Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.234154.2873 Volume 30, Issue 7, Oct. 2024
Manuscript ZUMJ-2406-3456 DOI . 10.21608/ZUMJ.2024.300085.3456
ORIGINAL ARTICLE

Study of relationship between vitamin D and ventilator associated pneumonia in the neonatal intensive care unit

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Submit Date: 28-06-2024
Revise Date : 15-07-2024
Accept Date: 24-07-2024

ABSTRACT

Background: Neonatal ventilator-associated pneumonia (VAP), which involves invasive mechanical ventilation, is a neonatal nosocomial lower airway infection that manifests after 48 hours. The current study aimed to determine the relationship between the development of VAP in intubated newborns and the serum 25- hydroxyvitamin D3 level. **Methods:** This was a prospective cohort study that included 48 neonates admitted to the Neonatal Intensive Care Unit (NICU) at the Pediatrics Department, Zagazig University Hospital. The patients were divided into 2 groups, the VAP group and the Non-VAP group, with 24 patients in each group. All neonates were subjected to complete history taking including personal data: age and gender, complaint, present, past and perinatal history, developmental and dietetic history, vaccination history and family history and full clinical examination either general examination or local examination for all systems by inspection, palpation, percussion, and auscultation. **Results:** In our study, in comparison to the Non-VAP group, the VAP group had considerably less 25(OH) vitamin D3 (29.8 ng/ml). Our research revealed a strong positive correlation between vitamin D3 and weight, Apgar score 1 m and 5 min, and PaO2, while there was a significant negative correlation between duration of NICU stay and mechanical ventilation (MV), White blood cells (WBCs), C-reactive protein (CRP) and PaCO2. In our study, at of 29.8, vitamin D3 showed 92.3% sensitivity and 100% specificity, with a p value <0.001. **Conclusion:** Insufficient serum levels of vitamin D3 may increase the likelihood of developing ventilator-associated pneumonia in neonates undergoing mechanical ventilation.

Key words: vitamin D3 Level; Ventilator-Associated Pneumonia; Neonatal Intensive Care Unit

INTRODUCTION

Neonatal ventilator - associated pneumonia (VAP) is defined as a nosocomial lower airway infection in intubated newborns with onset beyond 48 hours of invasive mechanical ventilation. Intubation and mechanical ventilation are known risk factors for the acquisition of nosocomial pneumonia. VAP is one of the most frequently diagnosed nosocomial infections and “second most

common cause for antibiotic use in neonatal intensive care units (NICUs) after early onset sepsis **[1].**

VAP, or ventilator-associated pneumonia, is a prevalent, substantial, and current public health concern. It is connected to a greater risk of bronchopulmonary dysplasia, extended use of mechanical ventilation, and longer hospitalizations in the neonatal intensive care unit (NICU). However, the absence of specific biomarkers and ambiguous clinical criteria pose challenges in making a diagnosis. When combined with the clinical symptoms and signs of pneumonia, biomarkers can provide supplementary information regarding the severity of the infection and aid in differentiating between bacterial and viral causes **[2].**

vitamin D3, a steroid hormone, controls bone metabolism, bone development, and the body's calcium and phosphorus balance. The body needs sunlight exposure to synthesize vitamin D3. Dietary sources of vitamin D3 are absorbed in the jejunum and duodenum. The liver catalyzes the hydrolysis of both substances, resulting in the production of 25hydroxy vitamin D3, the most common metabolite of vitamin D3 **[3].**

vitamin D3, in its active form (1,25-dihydroxyvitamin D3 [1,25(OH)2D3]), acts as a vitamin and prehormone. It can regulate the functional activity of B cell, T cell, monocytes, macrophages, dendritic cells, neutrophils, and platelets, among other immune cells. These cells express the nuclear receptor known as the vitamin D3 receptor (VDR), which is a transcription factor that is activated by ligands. The superfamily of nuclear receptors includes the VDR, which is a molecule that regulates transcription in a ligand-dependent manner **[4].**

The action of 1,25(OH)2D3 on target cells occurs through a specific mechanism. It starts with 1,25(OH)2D3 binding to the VDR in the cytoplasm. After that, it combines with retinoid X receptor-α (RXR-α) in the nucleus through a process called heterodimerization. The 1,25(OH)2D3-RXR-VDR complex is a complex that binds to certain DNA segments referred to as vitamin D3 response elements (VDREs) **[5].**

Adults with low serum levels of 25(OH) D3, indicating subclinical vitamin D3 insufficiency, had a greater risk of tuberculosis. There was also a reported correlation between subclinical low levels of vitamin D3 and acute lower respiratory infection in children who did not have rachitics **[6].** The objective of the present investigation was to identify the correlation between the level of serum 25-hydroxy vitamin D3 and the occurrence of ventilator-associated pneumonia (VAP) in neonates who were intubated.

PATIENTS AND METHODS

This prospective cohort study was conducted on 48 neonates admitted to the NICU at the Pediatrics Department, Zagazig University Hospital, from April 2023 to April 2024. The parents of the patients provided signed, informed consent. Each patient had a secret code number, and all parents were given an explanation of the study's objectives. It enrolled 24 neonates with pneumonia, and 24 apparently healthy term neonates under control

The inclusion criteria for both sexes were neonates ventilated for more than 48 hours and newborns with gestational ages greater than 32 weeks.

The exclusion criteria were neonates with a gestational age $\leq$ 32 weeks, neonates ventilated for $\leq$48 hours and neonates with congenital pneumonia or multiple congenital anomalies.

Grouping:

The patients were categorized into two groups: the VAP group, which consisted of 24 neonates with pneumonia, and the Non-VAP group, which also consisted of 24 neonates without pneumonia.

After enrolling the patients in the study, their serum level of 25-hydroxy vitamin D was determined. On the first day of diagnosis, antibiotic therapy of patients was started according to the protocol of our hospital

The prescribed treatment regimens for all patients consisted of a combination of vancomycin and carbapenem, along with a second antipseudomonas medication, which might be either ciprofloxacin or aminoglycosides. If there was a lack of response to therapy and the tracheal culture findings indicated, the treatment plan was adjusted accordingly.

All neonates were subjected to:

All neonates were subjected to a) Complete history taking including personal data: age and gender, complaint, present, past and perinatal history, developmental and dietetic history, vaccination history and family history. b) Full clinical examination either general examination or local examination for all systems by inspection, palpation, percussion, and auscultation.

Venous blood samples (3 cm) were obtained from each newborn who participated in the study and were then separated into two aliquots. One milliliter of venous blood was used to determine the complete blood count (CBC), while two milliliters of venous blood were allowed to clot. After centrifugation, the serum was separated and kept at -20°C to detect serum, liver function test (LFT), kidney function test (KFT), C-reactive protein (CRP), and vitamin D3 levels.

Blood analysis was completed with a Coulter device. Turbidimetry was used to measure C-reactive protein (CRP) (normal value <6). Tests of liver function. Tests for kidney function (creatinine, urea) were performed. Serum 25- droxy vitamin D3 level.

Enzyme-linked immunosorbent assay (ELISA) technology was used to measure the serum 25-hydroxy vitamin D3 level. Sterile venipuncture was performed to collect venous blood, which was then placed in tubes that were appropriately labelled with the patient's name. After the serum tubes were allowed to clot at room temperature to extract the serum from the entire blood sample, centrifugation was performed. The serum was kept at 2:8°C while submerged. Blood and endotracheal cultures when VAP was suspected and after two days of mechanical ventilation. Chest radiographs were taken upon admission and whenever necessary. Arterial blood gases ($PaCO_2$, PaO_2).

The measured ventilation parameters included the inspiratory time (Ti), respiratory rate, peak expiratory pressure, peak inspiratory pressure, and percentage of inspired oxygen (FIO2). Nonbronchoscopic bronchoalveolar lavage (NB-BAL)

Diagnosis of ventilator-associated pneumonia

The clinical pulmonary infection score (CPIS) was used for the diagnosis of ventilator-associated pneumonia (VAP). The CPIS incorporates clinical, adiological, physiological, and microbiological factors into a numerical score that indicates the presence of VAP if it exceeds 6. To assess the severity of ventilator-associated pneumonia (VAP), various factors are taken into account, including the length of time a patient has been on mechanical ventilation, the presence of positive culture results, and the rates of sepsis-associated mortality at 14 and 28 days. Mortality was assessed from the time of admission to the intensive care unit. The duration of the ICU stay was measured from the moment of ICU admittance **[7]**.

Radiological evaluation revealed the presence of fresh or deteriorating infiltrates on the thoracic CT scan or chest X-ray.

Culture and sensitivity tests were performed to determine the cause, specifically if the pneumonia was caused by bacteria or nonbacterial factors.

The clinical diagnosis was at least one fever above 38°C without any other explanation.

Leukopenia or leukocytosis was defined as a WBC/mm3 less than 4,000 or greater than or equal to 12,000. (A fresh outbreak of purulent phlegm or a shift in the phlegm's characteristics (color, odor, amount, consistency). wheezing, rhonchi, and auscultation that suggests something (rales or bronchial breath sounds). Deteriorating gas exchange (such as O_2 desaturation, higher oxygen needs, or higher ventilation demands) **[1].**

Determination of vitamin D3 status:

The VD status was assessed by quantifying the concentration of serum 25-vitamin D3 (25(OH)D), which is the main kind of VD detected in the blood. A blood level of at least 30 ng/mL 25(OH)D (vitamin D3) was considered to indicate a sufficient amount of vitamin D3. Blood 25-hydroxy vitamin D3 levels between 20 and 29 ng/mL were used to indicate vitamin D3 deficiency, while blood 25-hydroxy vitamin D3 concentrations below 20 ng/mL were utilized to indicate inadequate vitamin D3. The 25-hydroxyvitamin D (25(OH) VD) levels were measured with an enzyme-linked immunosorbent assay (ELISA) kit that is commercially available **[8].**

Outcome measurements

Demographic and clinical data of neonates including sex, gestational age, and the Maternal age, Weight(kg) and Mode of delivery, association between vitamin D levels and neonatal clinical outcomes including (duration of NICU stay, duration of MV, Apgar score 1 m, Apgar score 5 m, CRP, PaCO2 (mmHg) and PaO2 (mmHg) were recorded.

Follow-up: Each patient was followed for 2-3 weeks.

Ethical considerations

The study received approval from the Ethics Committee of the Faculty of Medicine, namely, the Pediatrics Department, at Zagazig University Hospital. The privacy of participants and confidentiality of the data are ensured through sufficient protection. The parents of the patients were provided with the option to abstain from participation in the study if desired. We assign a unique code number to each participant and store their name and address in a dedicated file. The patients' identities were anonymized while utilizing the research data. We strictly utilized the findings of the study solely for scientific purposes and refrained from employing them for any other objectives.

Statistical analysis

The data were gathered, encoded, and input into a spread sheet created with Microsoft Office Suite Microsoft Excel 2016 on Windows. Microsoft Excel was released in 2016 by Microsoft Corporation and is based in the United States. The IBM Statistical Package for Social Sciences (SPSS), notably IBM SPSS Statistics for Windows, was used to evaluate the data. Version 26.0 was developed by IBM Corp. in Armonk, NY. Continuous data are represented using the mean value together with the standard deviation, while categorical data are presented as numbers and percentages. A result less than 0.05 was considered to indicate statistical significance. The statistical analysis included correlation analysis using Spearman/Pearson's approach and receiver operating characteristic (ROC) curve analysis.

RESULTS

There was no significant differences between the two groups regarding demographing data (gestation age, Maternal age , birth weight, sex and mode of delivery). Duration of NICU was significantly higher in VAP group than Non-VAP group while Apgar score 1 minute and 5 minutes were significantly lower in VAP group than Non-VAP group. There was no significant difference between both groups regarding to duration on MV, CRP was significantly higher in VAP group than Non-VAP group. PaCO2 was significantly higher in VAP

group than Non-VAP group while PaO2 was significantly lower in VAP group than Non-VAP group **Table 1**.

The level of vitamin D3 25(OH) was significantly lower in the VAP group than in the non-VAP group **Table 2**.

There was significant positive correlation between vitamin D3 and weight, Apgar score 1m and 5 min and PaO2 while there was significant negative correlation with gestational age, maternal age, duration in NICU, duration on MV, CRP and PaCO2. **Table 3**

At a of 29.8, vitamin D3 showed 92.3% sensitivity and 100% specificity, with a p value <0.001, as shown in **Table (4) and Figure 1**.

Table (1): Demographic data among the studied groups.

		VAP group (n=24)	Non-VAP group (n=24)	P value
Gestational Age (weeks)	**Mean ± SD**	35.95±2.13	35.58±1.99	0.53
	Range	33-39	33-39	
Gestational Age	**Preterm (<37 weeks)**	19 (79.2%)	18 (75%)	0.38
	Full-term (≥37 weeks)	5 (20.8%)	6 (25%)	
Maternal age (years)	**Mean ± SD**	26±3.68	24.87±4.20	0.33
	Range	20-32	20-32	
Birth Weight (g)	**Mean ± SD**	2322.9167±140.5	2736.5417±273.6	0.004
	Range	2107-2581	2304-3197	
Sex	**Male**	18 (75%)	15 (62.5%)	0.35
	Female	6 (25%)	9 (37.5%)	
Mode of delivery	**NVD**	10 (41.7%)	10 (41.7%)	0.615
	CS	14 (58.3%)	14 (58.3%)	
Duration in NICU (days)	**Mean ± SD**	22.71±4.65	15.54±3.47	**0.02**
	Range	15-30	10-20	
Duration on MV (days)	**Mean ± SD**	11.21±2.08	7±1.71	0.15
	Range	8-14	4-10	
Apgar score 1 m	**Mean ± SD**	4.16±0.63	5.08±0.88	**0.001**
	Range	3-5	4-7	
Apgar score 5 m	**Mean ± SD**	5.83±0.82	7.25±0.79	
	Range	5-7	6-8	**0.001**
CRP	**Mean ± SD**	56.11±13.08	36.3±9.38	
	Range	30.5-75.4	20.4-47.9	**0.001**

		VAP group (n=24)	Non-VAP group (n=24)	P value
PaCO2 (mmHg)	**Mean ± SD**	47.42±5.24	40.45±2.73	**0.001**
	Range	40-57	36-45	
PaO2 (mmHg)	**Mean ± SD**	65.45±5.83	89±7.68	**0.001**
	Range	55-75	76-100	

Chi square test (X^2), were used to analyze categorical variables. Student "t" test was used to analyze normally distributed variables among 2 independent groups.
NICU: The Neonatal Intensive Care Unit; **MV:** Mechanical Ventilation; **CRP:** C-Reactive Protein; **PaCO2 :** Partial pressure of carbon dioxide; **PaO2:** Partial pressure of oxygen

Table (2): 25(OH) vitamin D3 among the studied groups.

		VAP group (n=24)	Non-VAP group (n=24)	P value
25(OH) vitamin D3 (ng/ml)	Mean ± SD	22.82±5.75	37.98±4.76	0.001
	Range	13.7-30	30.2-45	

Student "t" test was used to analyze normally distributed variables among 2 independent groups.
Table (3): Correlation between vitamin D and other parameters.

	25(OH) D(ng/ml)	
	r	p value
Gestational Age	-0.171-	0.246
Maternal age	-0.155-	0.292
Weight(kg)	0.535**	0.001
Duration in NICU (days)	-0.466-**	0.001
Duration on MV (days)	-0.630-**	0.001
Apgar score 1 m	0.467**	0.001
Apgar score 5 m	0.571**	0.001
CRP	-0.597-**	0.001
PaCO2 (mmHg)	-0.567-**	0.001
PaO2 (mmHg)	0.725**	0.001

NICU: The Neonatal Intensive Care Unit; **MV:** Mechanical Ventilation; **CRP:** C-Reactive Protein; **PaCO2 :** Partial pressure of carbon dioxide; **PaO2:** Partial pressure of oxygen

Table (4): ROC curve of vitamin D in prediction of VAP.

Cut-off	AUC	Sensitivity	Specificity	PPV	NPV	P value
29.8	0.89	92.3%	100%	100%	91.7%	<0.001

AUC: Area Under the Curve. **ROC** curve was used to detect cutoff values with optimum sensitivity and specificity.

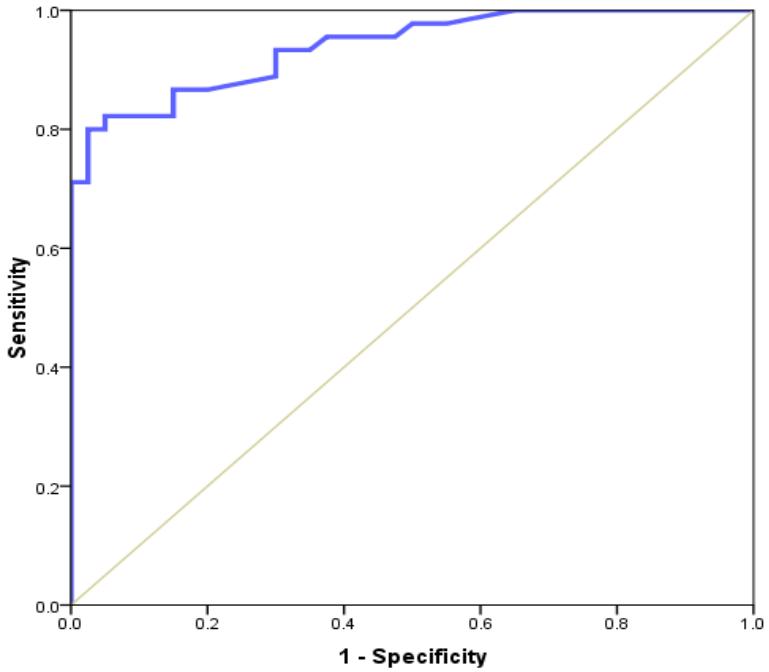

Figure (1): ROC curve of vitamin D in prediction of VAP.

DISCUSSION

Neonatal ventilator-associated pneumonia (VAP) is defined as a nosocomial lower airway infection in intubated newborns with onset beyond 48 hours of invasive mechanical ventilation. Intubation and mechanical ventilation are known risk factors for the acquisition of nosocomial pneumonia. VAP is one of the most frequently diagnosed nosocomial infections and "second most common cause for antibiotic use in neonatal intensive care units (NICUs) after early onset sepsis [9].

Vitamin D is a steroid hormone that has an important role in calcium and phosphorus homeostasis, bone metabolism and bone development. Multiple reports suggested the vital role of vitamin D in immune system function and regulation since 1,25 dihydroxy vitamin D3 can promote the innate immature response to the pathogen. Besides, many studies have identified an association of respiratory infectious diseases and inadequate serum vitamin D3[10].

This was a prospective cohort study that was conducted on 48 neonates who admitted to the NICU at the Pediatrics department, Zagazig University Hospital during the period of the study. They were divided into 2 groups (VAP group) and (Non-VAP group) 24 cases in each group to identify the correlation between the level of serum 25-hydroxy vitamin D3 and the occurrence of ventilator-associated pneumonia (VAP) in neonates who were intubated

The current study showed that there was no significant differences between the two groups regarding demographing data

(gestation age, Maternal age , birth weight, sex and mode of delivery). This slightly agrees with **Khattab et al. [11]** who aimed to determine the characteristics and risk factors of VAP in critically ill newborn infants admitted to the NICU in Benha Children's Hospital. They reported that, the mean birth weight of the VAP group was significantly lower than that of the non-VAP group (P = 0.05). the mean gestational age of infants diagnosed with VAP was significantly lower than that of the non-VAP group.

This result was in disagreement with other studies that reported that VAP rates significantly increase with decreasing gestational age [12]**.**

Studies showed that premature infants are at a higher risk for developing VAP. This is because of the fact that their need for MV is often for a prolonged interval of time, resulting in a greater number of ventilator days with a steady increase in VAP episodes [13]**.**

In our study, CRP was significantly higher in VAP group than Non-VAP group while there was no significant difference between both groups regarding to serum albumin, blood culture and other laboratory findings.

Afify et al., [14] explained by the fact that CRP level can be affected by any infectious or inflammatory focus and not specific for VAP.

In harmony, **Khattab et al. [11]** who reported that, there were significant differences between VAP and non-VAP groups regarding total leukocyte count and CRP titer. Hypoalbuminemia, which is considered an indicator of poor nutritional status, was significantly encountered in the VAP group, which may be due to favored hepatic production of acute-phase proteins such as globulins, fibrinogen, and haptoglobin.

In our study, duration of NICU was significantly higher in VAP group than Non-VAP group while there was no significant difference between both groups regarding to duration on MV.

This also partially agrees with **Khattab et al. [11]** who reported that, prolonged duration of NICU admission was a significant risk factor for VAP. Also, prolonged duration of ventilation generally increases the risk of infection due to exposure to other devices such as nebulizers, humidifiers, and ventilator circuits, which have been proven to be important sources and media for microorganisms.

An Egyptian study found that the incidence of VAP increased from 5% of patients receiving 1 day of mechanical ventilation to 65% of patients receiving 30 days of mechanical ventilation [16]**.**

In our study, PaCO2 was significantly higher in VAP group than Non-VAP group while PaO2 was significantly lower in VAP group than Non-VAP group.

This agrees with **Tayel et al. [17]** who reported that, an increased attacks of hypoxia (PO_2<50), and hypercapnia (PCO_2>55) were significantly higher in the VAP group.

In our study, 25 (OH) vitamin D was significantly lower in VAP group than Non-VAP group.

In harmony, **Ayad et al. [18]** investigated the association between neonatal VAP development and vitamin D levels and showed that vitamin D deficiency was a risk factor for VAP development. The mechanism by which vitamin D promotes immunity is complicated. It acts through the innate immune system by inducing antimicrobial peptides in epithelial cells, neutrophils and macrophages". Low levels of serum vitamin D may be significantly associated with neonatal pneumonia. They showed that serum level of vitamin D in VAP group was statistically significantly lower than in non-VAP group (11.54 ± 12.96 ng/ml and 34.99 ±10.1 ng/ml respectively).

That was in line with the results of **El-kassas et al. [19]** who reported that neonates with pneumonia showed significant lower levels of Vit. D compared to controls. Moreover, the authors showed that mechanically ventilated neonates revealed significant lower vit D levels compared to patients on free oxygen".

In our study, there was significant positive correlation between vitamin D and weight, Apgar score 1 m and 5 min, PaO2 while there was significant negative correlation with duration in NICU and duration in MV, WBCs, CRP and PaCO2.

In accordance, **Liu et al. [20**] found that the serum 25(OH)D_3 level in the cord blood serum of children was significantly positively correlated with Apgar score, and significantly negatively correlated with oxygenation index (OI), duration of oxygen support and continuous positive airway pressure ventilation. The possible mechanism is that, lung surface active substances are produced by alveolar type II epithelial cells, which have vitamin D receptors and renal tubules 1α-hydroxylase protein expression. Therefore, alveolar type 2 epithelial cells may be the target cells for vitamin D bioregulation, which will have a certain impact. For the developing fetus, the lack of vitamin D leads to insufficient alveolar surface-active substances, thus affecting the development of lung structure and function.

Remmelts et al [21] in a prospective cohort study on hospitalized patients with CAP stated that vitamin D deficiency was associated with an increased risk of ICU admission.

In our study, at a cut off 29.8, vitamin D showed 92.3% sensitivity, 100% specificity, with p value <0.001.

Ayad et al. [18] reported a cut off value of ≤17.35 ng/ml of serum 25-hydroxy vitamin D showed a sensitivity of 83.33%, specificity of 100% and area under curve (AUC) was 0.895 to predict neonatal VAP.

CONCLUSION

Insufficient serum levels of vitamin D3 may increase the likelihood of developing ventilator-associated pneumonia in neonates undergoing mechanical ventilation**.**

Conflict of interest: The authors declare no conflict of interest.

Financial Disclosures: This study was not supported by any source of finding.

Sources of funding: No specific grant was obtained for this research from governmental, private, or nonprofit funding organizations.

Author contribution: Authors contributed equally in the study.

Acknowledgement

The authors would like to appreciate all the participants and the hospital stuff who contributed to this study.

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Citation:
Alkhouly, U., Basha, H., Mohamed, S., Mahmoud, A., Ibrahim, M. Vitamin D Level in Ventilator Associated Pneumonia in the Neonatal Intensive Care Unit. *Zagazig University Medical Journal*, 2024; (3471-3480): -. doi: 10.21608/zumj.2024.300085.3456