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Investigation of the effectiveness of prone ventilation in patients followed up for acute respiratory distress syndrome in the intensive care unit

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Abstract. – OBJECTIVE: Prone positioning has been found to improve oxygenation in most patients with acute respiratory distress syndrome (ARDS). The study aimed to investigate the effectiveness of the prone position in patients with ARDS.

PATIENTS AND METHODS: The prone position is one of the ventilator techniques included in recent guidelines for acute respiratory distress syndrome. This study was a retrospective evaluation of the records of 100 ARDS patients who were administered prone position mechanical ventilation in our intensive care unit. All patients were placed in the prone position for a total of 12 hours per day at 4-hour intervals (supine-prone) while admitted to the intensive care unit.

RESULTS: This study included 100 participants. These patients were divided into two groups as survivors [(n=38, 16 females, 22 males, median age: 60 (24-86)] and non-survivors [(n=62, 19 females, 43 males, median age: 64 (21-93)], according to their intensive care follow-ups. Acute physiology and chronic health evaluation (APACHE) II score, the sequential organ failure assessment score (SOFA), and inflammation markers were statistically significantly higher in the non-survivor group. Between the two groups, there was no statistically significant difference in terms of fundamental characteristics. In the sub-group evaluation of the subjects in patients with ARDS with and without novel coronavirus disease 2019 (COVID-19) groups, the patients in the COVID-19 (+) group were older, had shorter hospital stays, had higher APACHE II and SOFA scores, and higher rates of cardiovascular disease and sepsis.

CONCLUSIONS: Applying prone-position mechanical ventilation in the cohorts of our patients with ARDS resulted in a demonstrable significant improvement in the oxygenation levels of our patients.

Key Words:
Acute respiratory distress syndrome, Prone positioning, Mechanical ventilation.

Introduction

Acute respiratory distress syndrome (ARDS) is characterized by persistent hypoxia and manifests on chest radiographs as bilateral pulmonary infiltrates in the absence of the features of heart failure. ARDS is associated with mortality rates of 25% to 40%[1]. Acute respiratory distress syndrome is a kind of non-cardiogenic pulmonary edema that results from systemic or pulmonary inflammation that damages the alveoli. The pathophysiology of ARDS is commonly divided into three stages: exudative, proliferative, and fibrotic. The earliest reaction to lung damage is the exudative phase. Both the alveolar endothelium and epithelial walls sustain damage at this stage. Increased protein-rich fluid inside the alveoli and decreased fluid outflow from the alveolar space as a result of the increased capillary permeability cause further alveolar damage and the production of pro-inflammatory cytokines. The lungs then draw in neutrophils and macrophages, and the release of toxic mediators causes further cell death, inflammation, and pulmonary edema. Developing intrapulmonary shunts leads to severe hypoxemia. The patient's lung starts to heal itself during the proliferative phase: epithelial integrity is restored, alveolar fluid is reabsorbed, and alveolar structure and function are recovered. The development of interstitial and alveolar fibrosis, as well as insufficient or delayed epithelialization,

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are the causes of the fibrotic phase, which may not occur in all individuals[2]. A large number of diseases and traumas, which are mostly categorized as pulmonary or systemic origin, cause the development of ARDS. Pneumonia is the most common risk factor for the development of ARDS, which is associated with high mortality. ARDS due to trauma also has the lowest mortality.

The European Society of Intensive Care Medicine Conference[3] held in Berlin in 2012 classified ARDS as follows: mild (ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen [PaO_2/FiO_2] of 200≤300 mm Hg), moderate (PaO_2/FiO_2 100≤200 mm Hg), or severe (PaO_2/FiO_2 ≤100 mm Hg).

Positive end-expiratory pressure (PEEP) is recommended to improve oxygenation with decreased pulmonary compliance and increased atelectasis that often occurs in ARDS. Prone ventilation is the application of mechanical ventilation therapy while the patient is in a prone position.

Prone positioning and ventilation to patients were first defined in the 1970s as a strategy to provide oxygenation in the treatment of ARDS[4]. Bryan[5] suggested prone posture, thinking that it would lessen pleural pressure gradients and restore aeration to dorsal lung segments to prevent additional atelectasis in injured lungs. Prone positioning has been found[6] to improve oxygenation in most (70-80%) patients with ARDS. In ARDS treatment guidelines updated in 2013, it is recommended to use the prone position in patients with severe ARDS[7].

The improvement of oxygenation during prone ventilation is multifactorial, but mainly by reducing lung compression and improving lung perfusion. Changes in the distribution of extravascular lung fluid and secretions may also play a role in the improvement in oxygenation. The prone position reduces the difference between dorsal and ventral transpulmonary pressure, makes ventilation more homogeneous, and leads to a decrease in ventral alveolar hyper-swelling and dorsal alveolar collapse[8].

The novel coronavirus disease 2019 (COVID-19) is a new type of virus that infects the respiratory system. ARDS is a common complication in patients diagnosed with COVID-19. In a study by Guerin et al[9], it was reported that 67% of patients with COVID-19 infection had ARDS.

In this study, we aimed to investigate the effectiveness of prone ventilation in patients with a diagnosis of ARDS who were hospitalized in the intensive care unit (ICU) with or without the diagnosis of COVID-19.

Patients and Methods

Study Population

Patients with severe ARDS who were hospitalized in the ICU for more than 24 hours were included in the study retrospectively.

One hundred patients diagnosed with ARDS between September 2020 and December 2021 were included in the study. Age, weight, clinical diagnosis, comorbidities, APACHE II, and SOFA scores were obtained. All the patients were diagnosed with ARDS according to the 2013 Berlin criteria[10].

The causes of ARDS, the day the patient was placed in the prone position, and the amount of fluid administered were recorded. The hemodynamic data and the blood gas values were obtained before and after the patients were administered prone position ventilation, respectively. The length of stay in the intensive care unit, duration of mechanical ventilation, and prognosis of all patients were recorded.

The diagnosis of COVID-19 in patients was made using polymerase chain reaction (PCR) results with clinical and radiological features. Hypertension (HT) was diagnosed in patients with known pre-ICU admission intake of antihypertensive drugs or with systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Diabetes mellitus (DM) was diagnosed in patients with known pre-ICU admission anti-diabetic drug intake or with a fasting glucose level ≥ 126 mg/dL or hemoglobin A1c (HbA1c) ≥ 6.5% according to at least two measurements. Our study was approved by the University Local Ethics Committee.

Statistical Analysis

IBM SPSS version 22.0 for Windows was used in the statistical analysis (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to evaluate the normality of the continuous variables. Parametric data were compared using the Student's *t*-test, non-parametric variables were compared using the Mann-Whitney U test, and categorical variables were compared using the Chi-square test. For non-parametric variables, the median (minimum-maximum) was used to represent the data, but for parametric variables, the mean± standard deviation was used. The *p*-values ≤ 0.05 were deemed to indicate statistical significance.

Results

One hundred patients [(35 females, 65 males, median age: 62 (21-93)] were hospitalized with

Table I. Demographic, clinical, and hematological features of ARDS survivors and non-survivors.

	All patients (n=100)	Survivors (n=38)	Non-survivors (n=62)	*p*-value
Age (Years)	62 (21-93)	60 (24-86)	64 (21-93)	0.094
Gender (Male) n (%)	65 (65)	22 (57)	43 (69)	0.244
Weight (kg)	80 (50-130)	80 (60-130)	80 (50-100)	0.874
Hospital stay (days)	14 (3-80)	20 (10-80)	10 (3-41)	<0.001
APACHE II score	17 (4-40)	15 (4-30)	18 (12-40)	0.002
SOFA score	8 (4-12)	4 (4-10)	8 (4-12)	<0.001
Diabetes n (%)	20 (20)	8 (21)	12 (19.3)	0.655
CVD n (%)	9 (9)	2 (5.2)	7 (11.2)	0.054
CAD n (%)	26 (26)	10 (26.3)	16 (25.8)	0.845
Sepsis n (%)	79 (79)	11 (28.9)	52 (83.8)	0.127
Covid pneumonia n (%)	42 (42)	21 (55.2)	21 (33.8)	0.042
Hypertension n (%)	26 (26)	10 (26.3)	16 (25.8)	0.874
White blood cell ($\times10^9$)	12.9 (0.79-36)	12 (1-24)	14.67 (4-37)	<0.001
Monocytes ($\times10^9$)	0.78 (0.12-23)	0.56 (0.1-1)	0.82 (0.12-23)	<0.001
Neutrophils ($\times10^9$)	10.5 (0.32-32.5)	8.8 (0.32-20)	12.39 (4-33)	<0.001
Platelets ($\times10^9$)	200 (16-776)	173 (100-334)	225.5 (16-776)	0.029
Lymphocytes ($\times10^9$)	0.8 (0.15-6.53)	0.9 (0.2-2.2)	0.63 (0.15-6.5)	0.051
CRP (mg/L)	120 (1.97-476)	82.04 (2-338)	150.5 (4-476)	0.004
D-dimer (mg/L)	2.17 (0.19-35.2)	1.78 (0.19-35)	2.37 (0.19-35)	0.043
Fibrinogen (mg/dl)	407 (56.1-935)	397 (150-935)	421 (56-900)	0.620
Ferritin (ng/ml)	830 (25-72,852)	366 (25-6,260)	1,950 (74-7,285)	<0.001
Procalcitonin (ng/ml)	0.44 (0.02-10.9)	0.18 (0.02-5)	0.71 (0.18-11)	<0.001
Troponin I (ng/l)	25 (3-1,100)	17 (3-1,100)	32.5 (5-437)	0.007
AST (IU/L)	39 (8-1,459)	23 (8-106)	78.5 (24-1,459)	<0.001
ALT (IU/L)	521 (346-869)	23 (9-128)	43 (6-869)	<0.001
INR	1.23 (0.87-10.9)	1.13 (1-10.9)	1.3 (1-3)	<0.001

CRP; C-reactive protein, AST; serum aspartate transaminase, ALT; alanine transaminase, INR; international normalized ratio, CAD; Cardiovascular disease, CVD; Cerebrovascular disease.

the diagnosis of ARDS in the ICU included in the study. These patients were divided into two groups: survivors (n=38) and non-survivors (n=62), according to their ICU follow-ups. The effectiveness of ventilation in the prone position was investigated in these patients. The demographic, clinical, and hematological characteristics of the study subjects were summarized in Table I.

APACHE II score, SOFA score, inflammation markers such as white blood cells, monocytes, neutrophils, ferritin, procalcitonin, C-reactive protein (CRP), D-dimer levels, liver enzyme levels, and international normalized ratio (INR) levels were statistically significantly higher in the non-survivor group. Hospitalization times were shorter in the non-survivor group. In terms of other data, the two groups were similar.

During the hospitalization period, the blood gas values of the patients before and after the prone position were registered and are summarized in Table II. The PaO_2/FiO_2 (mmHg) before prone, tidal volume after prone, and pH after prone levels were statistically significantly lower in the non-survivors group, respectively. Furthermore, the FiO_2 after prone, and $PaCO_2$ after prone levels were higher in the non-survivors group. There was no significant difference between the two groups in terms of blood gases and other data. In both groups, improvement was observed in PaO_2/FiO_2, tidal volume, and PaO_2 levels after applying the prone position. The severity of ARDS regressed in both the survivor and non-survivor groups after the prone position. However, the ARDS severity regression was higher in the survivor group (severity of ARDS stage after prone; 1/2/3 survivors =5/27/6 *vs*. non-survivors=10/27/25, p=0.018).

In the sub-group evaluation of the subjects into ARDS patients with or without COVID-19, the patients in the COVID-19 (+) group were older, had shorter hospital stays, higher APACHE II and SOFA scores, and had higher rates of cardiovascular disease and sepsis (Table III).

After applying for the prone position, tidal volume and FiO_2 levels were observed to be lower in the group with COVID-19 (+) compared to the group without COVID-19, respectively (p=0.003 *vs*. p=0.038). While ARDS stages before applying the prone position were higher in the group with

Table II. Blood gases and ventilator settings of patients before and after prone position.

	All patients (n=100)	Survivors (n=38)	Non-survivors (n=62)	*p*-value
Tidal volume before prone (ml)	450 (340-740)	430 (350-660)	420 (340-740)	0.145
PEEP before prone (mmHg)	12 (5-16)	12 (8-16)	12 (5-15)	0.746
FiO_2 before prone (%)	80 (55-100)	80 (55-100)	90 (60-100)	0.317
PaO_2 before prone (mmHg)	55 (34-95)	56 (38-90)	55 (34-95)	0.584
$PaCO_2$ before prone (mmHg)	47 (15-115)	37 (32-93)	53 (15-115)	0.077
pH before prone	7.38 (7.0-7.5)	7.38 (7.0-7.5)	7.34 (7.11-7.5)	0.135
Ventilator frequency before prone	16 (10-26)	16 (10-22)	16 (10-26)	0.488
PaO_2/FiO_2 (mmHg) before prone	74.2±20.2	73±22.6	64±18.8	0.004
Tidal volume after prone (ml)	460 (400-800)	480 (400-800)	460 (340-560)	0.004
PEEP after prone (mmHg)	12 (8-16)	12 (8-15)	12 (10-16)	0.120
FiO_2 after prone (%)	70 (50-80)	60 (55-77)	70 (50-80)	0.045
PaO_2 after prone (mmHg)	92 (58-207)	99 (63-175)	80 (58-207)	0.041
$PaCO_2$ after prone (mmHg)	43 (22-70)	36 (25-51)	48 (22-70)	0.048
pH after prone	7.3 (7.0-7.5)	7.4 (7.0-7.5)	7.3 (7.1-7.5)	0.001
Ventilator frequency after prone	16 (12-26)	16 (12-24)	15 (12-26)	0.544
PaO_2/FiO_2 (mmHg) after prone	139±69.9	153±60.1	118±75.8	0.012
Severity of ARDS before prone 1/2/3	0/9/91	0/6/32	0/3/59	0.063
Severity of ARDS after prone 1/2/3	15/54/31	5/27/6	10/27/25	0.018

ARDS; acute respiratory distress syndrome, PEEP; Positive End Expiratory Pressure, FiO_2; Fraction of inspired oxygen, SOFA Score; Sequential Organ Failure Assessment Score, APACHE II Score; Acute Physiology and Chronic Health Evaluation. Severity of ARDS = 1; mild, 2; moderate, 3; severe. All continuous variables are reported as median (minimum-maximum) or mean±standart deviation. Statistical significance set at 0.05.

COVID-19 (p=0.007), no difference was observed between the groups after applying for the prone position (p=0.618). When the two groups were compared in terms of mortality, 56% of the patients with COVID-19 (+) died, while it was 69% in the group with COVID-19 (+). This shows that prone positioning is more effective in reducing mortality in patients with COVID-19 (+), (p=0.002).

Discussion

In ARDS patients, moving from the supine to the prone position results in a more uniform distribution of lung stress and strain, as well as a more equal distribution of the gas-tissue ratios along the dependent-nondependent axis. A significant improvement in arterial blood gases typically follows the move to the prone position, which is primarily caused by better overall ventilation/perfusion matching. In our study, we observed this situation in all ARDS patients and patients with COVID-19 pneumonia. Patients with COVID-19 diagnosed with ARDS who received invasive ventilation in the prone position showed improvement in blood gas values.

In this study we conducted, we evaluated the improvement of oxygenation in our patients who were placed in the prone position due to severe ARDS, as a 20 mmHg increase from the previous PaO_2/FiO_2 ratio.

In the recent Proning Severe ARDS Patients (PROSEVA)[6], a multicenter randomized controlled trial involving severe ARDS cases (PaO_2/FiO_2<150), prone positioning for more than 16 hours a day (compared to standard protective lung ventilation in the supine semi-supine position) has been shown to provide a significant reduction in 28 and 90-day mortality. In another randomized controlled study[9] on this subject, improvement was observed in oxygenation, although no benefit was observed in survival. However, in a recent meta-analysis by Chua et al[11], an increase in survival was observed when the prone position was used in critically ill patients (PaO_2/FiO_2<100).

Despite all these benefits, there is no consensus on how long this treatment should be continued in patients who respond to treatment, and researchers still report that this treatment period cannot exceed 8-12 hours. Few studies[6,8] have demonstrated the benefits of the prone position in awake, non-intubated patients with hypoxemic respiratory failure. Cornejo et al[8] stated in their study that there was a significant improvement in PaO_2 with the prone position in 4 awake and non-intubated patients with hypoxemic respiratory failure.

Rollas and Şenoğlu[12] in their review titled "Management of COVID-19 patients in the in-

tensive care unit", mention the positive effect of prone positioning on hypoxemia developing in COVID-19 patients.

In the guide prepared by the Surviving Sepsis Campaign (SSC)[13], prone positioning is recommended as a recommendation in the management of COVID-19 patients.

We applied the prone position for a total of 12 hours per day at 4-hour intervals (supine-prone) to our patients who were admitted to the intensive care unit with pneumonia triggered by COVID-19. As a result, we observed a significant improvement in the oxygenation of our patients. The findings in this study are similar to the study of Valter et al[14]. The enhanced oxygenation in the prone posture may be explained by a variety of different possible processes. They include reduced shunting in the dorsal areas, decreased dead space ventilation in the ventral regions, and enhanced overall alveolar recruitment. Additionally, the prone position can decrease the dependent lung mass, reducing atelectatic unit hyperperfusion and ventilation-perfusion mismatch[15].

Limitations

Our study's weaknesses include its retrospective design and limited patient population. The blood tests and blood gas results from the samples collected from the patients are expected to vary over time during the intensive care follow-ups. Taking the average of all these data would have given us a more accurate result. Therefore, large-scale prospective studies are needed.

Conclusions

This study demonstrated the occurrence of a significant improvement in the oxygenation and PaO_2/FiO_2 in all of our patients after the prone position.

Table III. Blood gases and ventilator settings of patients after prone position.

	COVID-19 (+) (n=58)	COVID-19 (-) (n=42)	*p*-value
Age (Years)	64 (21-93)	60 (21-82)	0.022
Gender (Male), n (%)	35 (60.3)	30 (71)	0.251
Weight (kg)	80 (50-110)	80 (50-94)	0.162
Hospital stay (days)	12 (3-41)	18.5 (3-80)	<0.001
APACHE II score	18 (4-40)	16 (5-28)	0.020
SOFA score	9 (4-14)	8 (4-12)	<0.001
Diabetes n (%)	12 (20.1)	8 (19)	0.135
CVD n (%)	5 (8.6)	4 (9.5)	0.056
CAD n (%)	16 (27.5)	10 (23.8)	0.042
Sepsis n (%)	53 (91.3)	16 (38)	<0.001
Mortality n (%)	33 (56.8)	29 (69)	0.002
PEEP before prone (mmHg)	12 (8-16)	12 (5-15)	0.544
FiO_2 before prone (%)	60 (55-100)	65 (60-100)	0.417
PaO_2 before prone (mmHg)	50 (38-90)	54 (34-95)	0.563
$PaCO_2$ before prone (mmHg)	57 (32-93)	53 (15-115)	0.062
pH before prone	7.34 (7.0-7.54)	7.32 (7.11-7.5)	0.130
Ventilator frequency before prone	14 (10-22)	12 (10-26)	0.458
PaO_2/FiO_2 (mmHg) before prone	68±22.6	70±18.8	0.715
Tidal volume before prone (ml)	425 (350-660)	470 (340-740)	0.002
Tidal volume after prone (ml)	453 (340-760)	480 (340-800)	0.003
FiO_2 after prone (%)	70 (50-80)	75 (50-100)	0.038
PaO_2 after prone (mmHg)	81 (58-175)	98 (58-207)	0.226
$PaCO_2$ after prone (mmHg)	43.7 (22-70)	41.5 (22-66)	0.289
pH after prone	7.36 (7.0-7.50)	7.39 (7.16-7.51)	0.068
Ventilator frequency after prone	13 (12-26)	11 (12-26)	0.614
PaO_2/FiO_2 (mmHg) after prone	131.9±70.3	148.9±69.1	0.231
Severity of ARDS before prone 1/2/3	0/9/49	0/2/40	0.007
Severity of ARDS after prone 1/2/3	7/32/19	8/22/12	0.618

ARDS; acute respiratory distress syndrome, PEEP; Positive End Expiratory Pressure, FiO2; Fraction of inspired oxygen, SOFA Score; Sequential Organ Failure Assessment Score, APACHE II Score; Acute Physiology And Chronic Health Evaluation, CAD; Cardiovascular disease, CVD; Cerebrovascular disease, Severity of ARDS = 1; mild, 2; moderate, 3; severe.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Informed Consent
Patients and/or their families signed informed consent forms.

Authors' Contributions
CA, designed this study. İY, İY provided funding. DM and MTİ revised the manuscript. AG, CA, and İY finished the manuscript and analyzed the data. İY, CA, and AG collected the clinical data. AG contributed to the literature search.

Availability of Data and Materials
The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics Approval
The present study was approved by the Medical Ethics Committee of Trakya University with the ethics approval acceptance number TÜTF-BAEK 2021/78. The study conforms to the principles outlined in the Declaration of Helsinki.

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