 25-OHD vitamin-D and bronchopulmonary dysplasia we observed that 1ng ml^{-1} increases levels of vitamin-D in mothers and there is a decrease possibility of bronchopulmonary dysplasia in

newborn babies by 24% and 39% respectively, which showing that level of vitamin-D of mother and newborn was a predictor of bronchopulmonary dysplasia significantly. On the other hand, effect of maternal/neonatal levels of vitamin-D at the development of BPD that become observed in univariate logistic regression became not confirmed after controlling for other variables in the multivariate logistic regression model. The duration of oxygen therapy turned into found to be the simplest good sized predictor of BPD in multivariate logistic regression analysis, whereas different variables which include delivery weight, gestational age, preeclampsia, chorioamnionitis, postnatal sepsis, mechanical ventilation duration, continous positive airway pressure (CPAP), patent ductus arteries (PDA), and maternal/neonatal levels of 25-OHD were observed to have no impact on the development of bronchopulmonary dysplasia. Preeclampsia has also been identified as an unbiased hazard aspect for bronchopulmonary dysplasia.[38]

The qualities of this prospective investigation were that the conceivable relationship between maternal/neonatal vitamin-D levels and BPD development in preterm newborn children was appeared. Accordingly, it might be theorized that sufficient maternal 25-OHD level aimed pregnancy and related neonatal 25-OHD levels during child birth might be defensive against BPD development in preterm babies.

CONCLUSION

We conclude that maternal and neonatal vitamin 25-hydroxy vitamin-D levels were related with development of bronchopulmonary dysplasia (BPD). Vitamin-D appears to have a huge potential part to impact lung development. In this manner, it might be sensible to express the constructive outcome of suitable maternal vitamin-D supplementation aimed pregnancy, which counteractive action of bronchopulmonary dysplasia in premature babies.

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