Kritik Covid-19 Hastalarında D Vitamini Kullanımı

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Özet

Coronavirüs 19 hastalığı (COVID-19), Aralık 2019'da Çin'in Wuhan kentinde başlayan, ağır akciğer enfeksiyonu ve akut solunum yetmezliği ile karakterize pandeminin nedenidir. D vitamini enfeksiyon riskini azaltır. Bu çalışmada, kritik COVID-19 hastalarında D vitamininin akut faz reaktanları, oksijenasyon, hastane yatış süresi ve mortalite üzerindeki etkisini değerlendirmek amaçlandı. Hastalar, 01 Mart 2020 ile 15 Aralık 2020 tarihleri arasında geriye dönük olarak incelendi. Seksen dokuz hasta çalışmaya dahil edildi. Gerçek zamanlı polimeraz zincir reaksiyonu (RT-PCR) tüm hastalarda pozitifti. Tüm hastalar incelendi ve tek doz 50.000 IU D vitamini alan ve almayan olarak iki gruba ayrıldı. Otuz üç hasta (%37) D vitamini alırken, 56 hasta (%63) almadı. Hastaların ortanca yaşı 69 idi (33-101). Kırk hasta kadın (%45), 49 hasta ise erkekti (%55).Yoğun bakımda ilk gün invaziv mekanik ventilasyon uygulanan 21 hastanın 11'i (%12,3) yoğun bakımda D vitamini alırken, 10 hasta (%11,2) almamıştı. Yirmiyedi hasta (%30,3), 28 gün içinde öldü. D vitamini alan hastalarda prokalsitonin, nötrofil/lenfosit oranı, laktat dehidrojenaz 14 gün süresince değişmedi (p=0,78, p=0,19, p=0,11). Her iki grupta da, C-reaktif protein düzeyi azaldı ve lenfosit sayısı arttı (p<0,001, p<0,001). Her iki grupta da 14 gün içinde PaO_2/FiO_2 oranında artış vardı, ancak D vitamini alan hastalarda belirgin olarak anlamlıydı (p<0,001). Sonuç olarak, D vitamini alan COVID-19 hastalarında D vitamini almayanlara göre akut faz reaktanları, mekanik ventilasyon ihtiyacı, yoğun bakım ve hastanede yatış süresi ile mortalite açısından fark yoktu. D vitamini alan hastalarda oksijenasyondaki iyileşme daha belirgindi.

Anahtar Kelimeler: *D Vitamini, yoğun bakım, pnömoni, covid-19, kritik hastalık*

Use of Vitamin D In Critically ill Covid-19 Patients

Coronavirus 19 disease (COVID-19) is the cause of the pandemic that began in Wuhan, China, in December 2019, characterized by severe pulmonary infection and acute respiratory failure. Vitamin D reduces the risk of infections. This study aimed to evaluate the effect of vitamin D on acute phase reactants, oxygenation, length of stay in hospital and mortality in critically ill COVID-19 patients. Patients were retrospectively analyzed between 01 March 2020 and 15 December 2020. Eighty-nine patients were included in the study. The real-time polymerase chain reaction (RT-PCR) was positive in all patients. All patients were screened and divided into two groups as the patients who received a single dose of 50.000 IU vitamin D and those who did not. Thirty-three patients(37%) received vitamin D, 56 patients (63%) did not. The median age of the patients was 69 years(33-101). Forty patients (45%) were female, 49 (55%) were male. Eleven (12,3%) of 21 patients who underwent invasive mechanical ventilation on the first day at ICU stay received vitamin D in the intensive care unit, 10 patients (11,2%) did not. Twenty-seven (30,3%) patients died within 28 days. Over the 14 days, procalcitonin, neutrophil/lymphocyte ratio, lactate dehydrogenase, did not change in patients who received vitamin D (p=0,78, p=0,19, p=0,11). C-reactive protein decreased and lymphocyte count increased in both groups (p<0,001, p<0,001). There was increase in PaO_2/FiO_2 ratio over 14 days in both groups, however, it was distinctly significant in patients who received vitamin D (p<0,001). In conclusion, there was no difference in the acute phase reactants, the need for mechanical ventilation, the duration of intensive care, hospitalization, and mortality in COVID-19 patients who received vitamin D compared to those who did not. Improvement in oxygenation was more evident in patients who received vitamin D.

Keywords: *Vitamin D, intensive care, pneumonia, covid-19, critically illness*

Indtroduction

Coronavirus 19 disease (COVID-19) is the cause of the pandemic that began in Wuhan, China, in December 2019, characterized by severe pulmonary infection and acute respiratory failure. Mortality is high in patients with COVİD-19 pneumonia who require close follow-up in the intensive care unit due to acute respiratory failure. Unfortunately, there is no effective treatment for this viral disease, yet.

Vitamin D reduces the risk of infections (Martineau, 2017). It has been demonstrated that adequate vitamin D levels reduce the incidence and severity of diseases caused by enveloped viruses such as herpes zoster, Epstein-Barr, hepatitis, Ebola, HIV, dengue, measles and rubella (Beard J.A, 2011; Gunville C.F, 2013). Vitamin D reduces the risk of infection through various mechanisms. It helps maintain the cell-cell junctions and tight junctions in epithelial and endothelial tissues by E-cadherin (Gruber-Bzura B.M, 2018; Schwalfenberg, G.K, 2011). 1,25 dihydroxyvitamin-D3 partially strengthens cellular innate immunity by triggering the production of antimicrobial peptides such as cathelicidin, LL-37 and defensins (Liu, P.T, 2006; Adams J.S, 2009; Laaksi I, 2012). Cathelicidins exhibit direct antimicrobial activity against a broad spectrum of pathogens such as gram positive and negative bacteria, enveloped and non-enveloped viruses and fungi (Herr C, 2007).

Vitamin D also reduces the severity of the cytokine storm triggered by the innate immune system by improving cellular immunity. Innate immune system produces pro-inflammatory and anti-inflammatory cytokines in response to bacterial and viral infection (e.g. COVID-19 pneumonia) (Huang C, 2020). Vitamin D reduces the production of pro-inflammatory cytokines such as tumor necrosis factor and gamma-interferon (Sharifi A, 2019). In addition, 1,25-dihydroxyvitamin-D3 is considered as a regulator of adaptive immunity by suppressing the production of inflammatory cytokines such as gamma-interferon and IL-2 produced in response to Th1 cells (Lemire JM , 1985).

Hypovitaminosis D is common in the general population, with a seasonal occurrence, while low plasma concentrations of vitamin D have been repeatedly shown in critically ill patients. In the latter patients, deficiency has been associated with poor outcome, including excess mortality, longer length of stay, higher sepsis incidence, and longer mechanical ventilation. In critically ill patients with measured low plasma levels (25-hydroxy-vitamin D < 12.5 ng/ml, or 50 nmol/l) a high dose of vitamin D3 (500,000 UI) as a single dose can be administered within a week after admission (Singer P, 2019).

This study aimed to evaluate the effect of vitamin D on acute phase reactants, oxygenation, length of stay in hospital and mortality in critically ill COVID-19 patients.

Methods

Our single-center retrospective study was initiated after obtaining approval from the local ethics committee of Tepecik Training and Research Hospital. (Ethics committee decision no: 2020/13-31). Patients admitted to the intensive care unit with the diagnosis of COVID-19 pneumonia between 01 March 2020 and 15 December 2020 were retrospectively analyzed. The real-time polymerase chain reaction (RT-PCR) was positive in all patients.

One hundred sixty-seven patients over 18 years of age with positive RT-PCR test were included in the study. Forty-one patients died within the first 7 days and were excluded from the study. Thirty-seven patients were not included in the study because they were transferred to the infectious disease clinic within the first week after being taken to the intensive care unit. Figure-1 shows the flow chart of the study.

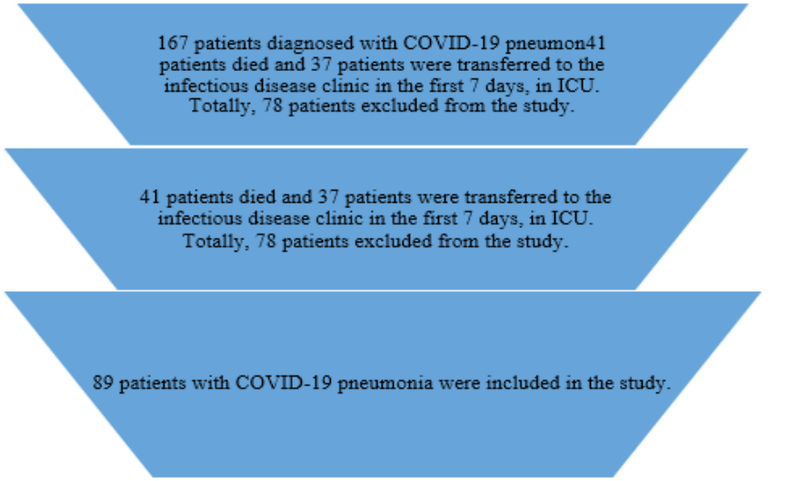

Figure-1: Flow chart showing the inclusion criteria of patients. Age>18 years and confirmed to be RT-PCR positive COVID-19 patients. Forty-one patients died and 37 patients who were transferred to the infectious disease clinic in the first 7 days in ICU were excluded from the study. Eighty-nine patients with COVID-19 pneumonia were included in the study.

Eighty-nine patients were screened and divided into two groups as the patients who received a single dose of 50.000 IU vitamin D (n:33) and those who did not (n:56). Demographic data, clinical features and laboratory findings of the patients including age, gender, comorbidity, Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) score, lymphocyte count, neutrophil/lymphocyte ratio, as well as acute phase reactants C-reactive protein (CRP), procalcitonin and lactate dehydrogenase (LDH) values were recorded at 1, 7 and 14 days. In addition, we evaluated the need for vasopressor, mechanical ventilation requirement, hospital and intensive care unite length of stay to assess the clinical response. The partial arterial oxygen pressure/fractionated inspiratory oxygen concentration (PaO_2/FiO_2 ratio) was recorded.

Data were presented as number of cases, percentage, or median (minimum and maximum). Categorical comparisons were made using Chi-square or Fischer tests. The Mann-Whitney U test was used to compare continuous variables. The Friedman test was used to test for differences in variables over time. P value<0.05 was considered statistically significant. Data analysis was performed using SPSS 22.0 statistical package (Statistical Package for the Social Sciences, USA) and graphics using GraphPad Prism (Version 8.0.0).

Results

Eighty-nine patients who met the criteria were included in the study. Thirty-three patients (37%) received vitamin D, 56 patients (63%) did not. The median age of the patients was 69 years (33-101). Forty patients (45%) were female, 49 (55%) were male. The median APACHE II score was 13 (5-41) in all patients, while the SOFA score was 3 (1-10). In terms of chronic comorbidities, 40 (44%) patients had hypertension, 28 (31%) diabetes mellitus, 5 (5,6%) coronary artery disease and 7 (8%) chronic lung disease.

Eleven (12,3%) of 21 patients who underwent invasive mechanical ventilation on the first day at ICU stay received vitamin D in the intensive care unit, 10 patients (11,2%) did not. The median length of stay in the intensive care unit was 14 (3-141) days in patients who received vitamin D and 12 (2-83) days in those who did not. The median length of hospital stay was 23 (5-141) days in patients who received vitamin D and 20 (3-86) days in patients who did not. Twenty-seven (30,3%) patients died within 28 days. Twelve of these 27 (13,4%) patients received vitamin D and 15 (16,8%) patients did not. Table-1 shows the characteristics of the patients.

Table-1: The characteristics of patients. It was shown as n= data number and n(%) percent of data and median (minimum-maximum). IMV (invasive mechanical ventilation).

	All patients (n=89)	Vitamin D supplementation (n=33)	Non vitamin D supplementation (n=56)	P value
Age, years	69 (33-101)	69 (35-101)	66.5 (33-95)	0,20
Gender, female n(%)	40(45)	17(51)	23(41)	0,33
APACHE II score	13 (5-41)	14 (5-30)	12 (5-41)	0,13
SOFA score	3 (1-10)	3 (2-8)	2.5(1-10)	0,48
Comorbidities, n(%)				
Hypertension	40(44)	15(45)	25(44)	0,94
Coronary artery disease	5(5.6)	0(0)	5(8.9)	0,15
Diabetes Mellitus	28(68)	9(27)	19(33)	0,51
Chronic respiratory disease	7(8)	2(6)	5(9)	1.00
First day IMV, n(%)	21(23)	11(33)	10(18)	0,09
Seventh day IMV	45(50)	16(48)	29(51)	0,41
Fourteenth day IMV	46(52)	15(45)	31(55)	0,31
Length of hospital stay (d)	22(3-141)	23 (5-141)	20(3-86)	0,29
Length of intensive care unit stay (d)	13(2-141)	14(3-141)	12 (2-83)	0,43
Mortality, n (%)	27(69)	12(66)	15(71)	0,74

Over the 14 days, procalcitonin, neutrophil/lymphocyte ratio, lactate dehydrogenase, did not change in patients who received vitamin D (p=0,78, p=0,19, p=0,11 respectively). C-reactive protein decreased and lymphocyte count increased in both groups (p<0,001, p<0,001 respectively). There was increase in PaO2/FiO2 ratio over 14 days in both groups, however, it was distinctly significant in patients who received vitamin D (p<0,001). There was no difference in need for invasive mechanical ventilation, length of hospital stay and length of stay in the intensive care unit between groups (p=0,09, p=0,29, p=0,43 respectively). Figure-2 demonstrates the change of C-reactive protein, PaO2/FiO2 ratio, lymphocyte count and neutrophile/ lymphocyte ratio who received vitamin D and did not, during the 14 day period in intensive care unit. Table-2 shows the change of patients' clinical and laboratory parameters on 1. ,7. and 14 days.

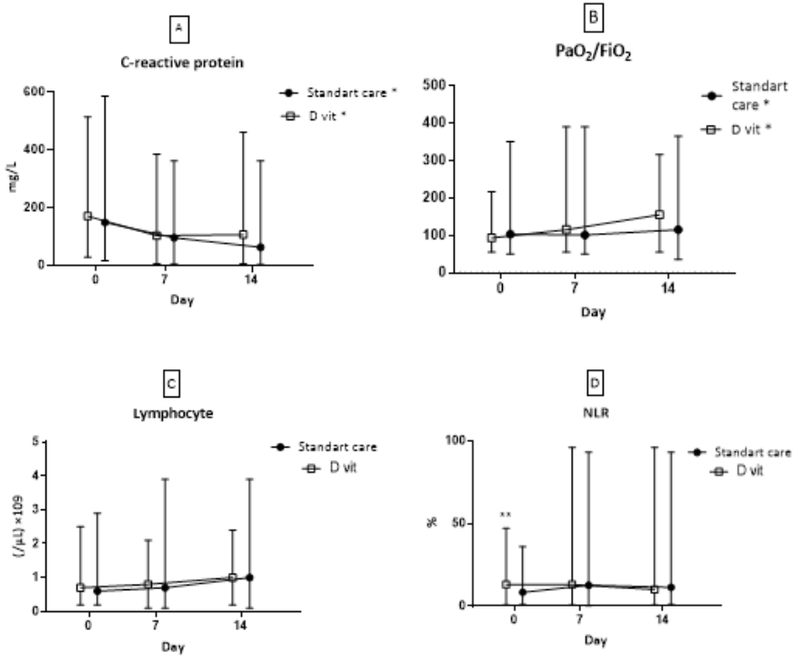

Figure-2: The change of C-reactive protein, PaO_2/FiO_2 ratio, lymphocyte count and neutrophile/lymphocyte ratio who received vitamin D and did not, during the 14 day period.

Table-2: The change of patients' clinical and laboratory parameters on 1. ,7. and 14 days.

	All patients (n=39)	Vit D supplementation (n=18)	Non Vit D supplementation (n=21)	P value (between two groups)
1th day PaO_2/FiO_2	101(50-350)	93(55-216)	103(50-350)	0.15
7th day PaO_2/FiO_2	108(50-390)	115(55-390)	101(50-390)	0.41
14th day PaO_2/FiO_2	127(35-365)	155(55-316)	115(35-365)	0.20
*P value (Friedman test, over time, inside group)	<0,001	<0,001	0,04	
1th day C-reactive protein (mg/L)	158(15-586)	170(28-514)	148(15-586)	0,058
7th day C-reactive protein (mg/L)	100(2.5-384)	102(5-384)	95(2.5-361)	0,75
14th day C-reactive protein (mg/L)	74(1.6-461)	106(4-461)	62(1.6-361)	0,20
*P value	<0,001	0,009	0,015	
1th day lymphocyte count (/µL) $\times 1^0 10^9$	0,6(0,2-2,9)	0,7(0,2-2,05)	0,6(0,2-2,9)	0,87

7th day lymphocyte count (/µL) $\times 10^9$	0,7(0.1-3.9)	0,8(0,1-2,1)	0,7(0,1-3,9)	0,96
14th day lymphocyte count (/µL) $\times 10^9$	1.0(0,1-3.9)	1.0(0,2-2,4)	1.0(0,1-3.9)	0,84
*P value	<0,001	0,02	0,001	
1th day Neutrophile/ lymphocyte ratio, %	11(0.08-36)	13 (0.08-47)	8.4(0,85-36)	<0,01
7th day Neutrophile/ lymphocyte ratio, %	12.7(0,07-96)	13(0,07-96)	12.6(2.1-93)	0,41
14th day Neutrophile/ lymphocyte ratio, %	10.8(0,07-96)	10.1(0,07-96)	11.4(0.9-93)	0,86
*P value	0,09	0,19	0,13	

Discussion

This study demonstrates the mortality, length of stay in hospital and intensive care unit, change in oxygenation and acute phase reactants during the 14 day period in COVID-19 pneumonia patients who received vitamin D in ICU. Additionally, after the administration of vitamin D, we also observed the relationship of vitamin D with lymphocyte count, neutrophil/ lymphocyte ratio as associated with cellular and humoral immunity.

Vitamin D deficiency is common in intensive care patients, and low levels are associated with adverse outcomes (Rech MA, 2014; Anwar E, 2017). In some large studies, it has been reported that people with low vitamin D levels are more susceptible to covid-19 disease (Meltzer D, 2020; D'Avolio A, 2020). In another study, it has been stated that, there is no difference in, intensive care acceptance rate and mortality in patients with low vitamin D levels (Baktash V, 2020). In this study, there was no

difference in the need for invasive mechanical ventilation, the length of intensive care and hospital stay, and mortality in the patients who received vitamin D compared to those who did not.

Many biomarkers for COVID-19 disease have been presented, including increased circulating C-reactive protein, LDH, cytokines (IL-6, IL-10 and tumor necrosis factor), and lymphopenia (low CD4+ and/or CD8+ T cells) (Chen G, 2019). Qin et al. have reported that COVID-19 patients with a neutrophil/lymphocyte ratio >5.2 constituted the group with the most severe course (Qin C, 2020).

Our study showed no significant difference in procalcitonin, lactate dehydrogenase, and neutrophil/lymphocyte ratios on the first, seventh, and 14th days in both groups. However, C-reactive protein decreased and lymphocyte count increased significantly over time. We interpreted this situation as the normal course of the disease associated with inflammation.

Some studies show that low vitamin D levels are associated with poor disease outcomes such as pneumonia, acute lung injury, and acute respiratory distress syndrome (ARDS) development (Leow L, 2011; Remmelts HH, 2012). Munshi et al. reported that low vitamin D levels have poor outcomes associated with admission to intensive care unit and the need for mechanical ventilation, ARDS development and mortality (Munshi R, 2021). In this study; the PaO_2/FiO_2 ratio improved in both groups over 14 day period. It was more significant in the vitamin D group than another.

This study has some limitations. First of all, the patient population was small in this retrospective research. To reach statistically more valuable data, patients who were transferred to the clinics or died in the first week after being taken to the intensive care unit were excluded from the study and the patient population decreased. Due to pandemic conditions, serum vitamin D levels could not be measured in patients admitted to the intensive care unit, with or without vitamin D supplement. Therefore, patients who have low or normal serum vitamin D levels are unknown.

In conclusion, there was no difference in the acute phase reactants, the need for mechanical ventilation, the duration of intensive care, hospitalization, and mortality in COVID-19 patients who received vitamin D compared to those who did not. Improvement in oxygenation was more evident in patients who received vitamin D. However, vitamin D supplementation may contribute positively to recovery in COVID-19 patients, randomized-controlled prospective studies can ensure the healthier results.

Ethics Committee: Tepecik Training and Research Hospital. (Ethics committee decision no: 2020/13-31
Author Contribution
İsa Sahar: Research design, literature search, collected the data, prepared the manuscript, corresponding author.
Nimet Şenoğlu: Collected the data, critically reviewed the manuscript.
Kazım Rollas: Collected the data, statistical analysis, critically reviewed, prepared the manuscript.
Taner Çalışkan: Collected the data, prepared the manuscript.
Işıl Köse Güldoğan: Collected the data, prepared the manuscript. Çiler Zinciroğlu: Collected the data, prepared the manuscript.
Aykut Sarıtaş: Collected the data, prepared the manuscript.
Uğur Uzun: Collected the data, prepared the manuscript.
No conflict of interest.

We have confirmed that neither the manuscript nor any part of it has been published nor being considered for publication elsewhere in any language. Declarations of interest: none
All authors approved the manuscript and this submission.

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