

Original Research Article

Association of serum vitamin D levels and transient tachypnea of newborn: a case control study

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ABSTRACT

Background: Transient tachypnea of newborn (TTN) is a common cause of respiratory distress in newborns with estimated incidence of 1-2% of all newborns. Although a self-limiting transient condition but it may cause severe morbidities. This study was conducted to find association of serum vitamin D levels in neonates who develop TTN as compared to normal healthy neonates.

Methods: With thorough history with structured questionnaire and lab tests, serum vitamin D levels of 45 neonates who develop TTN were compared with 56 healthy neonates in control group.

Results: Out of 45 neonates who develop TTN 39(86.7%) were deficient in vitamin D as compared to control group where 33(58.9%) out of 56 healthy neonates were deficient in vitamin D.

Conclusions: Lower vitamin D levels at birth in term neonates is associated with increased risk of developing TTN and vitamin D may have a role in its pathogenesis.

Keywords: Lower segment cesarean section (LSCS), Respiratory distress, Term newborns, Transient tachypnea of newborn (TTN), Vitamin D

INTRODUCTION

Respiratory distress is common in the early neonatal period and occurs in up to 7% of newborn infants.¹ Much of the focus has been on respiratory distress syndrome and chronic lung disease of prematurity in preterm infants (<37 weeks of gestation) but every year a significant number of term-born infants are admitted to neonatal units for management of their respiratory distress.²⁻⁶ The causes of respiratory distress in a newborn are diverse and multi-systemic. Pulmonary causes may be related to alterations during normal lung development or transition to extra uterine life. Multiple conditions can cause respiratory distress in term newborn infants which includes transient tachypnea of the newborn, respiratory distress syndrome,

pneumonia, meconium aspiration syndrome, pneumothorax, primary or secondary pulmonary arterial hypertension, hypoxic-ischemic encephalopathy, aspiration of milk or blood. Transient tachypnea of the newborn, also called wet lung syndrome is the most common cause of neonatal respiratory distress, constituting more than 40 percent of cases.⁷

Transient tachypnea of the newborn (TTN) is a parenchymal lung disorder characterized by pulmonary edema resulting from delayed resorption and clearance of fetal alveolar fluid.⁸ TTN is a common cause of respiratory distress in the immediate newborn period. In a review of 33,289 term deliveries (37 to 42 weeks), the incidence of TTN was 5.7 per 1000 births.⁹ Although thought to be a

benign, self-limited condition, there are increasing data to suggest that TTN increases a newborn's risk for developing a wheezing syndrome early in life.¹⁰

Delayed resorption of fetal lung fluid is thought to be the underlying cause of TTN. Fluid fills the air spaces and moves into the interstitium, where it pools in perivascular tissues and interlobar fissures until it is eventually cleared by the lymphatics or absorbed into small blood vessels.¹¹ Immaturity of epithelial sodium channels (ENaC) is now believed to be major factor in failure of lung fluid resorption. A surge in catecholamines and endogenous steroids increase the expression and activity of ENaC.^{12,13} The excess lung water in TTN results in decreased pulmonary compliance. Tachypnea develops to compensate for the increased work of breathing associated with reduced compliance.¹¹ In addition, accumulation of fluid in the peribronchiolar lymphatics and interstitium promotes partial collapse of the bronchioles with subsequent air trapping. Continued perfusion of poorly ventilated alveoli leads to hypoxemia, and alveolar edema reduces ventilation, sometimes resulting in hypercapnia.¹⁴

The clinical presentation includes tachypnea immediately after birth or within two hours, with other predictable signs of respiratory distress. Symptoms can last from a few hours to two days. Chest radiography shows diffuse parenchymal infiltrates, a wet silhouette around the heart, or intralobar fluid accumulation.⁵

Vitamin D plays important role in various disease processes starting from neonatal period to adulthood. Vitamin D deficiency is associated with respiratory tract infections in newborns and wheezing episodes later in life.¹⁵ Low vitamin D levels has also been considered as one of the risk factor for respiratory distress syndrome.¹⁶ Moreover, in fetal rat lung, vitamin D increases the synthesis and secretion of surfactant lipids and proteins in alveolar type II cells.^{17,18} As role of vitamin D in TTN has not been studied much, so we conducted present study in our hospital to find the association between serum vitamin D levels and TTN.

METHODS

The present study was a prospective case control study which was conducted in the department of pediatrics at Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab, India from January 2015 to June 2016. Total of 45 neonates diagnosed with TTN were included in the study and 56 healthy neonates were also included as controls for comparison. Neonates both in study and control group were born under similar indications for elective LSCS. Criteria used to diagnose or label a neonate having TTN were clinical signs of respiratory distress (tachypnea, grunting, nasal flaring, retractions and cyanosis), tachypnea which persisted 48-72 hours, chest X-ray consistent with TTN (hyperaeration, perihilar streaking, flattening of diaphragm and pleural or interstitial fluid) and absence of any diagnosis leading to

respiratory distress.¹⁹ Neonates with hypoglycemia, hypocalcemia, polycythemia, meconium aspiration, any congenital cardiac, respiratory or central nervous system malformation, septicemia and birth asphyxia were excluded. Controls were classified as neonates born at term gestation by elective LSCS due to one of similar sets of indications in mothers as of cases and who did not develop respiratory distress and had no other indication for admission at birth.

A detailed structured questionnaire was used to obtain information regarding maternal age, education, parity, detail history of first and second trimester including any fever, rash, any drug intake, supplements of vitamin D and calcium taken during pregnancy. Information regarding indication for LSCS, and any risk factors for neonatal sepsis were noted. Mothers with eclampsia and pre-eclampsia as indications of LSCS were excluded as association of vitamin D deficiency with these conditions have been seen.²⁰ Also information regarding assigned cases and controls were noted. Such information included weight, sex, respiratory rates at birth and subsequent intervals in cases group, modality of treatment used for respiratory distress. Informed written consent was obtained from parents/guardian of the children providing all the necessary information about the study.

Blood sample of the cases and controls were collected by venipuncture during first 24 hours of life in the red topped vials and sent to the lab after labelling it with patients MRD no. and name. Serum calcium, blood sugar, alkaline phosphatase (ALP), vitamin D[25(OH)D₃], complete blood counts, quantitative CRP levels were estimated. Blood culture sample was also sent in both study and control group. After centrifugation, serum was separated, stored at -20 degree Celsius until analyzed. Vitamin D level was estimated by Direct ELISA method, serum calcium by cresolphthalein complexone method and serum ALP by Pnnp (para nitro phenyl phosphate) method.²¹

Neonates who showed positive blood culture, raised CRP levels and other clinical features of sepsis were excluded from the study. Serum levels of vitamin D >30 ng/ml were taken as sufficient; insufficiency is said to be present between 20-30 ng/ml and <20ng/dl were designated as deficiency.²² Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean±SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected, then nonparametric test was used.

Statistical analysis

Data so obtained was statistically analyzed by Microsoft SPSS, Version 17.0. Statistical tests were applied and quantitative variables were compared using ANOVA/Kruskal Wallis Test (when the data sets were not normally distributed) between the groups. Qualitative variables were correlated using Chi Square test /Fisher's

exact test. A p value of <0.05 were considered as significant.

RESULTS

In the period of 18 months, 45 neonates were enrolled as cases who qualify the inclusion criteria and were labelled as neonates having TTN and 56 neonates born by LSCS with similar sets of indications for LSCS with full term gestation who did not develop respiratory distress were randomly selected as controls. In the cases group 15 neonates (33.3%) were females and 30 neonates (66.6%) were males whereas in the control group, 17 (30.4%) were females and 39 (69.6%) were males. It was observed that 26 (57.8%) neonates in cases group were born to primigravida mothers while 19 (42.2%) neonates were born to multigravida mothers. In control group 25 (44.6%) neonates were born to primigravida mothers and 31 (55.4%) to multigravida mothers. Parity, gestation age, birth weight and sex of neonates had no statistically significant association between the two groups ($p>0.05$).

In our study mothers of 31 (68.9%) neonates in cases group did not receive calcium and vitamin D supplementation (400 IU/day) in one or other form and 14 mothers (31.1%) did receive such supplements at onset of second trimester till delivery. In control group mothers of 19 (33.9%) neonates didn't get calcium and vitamin D supplements during antenatal period and 37 (66.1%) did received such supplements. This association was found statistically significant as p value was <0.05, so significant difference was found in vitamin D levels between neonates born to mothers who had vitamin D supplementation as compared to those born to mothers who had no supplementation during pregnancy.

Table 1: General characteristic of study and control groups. (* values are mean±SD).

	Cases (n=45)	Controls (n=56)	p value
Gestation age	38.52±0.78*	38.29±0.80*	0.072
Birth weight	2.90±0.37*	2.95±0.32*	0.416
Gender			
Males	30 (66.7%)	39 (69.6%)	0.749
Females	15 (33.3%)	17 (30.4%)	
Parity:			
Primigravida	26 (57.8%)	25 (44.6%)	0.189
Multigravida	19 (42.2%)	31 (55.4%)	
Vit D supplementation			
Received	14 (31.1%)	37 (66.1%)	<0.001
Not received	31 (68.9%)	19 (33.9%)	

The mean serum vitamin D level in study and control groups were 11.32±8.21 and 22.66±13.15 ng/ml, respectively showing that it was significantly lower in study group ($p<0.001$). There was no statistically significant difference in values of serum calcium and alkaline phosphatase (ALP) ($p>0.05$).

Table 2: Various lab parameters in study and control groups (values are mean±SD).

Lab parameters	Cases (n=45)	Controls (n=56)	p value
Vit D levels	11.32±8.21	22.66±13.15	<0.001
S. Calcium	9.47±1.07	9.74±0.80	0.151
ALP	177.71±52.07	179.86±60.39	0.851

Vitamin D levels were estimated and sub categorized in all the enrolled neonates. In study group 39 (86.7%) neonates had deficient levels, 3 (6.66%) had insufficient and 3 (6.66%) had sufficient vitamin D levels. In control group 33 (58.9%) had deficient vitamin D levels, 13 (23.2%) had insufficient and 10 (17.8%) had levels in the sufficient range. This showed that vitamin D deficiency had statistically significant association with neonates developing TTN ($P<0.05$).

Table 3: Sub categories of vitamin D levels in study and control groups.

Vitamin D	Cases (n=45)	Controls (n=56)	p value
Deficient	39 (86.7%)	33 (58.9%)	0.009
Insufficient	3 (6.66%)	13 (23.2%)	
Sufficient	3 (6.66%)	10 (17.9%)	

DISCUSSION

Respiratory distress is one of the common causes of admission in the early neonatal period with transient tachypnea of newborn as the commonest cause which resolves in the first three days of life. Vitamin D has been studied in various disease processes. It has important role in decreasing the mortality and morbidity in the neonatal period as it helps in prevention of sepsis. Vitamin D has a direct role in the production of antimicrobial peptides such as cathelicidin thus explaining the role in preventing infections.²³ Vitamin D status during pregnancy also has strong correlation with innate immune response of fetus.²⁴

Vitamin D plays important role in prevention of respiratory diseases like respiratory distress syndrome, pneumonias, wheezing episodes, asthma in later life. Vitamin D also has a role in prevention of acute lower respiratory infections in toddlers.¹⁶ The bronchial epithelium can convert the precursor 25(OH)D₃ to local active 1,25(OH)₂D₃, which reduces the production of inflammatory cytokines and chemokines and enhances the synthesis of antimicrobial peptides.

It promotes autophagy that has an important function in killing neoplastic cells and inhibits proliferation of airway smooth muscle.²⁵⁻²⁹ Specific binding sites for 1,25(OH)₂D₃ localized to type II pneumocytes have been found in fetal rat lungs and it has been shown that vitamin D accelerates type II pneumocyte maturation, increases the surfactant

synthesis and secretion and has a critical role in epithelial-mesenchymal interaction during lung growth.^{17,18}

In probable pathophysiology of TTN, immaturity of epithelial sodium channels (ENaC) is now believed to be major factor in failure of lung fluid resorption. A surge in catecholamines and endogenous steroids increase the expression and activity of ENaC.^{12,13} As hypothesized by Konca et al.³⁰ that vitamin D deficiency may decrease the expression of ENaC (as steroid hormone) and surfactant synthesis and develop TTN. Based on these observations we also studied association of vitamin D deficiency in transient tachypnea of newborns.

In our study it was found that total neonates who developed TTN were having deficient Vitamin D levels as compared to normal newborns in control group and the association between vitamin D levels and TTN were found to be highly significant. ($p=0.009$). Mean vitamin D levels in cases group was 11.32 ± 8.21 and in control group was 22.66 ± 13.15 . Similar results were found in the study done by Konca et al. in 2014 in which serum vitamin D levels were studied in infants diagnosed as TTN and those without TTN and found that the serum levels of $25(\text{OH})\text{D}_3$ were significantly lower in infants with TTN compared to infants with no respiratory distress ($p<0.01$).³⁰

The fetus is dependent on the mother for vitamin D in utero (the $25(\text{OH})\text{D}_3$ crosses the placenta).³¹ In our study we found statistically significant role of supplementation of vitamin D in pregnancy on serum vitamin D levels in neonates as these neonates were less deficient in vitamin D as compared to neonates whose mothers were not supplemented. Similar finding was also observed by Cadario et al.³² Though Konca et al. found no statistically significant difference in vitamin D levels of infants born to mothers who were supplemented with vitamin D as compared to those who were not supplemented.³⁰

CONCLUSION

To conclude, present study was done to find out any association of vitamin D levels in neonates who develop TTN and our data suggests that lower vitamin D levels are associated with an increased risk of TTN and vitamin D may have a role in the pathogenesis of TTN. Also supplementation of vitamin D during antenatal period in mothers have improved vitamin D levels in newborns born to them.

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