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Comparison of prone position effectiveness with percentage of injured lung area in awake non - intubated COVID-19 patients

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ABSTRACT

Aim: Prone position plays a key role in the treatment of both non-intubated and intubated patients because COVID-19 associated respiratory failure is gas exchange abnormalities based on shunt and dead-space ventilation. In this study, we aimed to compare the effect of prone position applied in awake non-intubated COVID-19 patients with percentage of injured lung area.

Material and Method: 65 patients with awake, non-intubated were included in this prospective, single-center study. Percentage of injured lung area was calculated using chest computer tomography taken during diagnosis of patients. The prone position cycle was applied as 6 hours prone, 4-6 hours supine position.

Results: The mean of percentage of injured lung area was 25.16±13.81. When percentage of injured lung area groups were compared with the 0th, 6th, 24th and 48th hour SpO_2/FIO_2 ratio and respiratory frequency; while the SpO_2/FIO_2 ratio increased in all hours with prone position in the 0-10% and 10-30% groups, a decrease was observed in the SpO_2/FIO_2 ratio over time in the ≥ 30% group.

Conclusions: The prone position is a safe and effective application that causes improvement in SpO_2/FIO_2 ratio and RR in awake non-intubated COVID-19 patients with less damage to the lung. However, it should be kept in mind that as the damage to the lung increases, the expected recovery might not be possible.

Keywords: Acute hypoxemic respiratory failure, COVID-19, prone position, critical care, lung injury

INTRODUCTION

Prone position (PP) has been used as a recruitment strategy in acute respiratory distress syndrome (ARDS) patients on mechanical ventilation support since 1976 (1). Prone position application corrects oxygenation by reducing ventilation/perfusion mismatch, providing a more homogeneous transpulmonary pressure distribution and recruitment of non-aerated dorsal regions of the lung by reducing ventral to dorsal axis and causing an increase in lung volume (2). Acute respiratory failure (ARF) has also had positive effects on oxygenation with PP in awake spontaneously breathing non-intubated patients (3). Considering that COVID-19 associated respiratory failure is gas exchange abnormalities based on shunt and dead-space ventilation, PP plays a key role in the treatment of both awake spontaneous breathing non-intubated patients and intubated patients (4). The application of PP can be affected by many conditions such as patient compliance, selected oxygen therapy method, duration of PP, severity of COVID-19 disease, severity of PP and COVID-19 released pulmonary lesions in early or late period (1,5-7)

In this study, we aimed to compare the effect of PP applied in awake non-intubated COVID-19 patients with percentage of injured lung area (ILA).

MATERIAL AND METHOD

65 COVID-19 patients with awake, non-intubated spontaneous breathing were included in this prospective, single-center study after approval by the Muğla Sıtkı Koçman University Ethics Committee (Decision No: 148 Date: 2021). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration. Inclusion criteria for the study is designed to be above 18 years of age, non-pregnant, SARS-CoV-2 RT-PCR test result is positive or COVID-19 pneumonia compatible

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with computer tomography (CT) lung screening patients with symptoms and clinical findings and CT lung screening those who need oxygen therapy in the last 24 hours. Those under the age of 18 and pregnant women and those who did not need oxygen therapy and those who were indicated for intubation were excluded from the study.

Age, sex, medical treatment, oxygen therapy method [non-invasive ventilation (NIV), high flow oxygen (HfO_2), nasal cannula (NC)], percentage of ILA and department in which the patient was admitted (intensive care unit (ICU) / ward) were registered.

Percentage of ILA was calculated using chest CT taken during diagnosis of patients. Chest CT shots were obtained without contrast agent injection, during deep inspiration, in the supine position. Radiological images were obtained with 256-section Toshiba-TCT-60 AX and 4-Section Siemens Somatom device localized in the emergency room only for COVID-19 patients. The parameters of tube voltage 120 kV, tube current modulation 100-250 mAs, spiral pitch factor 0.98 and collimation width 0.625 were used. The images were transferred to the VIA port system located in our hospital workstation and a 3-D reconstruction was made. The images were evaluated on a high-resolution medical screen.

3 lobes on the right lung and 2 lobes on the left lung were separately examined. Each lobe was accepted by 20% and lobe volume was measured. The areas in the view of the consolidated and ground-glass area were calculated by volumetric voxel and calculated on the computer through the program. Their percentages were calculated over the total volume. The percentage values of all lobes were collected and total loss of lung aeration was found.

For the applied PP, the head of the patient lying face down was brought to the right or left side and supported with a thin pillow. On the side where the head was turned, the arm was extended up and the other arm was extended down. A pillow was placed on the dorsal face of the foot to prevent the tips of the toes from coming into contact with the bed and staying under pressure. The position was applied 2 times a day in the form of 4-6 hours. The position cycle was applied as 6 hours PP, 4-6 hours supine position (SP), 6 hours PP and again 4-6 hours SP. Oxygen therapy with NIV, HFO_2, and NC was continued during PP and SP. SpO_2, respiratory frequency, FIO_2 were recorded before PP. The time when the first prone position was given was considered zero, and subsequent follow-ups were repeated at the 6^{th}, 24^{th}, and 48^{th} hours. SpO_2, respiratory rate (RR) and FIO_2 were re-recorded at the 6^{th}, 24^{th} and 48^{th} hours.

FIO_2 value, which was also set in mechanical ventilation in NIV and HFO_2, was recorded. **Table 1** was used to determine FIO_2 at low flow NC. A FIO_2 value corresponding to the oxygen current was obtained.

Table 1. Estimated inspired oxygen concentration (8)

Device	Reservoir Capacity	Oxygen flow (L/min)	Approximate FIO_2
Nasal Cannula	50ml	1	0.24
		2	0.28
		3	0.32
		4	0.36
		5	0.40
		6	0.44

SpO_2/ FIO_2 ratio was calculated from SpO_2 and FIO_2 values for all times.

The presence of invasive mechanical ventilation and intubation days, number of hospital admissions during treatment and discharge patterns (death/survival) were noted.

Statistical Analysis

Statistical analyses were performed using SPSS software version 23. The variables were investigated using analytical methods (Kolmogorow-Simirnov/Shapiro-Wilk test) to determine whether or not they are normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed variables (SpO_2/FIO_2 ratio and RR values). The Chi-square test or Fisher's exact test (when chi-square test assumptions do not hold due to low expected cell counts), where appropriate, was used to compare these proportions in different groups.

The Kolmogorov-Simirnov/Shapira-Wilks test was applied to examine the normal distribution of ILA percentage, SpO_2/ FIO_2 ratio and RR.

The Wilcoxon test was used to compare the change in SpO_2/ FIO_2 ratio and RR between initial 6, 24, 48 hour. While investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using Spearman test. A p-value of less than 0.05 was considered to show a statistically significant result.

The possible factors identified with univarite analyses were further entered into the Cox regression analysis, with backward section, to determine independent predictors of survival and risk of intubation; only those with clinical significance were included. The proportional hazards assumption and model fit was assessed by means of residual analysis. A 5% type-I error level was used to infer statistical significance.

RESULTS

The study included 75 patients. 6 patients could not tolerate PP and 4 patients were excluded from the study because they were intubated within the first 24 hours.

Statistical evaluation was performed on 65 patients who met the study protocol. 39 (60 %) of the patients were male and 26 (40 %) were female. The average age was 62.53±15.52, the average duration of hospitalization was 13.98±8.38, and the average percentage of ILA was 25.16±13.81. 7 (10,8 %) patients were provided with non-invasive ventilation (NIV), 34 (52,3 %) with HFO_2, 24 (36,9 %) with NC oxygen support. 11 (16.6%) patients were intubated and received invasive mechanical ventilation support, and 10 (15.4) patients died. Dexamethasone was used in the treatment of 30 (46.9%) patients, methylprednisolone was used in 25 (38,4%) patients and immunoglobulin was used 7 (10,8 %) patients. Percentage of ILA was grouped to be 0-10%, 10-30%, 30% and above. Percentage of ILA groups was combined for descriptive statistics. Percentage of ILA ≥ 30% of those with more advanced age, HFO_2 or NIV use, intubation, length of stay in hospital day and exitus were more observed and evaluated as statistically significant (respectively, p-value; 0,041, <0,001, 0,045, 0,013, 0,023) Looking at initial RR and SpO_2/FIO_2 ratio, lower SpO_2/FIO_2 and higher RR were found in the group with percentage of ILA ≥ 30%, and this was statistically significant (p-value <0.001) (**Table 2**).

Compared with percentage of ILA 6th, 24th and 48th hour SpO_2/FIO_2 ratio and RR; moderately negative between the ILA percentage and the 6th and 24th hour SpO_2/FIO_2 ratio (r: -0.466, -0.635, respectively; p value <0.001); and a moderate positive correlation was found with 6th and 24th hour RR (r:0.668, 0.630, respectively; p value <0.001). A strong correlation was found when the percentage of ILA was compared with the 48th hour SpO_2/FIO_2 ratio and respiratory frequency (r: -0.819, 0.980, respectively; p-value <0.001). Low positive correlation was found when the percentage of ILA was compared with invasive mechanical ventilation (r: 0.378; p-value <0.001).

When percentage of ILA groups were compared with the 0th, 6th, 24th and 48th hour SpO_2/FIO_2 ratio and RR; while the SpO_2/FIO_2 ratio increased in all hours with PP application in the 0-10% and 10-30% groups, a decrease was observed in the SpO_2/FIO_2 ratio over time in the ≥ 30% group. Although RR decreased in all groups and at all hours, it was found to be statistically significant only at the 6th hour (**Table 3**).

Table 2. Baseline characteristic of patients and descriptive statistical analyses for percentage of ILA

	Percentage of ILA		Total (n:65)	P values
	0-30% (n: 37)	>30% (n: 28)		
Gender (n)				
Female	73.1% (19)	26.9% (7)	40% (26)	0.42
Male	46.1% (18)	53.9% (21)	60% (39)	
Age (mean ±SD)	41.56±18.29	67.45±14.96	62.53 ± 15.52	0.041*
O_2 Therapy (n)				
Nasal cannula	87.5 % (21)	12.5 % (3)	% (24)	<0.001*
HFO_2 or NIV	39.1 % (16)	60.9 % (25)	%(41)	
Mechanical Ventilation (n)				
Yes	27.3% (3)	72.7% (8)	16.9% (11)	0.045*
No	62.9% (34)	%37.1 (20)	83.1% (54)	
Exitus (n)				
Yes	18.18% (2)	81.8% (9)	15.4 % (11)	0.013*
No	%64.8 (35)	35.18% (19)	84.6% (54)	
Length of stay in hospital (mean ±SD)	8.5±2.22	16.08±8.92	13.98 ± 8.38	0.023*
SpO_2/FIO_2 ratio (mean ±SD)	248.18±26.19	146.53±13.57	204.89 ±108.73	<0.001*
Respiratory rate (mean ±SD)	20.30±3.12	27.85±2.36	23.64 ±4.84	<0.001*

ILA: injured long area HFO_2 : High flow oxygen, NIV: non invaisve ventilation, * p values <0.05

Table 3. Comparison of percentage of ILA with SpO_2 /FIO_2 and RR

	Percentage of ILA			P values
	0-10% (n: 17)	10-30 % (n:20)	>30% (n:28)	
Initial SpO_2/FIO_2 ratio (mean ±SD)	257.47±25.43	241.90±26.76	146.53±13.57	<0.001*
SpO_2/FIO_2 6 hr (mean ±SD)	259.64±28.33	241.95±28.75	137.92±13.30	0.105
SpO_2/FIO_2 24 hr (mean ±SD)	301.70±30.71	252.05±28.97	137.75±13.81	0.001*
SpO_2/FIO_2 48 hr (mean ±SD)	334.94±29.80	270.80±30.47	137.42±14.99	<0.001*
Initial Respiratory rate (mean ±SD)	18.41±2.85	22.20±3.39	27.85±2.36	<0.001*
Respiratory rate 6 hr (mean ±SD)	17.64±2.5	20.70±3.64	25.07±4.12	0.011*
Respiratory rate 24 hr (mean ±SD)	16.23±1.95	20.50±5.17	27.42±4.77	0.149
Respiratory rate 48 hr (mean ±SD)	15.88±2.36	22.60±8.41	27.21±6.74	0.262

SD: standart deviation, ILA: injured long area, RR, respiratory rate, * p values <0.05

Comparison of percentage of ILA with inflammatory markers was shown in **Table 4**.

When looking at the effect of prone position on SpO_2, FIO_2, RR and SpO_2/FIO_2 regardless of percentage of ILA; while an increase in SpO_2/FIO_2 ratio was detected in most of the patients at the 6th and 24th hours according to the baseline; at 48th hour, most of the patients had a decrease in the SpO_2/FIO_2 ratio, and this decrease was statistically significant (p-values; 0.005). Looking at the prone position and RR relationship; RR decreased in all hours with PP application (**Table 5-6**). There was no complication due to PP.

The use of awake-PP did not reduce the risk of being intubated [hazard ratio (RR) 0.1,007 (95% Confidence Interval (CI) 0.981– 1.035), p-value 0.589] and the 28-day mortality risk was not influenced by the use of awake-PP [RR 0,993 (95% CI 0.977-1,009), p-value 0.409)].

DISCUSSION

Although COVID-19 pneumonia fits the ARDS Berlin Definition, it is a specific disease with distinctive phenotypes. Disruption of lung interstitium and vascular endothelium, ventilation perfusion mismatch that disrupts pulmonary vasoregulation and fosters thrombogenesis are considered in the pathogenesis (9). The most characteristic feature is respiratory mechanics incompatible with the severity of hypoxemia (10). In early stage of infection, relatively good compliance is observed in patients against very poor oxygenation. Chest imaging mainly manifests as multiple small patch lesions and interstitial changes, especially in the lung periphery. As the disease progresses, bilateral lungs show a ground-glass pattern. Marini and Gattinoni (11) defined this patient group as 'type L' characterized by low lung elastance, high compliance and lower lung weight. 'Type H', which is

Table 4. Comparison of percentage of ILA with inflammatory markers

		Percentage of ILA			P values
		0-10% (n: 17)	10-30 % (n:20)	>30% (n:28)	
Lymp (103/μL)	Mean ±Sd Min-Max	0.7±0.34 0.22-1.7	0.73±0.33 0.22-1.7	0.66±0.33 0.22-0.99	0.854
D-Dimer (ng/mL)	Mean ±Sd Min-Max	914 .95±883.87 150- 8816	941.65±1326.17 144-8816	2357.08±2470.61 144-8816	0.001*
Ferritin (ng/mL)	Mean ±Sd Min-Max	335.35±439.41 2.68-3145	391.41±466.75 2.68-3145	758.13±483.29 82.2-2000	0.001*
Fibrinogen (mg/dL)	Mean ±Sd Min-Max	317±123.08 127-679	429.34±190.17 88.6-987	418.89±290.17 118-968	0.739
CRP (mg/L)	Mean ±Sd Min-Max	47.33±58.35 4-257	92.87±67.12 9.6-246	107±80.39 20-327	0.001
LDH (U/L)	Mean ±Sd Min-Max	403.28±182.54 167-906	458.5±288.03 227-1403	490.39±370.28 190-1661	0.721

Lymp; Lymphocyte count, LDH; Lactate dehydrogenase, CRP; C-reactive protein, * P-value<0.005

Table 5. Wilcoxon Signed Ranks Test to to compare mean values between SpO_2 /FIO_2 initial and 6,24,48 hour values

Variables	n	Mean Ranks	Sum of Ranks	z	P values
SpO_2 /FIO_2					
6th hr -Initial				-1.400	0.162
Neg Ranks	23[a]	40.70	936.0		
Poz Ranks	32[b]	18.88	604.0		
Ties	10[c]	-	-		
24th hr - Initial				-1.718	0.086
Neg Ranks	27[a]	30.0	810.0		
Poz Ranks	38[b]	35.13	1335.0		
Ties	0[c]	-	-		
48th hr - Initial				-2.803	0.005*
Neg Ranks	38[a]	23.85	644.0		
Poz Ranks	27[b]	39.50	1501.0		
Ties	0[c]	-	-		

a. SpO_2/FIO_2 6-24-48th hr < Initial SpO_2/FIO_2, b. SpO_2/FIO_2 6-24-48th hr > Initial SpO_2/FIO_2, c. SpO_2/FIO_2 6-24-48th hr=Initial SpO_2/FIO_2

Table 6. Wilcoxon Signed Ranks Test to compare mean values between Respiratory rate initial and 6,24,48 hour values

Variables	n	Mean Ranks	Sum of Ranks	z	P values
Respiratory rate (/dk)					
Initial-6 hr				-5.244	>0.001*
Neg Ranks	44[a]	30.53	1343.5		
Poz Ranks	10[b]	14.15	141.5		
Ties	11[c]	-	-		
Initial-24 hr				-2.565	0.010*
Neg Ranks	42[a]	24.71	1038		
Poz Ranks	12[b]	37.25	447.0		
Ties	11[c]	-	-		
Initial-48 hr				-1.252	0.211
Neg Ranks	37[a]	31.16	1153		
Poz Ranks	25[b]	32	800		
Ties	3[c]	-	-		

a. Respiratory rate 6-24-48th hr < Respiratory rate, b. Respiratory rate 6-24-48th hr > Respiratory rate, c. Respiratory rate 6-24-48th hr=Respiratory rate

clinically compatible with typical ARDS and is generally observed in ICU, that is high elastance, low compliance and higher lung weight often appears with consolidations in CT (11). Pleural effusion is rare. The patients present high respiratory drives, strong inspiratory efforts and highly negative intrathoracic pressures (10). Therefore, when pulmonary consolidation is detected in imaging, the disease has already deteriorated and the lungs have been damaged for quite a long time. In our study, we tried to reveal the severity of injury in the lung by calculating the percentage of ILA from the consolidation and ground-glass pattern areas from CT images.

PP used as recruitment maneuver; in ARDS, the compression of the heart and increased lung weight cause an increase in the compliance of the dorsal lung areas that are prone to atelectasis and thus an improvement in gas exchange. PP, which has been used in ARDS patients with mechanical ventilation support for many years, is now also being used in awake non-intubated ARDS patients (1). The prone position that is frequently used in COVID-19 pneumonia, acts with different mechanisms in Type L and type H. PP positively affects oxygenation by providing redistribution of pulmonary blood flow rather than opening collapsed areas as in type H in Type L. We compared the efficacy of PP administered in awake non-intubated COVID-19 patients with percentage of ILA. While Percentage of ILA improves the oxygenation and RR in patients with less than 30%, it has been observed that it has no positive effect on oxygenation in patients with lung damage 30% and above.

The massive number of cases that occur with the COVID-19 pandemic are admitted to hospital and the rapid evaluation respiratory failure have quickly depleted critical care resources, such as respiratory support equipment especially ventilators, HFO_2, and ICU beds. Therefore recruitment maneuvers such as PP have been started to be applied in out-of-ICUs such as emergency services. Coputo et al applied PP to awake non-intubated COVID-19 patients early in the emergency room and showing a significant improvement in peripheral oxygen saturation (12). On the other hand Coppo et al emphasized that PP can be applied safely in out-of-ICUs, and stated that early PP application is effective in improving oxygenation even in short-term resupination. (13). In addition to all these studies, we tried to determine the severity of lung injury with percentage of ILA. We found that PP applied to patients with low percentage of ILA resulted in improvement in oxygenation and RR, while the same improvement was not seen as the percentage of ILA increased.

Regardless of percentage of ILA, when PP is evaluated, its positive effect on SpO_2/FIO_2 ratio and RR is similar to other studies (5,14,15). Despite finding similar results, Ferando et al emphasized that PP does not reduce the risk of intubation and may even delay intubation (16). It has been shown that PP does not reduce the risk of intubation and 72.7% of the intubated patients have 30% and above percentage of ILA in our study. We think that the lack of positive effect of PP on SpO_2/FIO_2 in this patient group can be explained by patient self-inflicted lung injury (P-SILI). Strong respiratory efforts and high respiratory drives that lead to large negative swings in pleural pressure creating excessive lung stress and strain and increased lung edema due to negative trans alveolar pressure may worsen lung injury and result in P-SILI (17).

Our study has potential limitations. The study was designed as a single center. This situation has limited the number of patients. Arterial blood gas sampling was not performed from the patients. The percentage of ILA of the patients were calculated once during the study period. Percentage of ILAs may be higher considering rapid COVID-19 progression.

CONCLUSION

The prone position is a safe and effective application that causes improvement in SpO_2/FIO_2 ratio and RR in awake non-intubated COVID-19 patients with less damage to the lung. However, it should be kept in mind that as the damage to the lung increases, the expected recovery may not be possible. We think that calculating the percentage of ILA of the patients from CT may be a guide when planning prone position..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Muğla Sıtkı Koçman University Ethics Committee (Date: 2021, Decision No: 148).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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