

To Study Serum Vitamin D Levels in Preterm Neonates and Its Association with Respiratory Distress Syndrome

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Abstract

Background: It seems Vitamin D deficiency may be an important risk factor for Respiratory Distress Syndrome in Preterm neonates. There are limited studies on vitamin D deficiency as risk factor for RDS in preterm neonates, so this study was conducted to test above mentioned association.

Methods: Hospital based observational study conducted at Department of Pediatric Medicine, SMS Medical College and attached group of hospitals, Jaipur.

Results: Mean vitamin D level of study subjects was 14.85 ± 10.65 ng/ml. RDS developed in 52/200 preterm neonates. RDS developed in 40/102 (39.2%), 11/66(16.7%) and 1/19(5.3%) neonates with severe vitamin D deficiency, moderate vitamin D deficiency, and neonates with insufficiency respectively. RDS was more common in neonates who were severely deficient neonates ($p < 0.001$).

Conclusion: Vitamin D deficiency was found to be associated with increased risk of RDS in preterm neonates and risk of RDS was highest with severe vitamin D deficiency.

Keywords: Vitamin D, RDS, Preterm.

Introduction

Preterm birth, defined as birth prior to 37 weeks gestation, affects 15 million newborns every year.¹ It is leading cause of under five child mortality worldwide and accounts for one million deaths annually.²

Respiratory disorders are the most frequent cause of admission for neonatal intensive care in both term and preterm infants. Respiratory distress syndrome formerly known as hyaline membrane disease is most common cause of respiratory distress, morbidity and mortality in preterm neonates.³

Respiratory distress syndrome occurs in 60 – 80 % of neonates <28 weeks gestational age, in 15-30% of those between 32 and 36 weeks gestational age and rarely in those ≥ 37 weeks gestational age.⁴

Surfactant deficiency, which increases surface tension in the alveoli, resulting in micro atelectasis and low lung volumes, is the primary cause of Respiratory Distress Syndrome. Surfactant is a complex mixture of 90% lipids and 10% proteins produced by type 2 pneumocytes of alveolar epithelium.⁵

Lung maturity occurs with differentiation of type 2 pneumocytes. Vitamin D has been shown to play roles in musculo-skeleton function, regulation of hormonal secretion, immune system function and has significant effects on embryogenesis, cellular growth and differentiation of fetal organs including lung development^{6,7}. Vitamin D has positive effects on the alveolar type II cell via Vitamin D receptors, fibroblast proliferation, surfactant synthesis, and alveolarization⁸. Maternal vitamin D deficiency increases the risk of premature delivery, preeclampsia, gestational diabetes mellitus and intrauterine growth restriction.⁹⁻¹¹. These perinatal complications trigger preterm delivery and these premature infants have a greater risk of vitamin D deficiency.

Vitamin D deficiency is common in pregnant and lactating women. Fetus has no mechanism for endogenous production of vitamin D and is dependent on maternal serum Vitamin D which is transferred from mother to fetus predominantly during 3rd trimester.¹² Therefore Preterm neonates are at increased risk of Vitamin D deficiency.¹³ Early recognition of vitamin D deficiency makes early and appropriate supplementation possible to prevent the increased risk of possible vitamin D related morbidities.

It seems Vitamin D deficiency may be an important risk factor for Respiratory Distress Syndrome in Preterm neonates. There are limited studies on vitamin D deficiency as risk factor for RDS in preterm neonates, so this study was conducted to test above mentioned association.

Material and Methods

Setting: Department of Pediatric Medicine, SMS Medical College and attached group of hospitals, Jaipur.

Study Design: Hospital based observational study.

Duration of Study: From May 2018 to September 2019

Sample Size: Sample size was calculated at 95% confidence level and alpha error of 0.05 assuming 14% respiratory distress syndrome observed in mild to moderate vitamin D Deficiency among the preterm neonates as per the reference article "Is vitamin D deficiency a risk factor for respiratory distress syndrome". At absolute allowable error of 5% the required sample size was 200 preterm neonates

Inclusion criteria

- All preterms born at <37 weeks of gestational age
- Prior informed consent

Exclusion criteria:

- Refusal for consent
- Major congenital anomaly
- Neonates with sepsis
- Perinatal asphyxia
- Maternal Prolonged rupture of membranes, Gestational diabetes mellitus, Pregnancy induced hypertension, Chorioamnionitis.

Methodology

The study was conducted on preterm neonates of <37 weeks gestational age delivered and admitted in NICU in SPMCHI and attached group of hospitals S.M.S Medical College Jaipur over the study period. Written consent was taken from parents/attendants and after applying inclusion and exclusion criteria detailed antenatal history, natal history, post natal history, general physical and systemic examination of the neonate was done and data entered into the structured proforma.

2 ml of venous blood samples for Serum Vitamin D (25 Hydroxy vitamin D) levels was collected within 24 hours of birth of neonate from both neonate and mother

in plane vial. Serum Vitamin D levels was measured using the ADVIA Centaur Vitamin D Total Assay.

Normal Vitamin D levels was defined as >30ng/ml, insufficiency as 20-30ng/ml, moderate deficiency as 10-20ng/ml and severe deficiency as <10ng/ml according to U.S Endocrine society guidelines. Subjects were divided as having normal serum vitamin D levels and deficient serum vitamin D levels which was further classified as insufficiency, moderate deficiency and severe vitamin D deficiency.

Data was collected and then subjected for statistical evaluation.

Statistical Analyses

- All statistical analyses was done using Epi info version 7.2.1.0.
- Nominal / categorical variables were summarized as frequency and percentage and were analyzed using Chi square test.
- Continuous variables were summarized as mean and standard deviation and were analyzed ANOVA test for multiple group comparison.
- A p value < 0.05 was taken as statistically significant.

Observations

Table 1: Distribution of study subjects according to gestational age

Gestational age (Mean ± SD)	32.19 ± 2.04 weeks
Male : Female	109:91

Mean gestational age of study subjects was 32.19±2.04 weeks. 109 (54.5%) neonates were male and 91 (45.5%) neonates were female.

Table 2: Vitamin D levels among preterm neonates

Vitamin D levels	N	Percentage (%)
Normal (> 30 ng/ml)	13	6.5
Insufficiency (20 – 30 ng/ml)	19	9.5
Moderate deficiency (10 – 20 ng/ml)	66	33
Severe deficiency (<10 ng/ml)	102	51
Total	200	100
Mean ± SD	14.85 ± 10.65 ng/ml	

There were 200 preterm neonates; among which 13 (6.5%) neonates had normal vitamin D levels, 19(9.5%) neonates had insufficiency , 66(33%) neonates had moderate vitamin D deficiency and 102(51%) neonates had severe Vitamin D deficiency.

Mean vitamin D level of study subjects was 14.85 ± 10.65 ng/ml.

Table 3: Respiratory distress syndrome in relation to Vitamin D levels of neonates

Neonates Vitamin D	RDS		No RDS		Total	
	N	%	N	%	N	%
Normal	0	0	13	100	13	100
Insufficiency	1	5.3	18	94.7	19	100
Moderate deficiency	11	16.7	55	83.3	66	100
Severe deficiency	40	39.2	62	60.8	102	100
Total	52	26	148	74	200	100

Chi-square = 21.062 with 3 degrees of freedom; P < 0.001 (S)

Table 3 shows that RDS developed in 52/200 preterm neonates. RDS developed in 40/102 (39.2%), 11/66(16.7%) and 1/19(5.3%) neonates with severe

vitamin D deficiency, moderate vitamin D deficiency, and neonates with insufficiency respectively. RDS was more common in neonates who were severely deficient neonates ($p < 0.001$). Also none of neonates who had normal serum vitamin D levels developed RDS.

Discussion

Respiratory distress syndrome is most common cause of respiratory distress, morbidity and mortality in preterm neonates. Surfactant deficiency is the primary cause of Respiratory Distress Syndrome. Surfactant is produced by type 2 pneumocytes of alveolar epithelium. Vitamin D has positive effects on the alveolar type II cell via Vitamin D receptors, fibroblast proliferation, surfactant synthesis, and alveolarization. There are limited studies on vitamin D deficiency as risk factor for RDS in preterm neonates, so this study entitled "To study serum vitamin D levels in preterm neonates and its association with respiratory distress syndrome" was conducted to test above mentioned association.

In our study, RDS developed in 52/200 (26%) of preterm neonates. RDS developed in 40/102 (39.2%), 11/66 (16.7%) and 1/19 (5.3%) neonates with severe vitamin D deficiency, moderate vitamin D deficiency, and neonates with insufficiency respectively. RDS was more frequent in babies with severe deficiency ($p < 0.001$). Risk of RDS was 2.5 times more in severely deficient neonates as compared to moderately deficient neonates. None of the patient who developed RDS had normal serum vitamin D levels.

These results were comparable to **Ataseven et al in 2014**¹⁴ who investigated 152 neonates of 29-35 weeks gestation and found that RDS was more more common in neonates with severe vitamin D deficiency; 27/97 (28%) as compared to neonates with moderate to mild deficiency combined; 8/55 (14%) ($p < 0.05$). RDS risk

was reduced 3.34 times in babies with higher vitamin D levels. Similarly **Fetteh et al**¹⁵ investigated the relationship between cord blood 25(OH)D levels with RDS in preterm neonates and it was observed that development of RDS in vitamin D deficient group was higher than the group with normal vitamin D levels ($p < 0.001$) which was similar to our study. Multivariate analysis showed that higher 25(OH)D level was preventive for the development of RDS (odds ratio, 0.6; 95% confidence interval (0.5-0.8); $p = 0.001$).

Ian Kim et al¹⁶ studied association between low vitamin D levels at birth and neonatal morbidities in 188 preterm neonates and found higher incidence of RDS and broncho-pulmonary dysplasia in neonates with vitamin D deficiency ($p < 0.05$). Logistic analysis shows that a low serum 25(OH)D level (< 20 ng/mL) was a risk factor for respiratory distress syndrome (odds ratio; 4.32, $p = 0.010$) and bronchopulmonary dysplasia (OR; 4.11, $p = 0.035$).

Conclusion

Vitamin D deficiency was found to be associated with increased risk of RDS in preterm neonates and risk of RDS was highest with severe vitamin D deficiency.

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