Original Article

# Preoperative Vitamin D Levels and Respiratory Complications of General Anesthesia

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**Abstract**

**Aims:** This research aims to investigate whether there is a correlation between the respiratory complications occurring in patients under general anesthesia and preoperative Vitamin D levels. **Settings and Design:** The study was a prospective observational study. **Materials and Methods:** This study included 95 adult cases. The cases had total 25-hydroxyvitamin D (25OHD) levels identified in blood samples before the operation. Patients given routine general anesthesia and were assessed in terms of respiratory complications during anesthesia induction, extubation, anesthesia recovery, and the first 24-h postoperative. **Statistical Analysis Used:** The Shapiro–Wilk test, Student's-*t*-test, one-way ANOVA test, Pearson correlation coefficient, and Chi-square tests were used. **Results:** The mean 25OHD vitamin level identified in the preoperative period was 13.00 ± 6.57 ng/mL, with 25OHD vitamin levels found to be significantly low in female cases compared to male cases ($P < 0.05$). There was a statistically significant negative relationship between age and 25OHD vitamin levels identified ($P = 0.045$). When assessed in terms of surgery types, there was no significant difference found in Vitamin D levels in terms of surgery type. When examined for complications in the induction, extubation period, and postoperative recovery period, there was a significant difference identified between 25OHD vitamin levels and these complications ($P < 0.01$). **Conclusions:** This research observed that patients with low preoperative 25OHD vitamin levels encountered respiratory complications related to general anesthesia more often. Especially, in the early postoperative period, there is a very significant difference between complications and low 25OHD vitamin levels.

**Keywords:** *General anesthesia, respiratory complications, Vitamin D*

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## Introduction

Vitamin D is a fat-soluble steroid prohormone mainly obtained by the photochemical route from dehydrocholesterol in the skin. Vitamin D deficiency is a commonly observed health problem throughout the world.[1,2] It is known that there is a correlation between serum Vitamin D levels with lung capacity and inflammatory processes. This correlation is very clear in lung diseases such as asthma, chronic obstructive pulmonary disease, and pneumonia.[3,4] Research into smooth muscle cells in the airway showed that Vitamin D may have a modulatory effect on the inflammation, contraction, and remodeling pathways of these cells.[5]

In the general population, the prevalence of Vitamin D deficiency is increasing every day, and there is increasing evidence that Vitamin D has a very important role related to respiratory health.[6,7] Vitamin D deficiency increases mortality in respiratory tract infections and respiratory tract diseases.[8] Surgical interventions and anesthesia administration cause unwanted effects on the cardiopulmonary functions of patients. Respiratory

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complications with high mortality and morbidity are more commonly encountered in general anesthesia administration compared to other anesthesia methods.[9] It is important to complete the preoperative evaluation thoroughly, especially for patients with additional respiratory diseases or with the potential risk of these additional diseases. Although there are many clinical studies related to Vitamin D deficiency involving general disease situations such as the musculoskeletal system and respiratory system, there appear to be a low number of studies on these topics in surgical patients. The majority of these few studies are related to situations such as postoperative infection, cardiac morbidity, and postoperative pain.[2,10] There was no study encountered in the literature on whether there is a correlation between respiratory complications and Vitamin D levels. In this research, we aimed to investigate whether there was a correlation between preoperative Vitamin D levels and respiratory complications in the induction, extubation, recovery, and early postoperative period in patients undergoing general anesthesia.

## Materials and Methods

This prospective study was approved by the local Ethics Committee (Ordu University, 2015/11) and clinical trials number is NCT03342651.

Inclusion criteria: 95 cases aged from 18 to 65 years in the American Society of Anesthesiologists I-II (ASA I-II) class operated under general anesthesia. Exclusion criteria: thoracic surgery; patients with severe respiratory, neuromuscular, or endocrine system diseases; those with difficult intubation, morbid obesity, using Vitamin D supplements; and those who smoked.

### Anesthesia management

When the patients arrived in the operating room, heart rate, noninvasive arterial pressure, pulse-oximeter, end-tidal carbon dioxide monitoring, and neuromuscular block monitoring (train-of-four (TOF) Watch SX monitor) were performed. After patients had an intravenous line performed in the back of the hand with a 20 Gauge intracath, maintenance fluids were begun. Standard anesthesia protocol was applied, after induction with propofol (2–2.5 mg/kg), rocuronium (0.6 mg/kg), and fentanyl (0.5 μg/kg), the patients were intubated when TOF = 0 was obtained. Anesthesia was maintained with sevoflurane 2%, remifentanil 0.25 μg/kg/min infusion, 2l oxygen + 2l dry air with 0.8 ml/kg tidal volume, and frequency of 12/min to maintain end-tidal $CO_2$ at 30–35 mmHg. At the end of surgery and when two responses were achieved from TOF stimulation, neostigmine 0.05 mg/kg and atropine 0.02 mg/kg were administered and the patients were extubated. All patients were monitored according to the routine general anesthesia procedure.

### Operational definitions of outcome and complications

In this study, postoperative outcomes (respiratory complications) were defined only postoperative acute period and postoperative 24-h episode. According to the study protocol, bronchospasm during induction; cough, bronchospasm, and desaturation during extubation; desaturation, postoperative reintubation and requirements for mechanical ventilation support during recovery; and any respiratory complication within 24-h postoperative were recorded. Bronchospasm was defined as Rhonci heard in the main bronchi during expirium, and desaturation is defined as oxygen saturation <90% from the initial $SpO_2$ of >90% and <95% in postanesthesia care unit with room air.[11] Postoperative requirements for mechanical ventilation support was defined as acute respiratory failure (acute respiratory failure was defined as acute severe dyspnea, respiratory rate higher than 25 breaths/min, and active contraction of accessory muscles).[12]

### Laboratory protocol

Due to diurnal rhythm of Vitamin D and for standardization of the timing of sample collection, fasting sample were collected from all participants in the early morning 2 h before anesthesia induction. Serum samples were used for 25-hydroxyvitamin D (25OHD) determination. All the samples were treated according to our preanalytical procedure and blood samples were centrifuged at 2000 rpm for 10 min in a refrigerated centrifuge to separate serum samples and all samples were stored −70°C until they were analyzed. Serum total 25OHD assay was performed using commercial kits (Abbott Architect) based on a delayed one-step immunoassay that uses a polyclonal anti-Vitamin D antibody with sheep origin coated on paramagnetic particles and a biotinylated Vitamin D anti-biotin acridinium-labeled conjugated complex.

### Sample size and power analysis

Sample size and power analysis: A sample size of 44 was determined for each group, according to the power analysis and sample size test for alpha = 0.05 and test power of 90%.

### Statistical analysis

To check the assumption of normality for sex, age, anesthesia duration, and all other comparative parameters with Vitamin D values, the Shapiro–Wilk test was used ($P > 0.05$). Differences in terms of Vitamin D levels and sex, induction, extubation and recovery room

respiratory complication, and postoperative re-intubation and mechanical ventilation support in the postoperative 24 h were assessed with the Student's-*t*-test, with differences between these values according to surgical operation type tested with the one-way ANOVA. The correlation between age and Vitamin D levels was determined with the Pearson correlation coefficient. Differences between observation of complications according to each operation type in terms of Vitamin D levels were determined with the Student's-*t*-test, with observation of complications according to operation types determined with the Chi-square test. The research results are presented as n (%), mean, and standard deviation. Data were analyzed using the SPSS statistical package (SPSS Windows, version 21.0, SPSS Inc., Chicago, IL, USA).

## Results

The age, body weight, anesthesia duration, and Vitamin D levels for all cases included in the study are presented in Table 1. The mean age of cases was 48.36 ± 13.46, with the mean body weight of 74.94 ± 11.84 kg. Of cases, 46 (48.4%) were female and 49 (51.6%) were male, with 43 cases (45.3%) in ASA I and 52 cases (54.7%) were in ASA II risk group. Mean Vitamin D level determined in the preoperative period was identified as 13.00 ± 6.57 ng/ml (3.20–35.0 ng/mL). There was no significant difference between female and male cases in terms of age, body weight, and anesthesia durations ($P > 0.05$), while Vitamin D levels were found to be significantly low in female cases compared to male cases ($P < 0.05$). When the correlation between age and Vitamin D levels is assessed, there was a 20.6% weak negative correlation determined ($P = 0.045$, $r = 0.206$).

The distribution of cases according to operation type is given in Table 2. For all cases, lower abdominal surgery was most common (29.5%), with extremity and spinal surgeries (6.3%) were least common. The most commonly observed complication was desaturation in the recovery period observed in 33.7% of our cases. The complications and prevalence are presented in Table 3. No case required reintubation or had any respiratory complications within the postoperative 24 h or required mechanical ventilator support.

When the effect of Vitamin D levels on complications is assessed, the Vitamin D levels of cases developing complications were identified to be significantly low compared to cases who did not develop complications [$P < 0.05$, Table 4]. The complications according to operation types and Vitamin D levels and differences between these complications are given in Table 5. When the distribution of complication incidence according to operation types is assessed, there was no statistical significance found between the complication distributions in terms of operation types ($P > 0.05$).

**Table 1: Age, weight, Vitamin D levels, and anesthesia duration in patients**

| Parameters | Gender | *n* | Mean | SD | *P* |
|---|---|---|---|---|---|
| Age (year) | Female | 46 | 48.63 | 1.953 | 0.850 |
| | Male | 49 | 48.10 | 1.970 | |
| Weight (kg) | Female | 46 | 73.02 | 1.941 | 0.131 |
| | Male | 49 | 76.73 | 1.468 | |
| Vitamin D (ng/mL) | Female | 46 | 11.626 | 0.9831 | 0.047 |
| | Male | 49 | 14.300 | 0.8977 | |
| Duration (min) | Female | 46 | 62.39 | 2.960 | 0.076 |
| | Male | 49 | 70.20 | 3.188 | |

SD=Standard deviation

**Table 2: Distrubition of the cases according to operation types**

| Surgery type | Frequency (%) |
|---|---|
| Lower abdominal | 28 (29.5) |
| Upper abdominal | 12 (12.6) |
| Extremity | 6 (6.3) |
| Eye | 10 (10.5) |
| Upper airway | 16 (16.8) |
| Head–neck | 17 (17.9) |
| Spine | 6 (6.3) |
| Total | 95 (100.0) |

**Table 3: Types and frequencies of respiratory complications in patients**

| Period | Complication | *n* (%) |
|---|---|---|
| Induction | Bronchospasm | 12 (12.6) |
| Extubation | Cough | 18 (18.9) |
| | Bronchospasm | 9 (9.5) |
| | Desaturation | 28 (29.5) |
| Recovery | Desaturation | 32 (33.7) |

**Table 4: Vitamin D levels in cases with or without complications**

| Complication type | Complication | | | | | | *P* |
|---|---|---|---|---|---|---|---|
| | No | | | Yes | | | |
| | *n* | Mean | SD | *n* | Mean | SD | |
| Bronchospasm; I | 83 | 13.62 | 0.70 | 12 | 8.72 | 1.71 | 0.015 |
| Cough; E | 77 | 13.96 | 0.71 | 18 | 8.88 | 1.47 | 0.003 |
| Bronchospasm; E | 86 | 13.54 | 0.70 | 9 | 7.83 | 1.73 | 0.012 |
| Desaturation; E | 67 | 14.77 | 0.80 | 28 | 8.76 | 0.78 | <0.001 |
| Desaturation; R | 63 | 15.04 | 0.82 | 32 | 8.99 | 0.79 | <0.001 |

Bronchospasm; I=Bronchospasm during induction; Cough; E=Cough during extubation; Bronchospasm; E=Bronchospasm during extubation; Desaturation; E=Desaturation during extubation; Desaturation; R=Desaturation during recovery; SD=Standard deviation

**Table 5: Differences between observation of complications according to each operation type in terms of Vitamin D levels**

| Surgery type | Complication type | Complication | | | | | | *P* |
|---|---|---|---|---|---|---|---|---|
| | | No | | | Yes | | | |
| | | *n* | Mean | SD | *n* | Mean | SD | |
| Lower abdominal | Bronchospasm; I | 24 | 12.04 | 5.75 | 4 | 7.03 | 0.88 | <0.001 |
| | Cough; E | 25 | 11.02 | 4.67 | 3 | 13.83 | 12.34 | 0.423 |
| | Bronchospasm; E | 24 | 11.53 | 5.45 | 4 | 10.10 | 7.27 | 0.646 |
| | Desaturation; E | 19 | 12.36 | 5.77 | 9 | 9.14 | 4.83 | 0.161 |
| | Desaturation; R | 18 | 12.69 | 5.74 | 10 | 8.86 | 4.64 | 0.083 |
| Upper abdominal | Bronchospasm; I | 11 | 11.60 | 6.60 | 1 | 21.0 | - | 0.202 |
| | Cough; E | 8 | 13.20 | 6.99 | 4 | 10.75 | 7.26 | 0.584 |
| | Bronchospasm; E | 10 | 13.66 | 6.76 | 2 | 6.00 | 2.69 | 0.050 |
| | Desaturation; E | 9 | 14.62 | 6.40 | 3 | 5.67 | 1.99 | 0.043 |
| | Desaturation; R | 8 | 15.20 | 6.59 | 4 | 6.75 | 2.71 | 0.036 |
| Extremity | Bronchospasm; I | 6 | 15.50 | 5.01 | - | - | - | - |
| | Cough; E | 6 | 15.50 | 5.01 | - | - | - | - |
| | Bronchospasm; E | 6 | 15.50 | 5.01 | - | - | - | - |
| | Desaturation; E | 6 | 15.50 | 5.01 | - | - | - | - |
| | Desaturation; R | 6 | 15.50 | 5.01 | - | - | - | - |
| Eye | Bronchospasm; I | 9 | 13.98 | 5.98 | 1 | 5.00 | - | 0.192 |
| | Cough; E | 6 | 16.67 | 5.16 | 4 | 7.70 | 3.28 | 0.010 |
| | Bronchospasm; E | 10 | 13.08 | 6.31 | - | - | - | - |
| | Desaturation; E | 7 | 14.86 | 6.52 | 3 | 8.93 | 3.87 | 0.188 |
| | Desaturation; R | 6 | 16.50 | 5.32 | 4 | 7.95 | 3.72 | 0.018 |
| Upper airway | Bronchospasm; I | 14 | 15.24 | 7.41 | 2 | 6.90 | 0.99 | 0.001 |
| | Cough; E | 13 | 15.65 | 7.57 | 3 | 7.93 | 1.50 | 0.004 |
| | Bronchospasm; E | 15 | 14.72 | 7.43 | 1 | 6.40 | - | 0.296 |
| | Desaturation; E | 10 | 16.66 | 7.94 | 6 | 10.10 | 4.67 | 0.050 |
| | Desaturation; R | 10 | 16.66 | 7.94 | 6 | 10.10 | 4.67 | 0.050 |
| Head–neck | Bronchospasm; I | 14 | 16.57 | 7.43 | 3 | 9.43 | 10.03 | 0.172 |
| | Cough; E | 15 | 16.87 | 7.25 | 2 | 3.65 | 0.64 | 0.024 |
| | Bronchospasm; E | 16 | 16.07 | 7.70 | 1 | 3.20 | - | 0.126 |
| | Desaturation; E | 13 | 17.39 | 7.82 | 4 | 8.55 | 4.88 | 0.026 |
| | Desaturation; R | 12 | 17.09 | 8.09 | 5 | 11.04 | 6.99 | 0.166 |
| Spine | Bronchospasm; I | 5 | 10.00 | 2.92 | 1 | 8.50 | - | 0.663 |
| | Cough; E | 4 | 11.25 | 0.96 | 2 | 6.75 | 2.47 | 0.025 |
| | Bronchospasm; E | 5 | 10.00 | 2.92 | 1 | 8.50 | - | 0.663 |
| | Desaturation; E | 3 | 11.33 | 1.15 | 3 | 8.17 | 3.01 | 0.164 |
| | Desaturation; R | 3 | 11.33 | 1.15 | 3 | 8.17 | 3.01 | 0.164 |

Bronchospasm; I=Bronchospasm during induction; Cough; E=Cough during extubation; Bronchospasm; E=Bronchospasm during extubation; Desaturation; E=Desaturation during extubation; Desaturation; R=Desaturation during recovery; SD=Standard deviation

## Discussion

Respiratory complications are the most important factor causing increased morbidity and mortality related to general anesthesia.[9] The most commonly observed complications are desaturation, laryngospasm, bronchospasm, cough, and excessed secretions.[13,14] Desaturation was identified as the most common complication among the cases in our study [Table 3]. Considering the strong correlation between desaturation and similar perioperative respiratory complications with comorbidities, the necessity to effectively perform preoperative evaluation and preparation is obvious.[15] A fully-performed preoperative evaluation can reduce the morbidity and mortality linked to these complications.[16]

Many studies have shown that a strong correlation exists between serum Vitamin D levels and lung functions in adults. Low Vitamin D levels reduce lung capacity and contribute to lung parenchyma destruction. Anesthesia-related pulmonary complications such as respiratory failure, bronchospasm, and reintubation are related to admission to postoperative intensive care and increased mortality rates.[15] Low Vitamin D levels in

the prehospitalization period in patients is known to be related to acute respiratory failure.[10]

Anesthesiology and reanimation specialists commonly encounter patients with Vitamin D deficiency in the perioperative period, during severe treatment and in the Intensive Care Unit. Hypovitaminosis D is reported to be related to poor clinical conditions in the general population, though there are insufficient studies on this topic involving surgical patients. A retrospective study of 3509 patients undergoing noncardiac surgery assessed the effect of Vitamin D levels on postoperative mortality and reported that Vitamin D levels below 13 ng/ml were correlated with increased mortality and morbidity.[2] Again, research by Quraishi *et al*. on bariatric surgery showed that low Vitamin D levels were related to postoperative infection.[10] The National Health and Nutrition Examination Survey 2001–2006 data show that though low Vitamin D levels are significantly correlated with the respiratory symptoms.[6,17] In our study, there was a significant correlation observed between serum Vitamin D levels in our patients and early respiratory complications related to general anesthesia. In terms of bronchospasm in the induction period, and cough, bronchospasm, and desaturation in the extubation period and early postoperative recovery period, there was a significant difference identified for the preoperative Vitamin D levels in our patients and these complications. According to our study, the serum Vitamin D levels of patients with bronchospasm during extubation were at lowest levels among all patients encountering any complications [Table 4]. Again our patients experiencing perioperative bronchospasm and desaturation in the recovery period had significantly lower levels of Vitamin D compared to cases without complications. The most significant postoperative pulmonary complication of reintubation is known to increase the mortality risk by ten times.[15] In our study, though requirements for reintubation and mechanical ventilation support were not observed, it is known that low Vitamin D levels are related to poor clinical outcomes and these low levels cause nerve dysfunction, weakened gas exchange, and muscle weakness in patients which affects the need for a mechanic ventilator.[8,18] In addition, Vitamin D deficiency is present in more than half of all patients admitted to hospital in general and this deficiency is known to be related to muscle weakness most often in the proximal muscle groups.[2,19]

The increasing Vitamin D deficiency in the general population is worrying due to the correlation with pulmonary disorder.[6] Some studies have determined that Vitamin D deficiency is related to more common asthma attacks and wheezing.[3,6] The most common cause of bronchospasm and wheezing occurring during anesthesia induction or the recovery stages is airway irritation, though exposure to allergic reactions and anesthetic agents causes bronchospasm and atelectasis for an unknown reason. Anesthesia-related bronchospasm is a significant factor increasing mortality and morbidity.[20,21] In our study, the Vitamin D levels of patients with bronchospasm during the induction and extubation stage were found to be lower by a significant degree compared to patients with no bronchospasm. Vitamin D shows antiproliferative effect and is reported to contribute to amelioration of asthma by preventing stenosis of the respiratory tracts.[22]

Postoperative pulmonary complications are more commonly encountered with advanced age, though age is among the unchangeable risk factors. In our study, there was a statistically negative significant correlation between age and Vitamin D levels identified. With higher numbers of patients in the advanced age group taken for surgery, we believe this negative correlation between age and Vitamin D may be related to bronchospasm observed in eye surgery patients. When assessed from this aspect, it is possible to say that identification of potential risk factors that may cause pulmonary complications in the early period is important in terms of taking precautions against these complications.[23] It has been long considered that Vitamin D deficiency causes weakness of the diaphragm and intercostal muscles making it difficult to clear respiratory secretions.[18] Disruption of the chest wall mechanics and reduction of pulmonary volumes are the most significant causes of the common observance of pulmonary complications.[16]

There are studies showing a tight link between Vitamin D and baseline lung functions ($FEV_1$ and forced vital capacity).[24] An experimental study by Zosky *et al*. showed that Vitamin D deficiency primarily causes differences in lung volumes. The researchers emphasized that Vitamin D reduced lung functions and that increasing Vitamin D deficiency among the population was a significant factor affecting lung health.[25,26] In our study, we showed that there may be a correlation between anesthesia-related perioperative respiratory complications and low Vitamin D levels. Although the most significant limitation of our study is that preoperative respiratory function tests (RFT) were not performed to assess lung capacities and volumes of patients, when the general procedure is examined RFT is not a routine method in preoperative examination. It is known that, in general, Vitamin D deficiency is present in more than half of all patients staying in hospital. As a result, it is appropriate to assess and research patients in this way during the perioperative period.

## Conclusions

Identifying Vitamin D deficiency in all patients in hospital in the preoperative period and bringing the levels back to normal requires a long treatment process. Emergency surgery cases clearly cannot wait for Vitamin D levels to reach appropriate levels in preoperative period. However, for elective surgery and especially patients in the advanced age group, we believe optimizing the Vitamin D levels in the preoperative period will be beneficial in terms of preventing respiratory complications. In addition, we believe the results of our study should be supported for different surgical groups and broader patient series.

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### Conflicts of interest

There are no conflicts of interest.

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