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Comparison of prone and supine status on oxygenation of patients with COVID-19 with acute hypoxemia treated using reservoir mask; a randomized clinical trial

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Abstract

Introduction: In early December of 2019, the first coronary pneumonia cases were identified, an emerging disease which is associated with higher mortality and morbidity and a higher proportion of deaths in population.
Objectives: A significant number of patients progress towards acute respiratory distress syndrome (ARDS). Therefore, if we can control pulmonary involvement in the initial stages and before reaching severe degrees of ARDS, we will have given a great assistance to patients.
Patients and Methods: A randomized clinical trial was conducted on 30 SARS-CoV-2 patients with acute respiratory hypoxia. The study population was randomly divided into two equal parts including group P (prone) and group S (supine). Patients in the prone group were placed in the prone position, six hours per day for three days, while received oxygen therapy by reserve bag and another group received oxygen therapy in the supine position by using reserve bag. Finally, the data were analyzed using statistical software.
Results: In total, both groups showed significant results during three days of hospitalization, however, the considered variables of relative arterial oxygen pressure and PA/FiO2 during three days of the hospitalization in the prone group were significantly higher than the supine group ($P=0.022$ and $P=0.012$). Other variables did not show any statistically significant differences.
Conclusion: Relative arterial oxygen pressure and PA/FiO2 in the prone group were significantly higher than the supine group. This finding shows the importance of prone status in the process of oxygenation and recovery of patients.
Trial Registration: The trial was registered by the Iranian Registry of Clinical Trials (identifier: IRCT20151020024625N12; https://www.irct.ir/trial/55690/view, Ethical code# IR.SEMUMS.REC. 1399.201).

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Introduction

Coronavirus disease 2019 (COVID-19) is one of the most common viruses infected with the human respiratory system, which causes severe damage to the lung tissue by causing acute pneumonia. Prior to the outbreak of coronavirus, severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) had been recognized as a threat to public life (1). COVID-19 first was reported in China, which genetically was similar to the SARS virus. However, the prevalence rate of COVID-19 is very high across the world and approximately 109 million people have been infected with coronavirus and due to this disease 2.4 million of them have died (2,3). In Iran, the first official announcement of this disease was in March 2019. After identifying cases of the disease in relation to its signs and symptoms, it was stated that the initial mild symptoms of the disease are similar to the common cold when it occurs and progresses to pneumonia on the ninth day of the disease (4). In the United States, the first human-to-human transmission to COVID-19 was reported in January (5). The mortality rate of COVID-19 was approximately 2% and the mean age of mortality was 75 (ranging between 48 to 89)

Key point

Coronavirus disease 2019 (COVID-19) is a worldwide disease with a higher mortality rate. Due to its emergence, a suitable medicine has not yet been known to treat it, because most measures are focused on symptomatic treatment and reducing its complications. One of the major problems in these patients is hypoxia. In this randomized clinical trial, we showed the positive effect of prone position in improving oxygenation.

years (6).

Symptoms of COVID-19 infection appear after a latency period of approximately 5 to 6 days (7). The onset period of COVID-19 symptoms depends on the patient's age and the condition of the patient's immune system while it is less weak in patients under 70 years old than in patients over 70 years old. The most common symptoms of COVID-19 disease are fever, cough and fatigue, since other symptoms including sputum, headache, bleeding, diarrhea, indigestion and lymphopenia (1). Clinical features on chest CT were detected as pneumonia and non-specific features including acute respiratory syndrome, acute cardiac complications, and gran-glass opacities that can cause death, which are observed too. In some cases due to the severe immune system and inflammation, grand-glass opacities are seen in the frame of both lungs (3). Recently, some patients with COVID-19 infection have experienced gastrointestinal symptoms including diarrhea (8).

Laboratory symptoms of COVID-19 contain increased leukocyte counts, abnormal respiratory findings, and elevated levels of inflammatory plasma cytokines. Furthermore, increased C-reactive protein (CRP) and deposition of erythrocytes and D-dimer have also been observed (3). Significant increase in blood levels of cytokine and chemokine have been observed in patients with coronary artery diseases, in the case of hospitalized patients, have shown higher rate of anti-inflammatory cytokines including interleukin-2 (IL2), interleukin-7 (IL7), interleukin-10 (IL10), granulocyte-colony-stimulating factor, interferon γ–induced protein-10 (IP10), monocyte chemoattractant protein 1, macrophage inflammatory protein-1α and tumor necrosis factor α (1). Early deaths of prevalence of COVID-19 occur primarily in the older people, possibly due to a weaker immune system that allows the viral infection to progress at a higher speed (9).

Currently, there is no confirmed antiviral medicine against COVID-19 infection for the treatment or prevention in humans. The only available option is using a wide spectrum of antiviral medicine including nucleoside analogues as well as HIV-protease inhibitors which can reduce virus infection until a specific antivirus will be accessible (9).

An important issue which is common in patients is acute pneumonia and in a significant number of patients the incidence of acute respiratory distress syndrome (ARDS) (10). Recent researches suggested that prone position can increase PaO2/FiO2 up to 35% as well as can decrease mortality of medium and ARDS, in particular with neuromuscular blocker (NMB) and ventilation tidal volume (11). Moreover, numerous reviews demonstrated that prone position can prevent lung damage caused by a ventilator (12). In addition, several meta-analyses have also shown a significant effect on the recovery of patients with prone position compared to the supine position (13).

Objectives

Insufficient studies were conducted on patients with ARDS receiving non-invasive oxygen therapy. On the other hand, in acute cases, ARDS in infected patients with COVID-19 have been observed. Due to the repeated recommendations by physicians to delay incubation in patients, the supportive measures that can delay the patients' incubation have been considered. Placing patients in the prone position during oxygen therapy is the first priority among other action. It has been experimentally observed that patient with ARDS in the COVID-19 position increase dramatically; often saccharomyces of patients is increased during the first hour by being in the prone position. Regarding availability and low cost and uncomplicated plan for the patients during hospitalization, it is expected that this treatment method can provide assistance to accelerate the improvement of pulmonary involvement and thus decrease the hospitalization time and the cost of entering the medical system.

The aim of this study was to compare the prone position and supine position on the rate of oxygenation in patients with acute hypoxemia treated with bag reserve mask.

Patients and Methods

Study design

The quasi-experimental study was conducted on 30 patients with SARS-CoV-2 with acute hypoxia and hospitalized from April to August 2020 in the COVID-19 ward of Kosar hospital.

Inclusion and exclusion criterion

Inclusion criterion included patients admitted to the ward with SARS-CoV-2 whose diagnosis was confirmed by polymerase chain reaction (PCR) test of the pharyngeal sample or radiological findings; acute hypoxemia PaO2/FiO2 was between 150-300 and their age was between 18 and 70 years old. Exclusion criteria included contraindication to use NIV (non-invasive ventilation) (respiratory arrest or unstable cardiorespiratory condition, inability to protect the airways, apnea and decreased level of consciousness), patient's intolerance of prone position and patient's unwillingness to participate in the study. In addition, patients with facial and oral trauma during the last two weeks, pulmonary embolism or deep venous thrombosis that was treated in the last two years, cardiac pacemaker implantation in the last two days, pregnancy and systemic diseases including asthma, chronic obstructive pulmonary disease, heart failure and unstable angina pectoris excluded from study.

Variables and data gathering

The consideration of intended variables was fulfilled using a checklist and the consideration of effective blood factors by collecting blood samples of patients. The considered variables included age, gender, PaO2/FiO2, oxygen saturation in the blood, the number of breaths

per minute, CRP, erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), the ratio of neutrophils to lymphocytes.

Test method

The diagnoses were confirmed by a specialist physician and patients randomly divided into two groups by the scientific team. Totally, 42 patients were studied, nine patients were excluded from the study due to history of unstable angina (n = 4), asthma/chronic obstructive pulmonary disease (COPD) (n = 3) and heart failure (n = 2). Three patients were excluded during the study, one patient in control group for losing to follow-up (early discharge) and two patients in intervention group for occurring of apnea and decreased level of consciousness. For randomization, at first stage, 30 spheres from one to 30 are considered and following that was randomly divided into two equal parts, including P (prone) and group S (supine), and then using a lottery container, the ball of each group was taken out and the intended sequence was recorded). The patients needed to receive oxygen with the help of a reserve bag. Oxygen therapy in these patients was conducted continuously with a reserve bag according to the standard of the country's treatment protocol, therefore in the prone group, the position change was stopped. The prone group for three days, 6 hours, were placed in the prone position (three hours in the morning and three hours in the afternoon), while the patients oxygen therapy was continued with the help of a reserve bag and the group received oxygen by reserve bag in the supine position (normal). At the early days of hospitalization, the rate of CRP, ESR, neutrophil/lymphocyte and the level of blood oxygen saturation, initial value of PaO2, FiO2, and their proportion were registered. Blood oxygen saturation levels were measured while the patient was in the supine and prone position and after three hours, in the normal position, blood oxygenation and its changes were measured. Following the study, after three days of receiving reserve bag, arterial blood gas, CRP, ESR, and neutrophil/lymphocyte of patient were rechecked, in addition, the value of PaO2, FiO2 of patient were checked, and its changes were evaluated based on the initial value. At the end of three days, the results of the two pollen experiments were compared with each other. During the study, the patients' oxygen level was set at seven liters per minute. The patients were active participants in the study until the end of the hospitalization period and thereafter underwent treatment after discharge.

Statistical analysis

The gathered data was recorded and analyzed by SPSS software version 25. In order to describe the data, frequency, and mean were used, as well as independent *t* test, chi-square and Fisher's exact tests were used. In addition, a significant level was set as 0.05.

Results

Thirty patients ranging in age from 18 to 70 years old were studied. Around 63.8% of them were men and 36% were women (Table 1). The obtained results of analysis illustrated that there was no significant relationship between patients' gender and studied variables.

The mean of variables in the two groups is demonstrated in Table 2. Comparative studies showed that the variables were distinct at the beginning of hospitalization compared to three days of hospitalization.

Table 3 shows the mean of the studied variables in two groups of supine and prone. Variables including FiO2, oxygen saturation in the blood, the number of breaths per minute, ESR, CRP, neutrophils and the ratio of neutrophils to lymphocytes at the beginning of hospitalization in comparison with three days after hospitalization were different in both groups, and this difference was significant ($P < 0.05$). However, the amount of LDH in the supine group and the lymphocytes counts in the prone group were not significantly different at the 3rd day compared to the first day of hospitalization ($P > 0.05$).

The comparison of the mean of the studied variables in the two experimental groups using t-test illustrated that the variables of relative arterial oxygen pressure (PaO2)

Table 1. Frequency and relationship of variables with gender in patients

Variables		Percent (%)	*P* value
Gender	Male	63.8	0.65
	Female	36.2	
Comorbidity	Cardiovascular disorders	6.6	0.097
	History of hypertension	3.3	
	Gastrointestinal disorders	6.6	
	Diabetes	26.4	

Table 2. Mean ± SD of variables in patients

Variables		Mean ± SD	*P* value
WBC (per µL)	At admission	7901.00 ± 3409.17	<0.001
	3 Days later	7553.33 ± 2778.45	
Neutrophil (per µL)	At admission	5797.13 ± 2805.66	0.007
	3 Days later	5037.51 ± 2441.51	
Lymphocyte (per µL)	At admission	1489.85 ± 679.88	0.21
	3 Days later	1585.70 ± 557.46	
Neutrophil-lymphocyte ratio	At admission	4.84 ± 4.08	0.008
	3 Days later	3.73 ± 2.11	
CRP (mg/L)	At admission	12.60 ± 22.82	<0.001
	3 Days later	9.57 ± 9.45	
Platelets (per µL)	At admission	208.63 ± 64.49	0.002
	3 Days later	221.80 ± 65.88	
ESR (mm/h)	At admission	42.37 ± 31.83	0.03
	3 Days later	39.13 ± 34.68	
LDH (U/L)	At admission	420.13 ± 118.76	0.093
	3 Days later	422.17	
PaO2 (mm Hg)	At admission	56.01	<0.001
	3 Days later	62.44	
PA/FiO2 (mm Hg)	At admission	256.31	<0.001
	3 Days later	284.04	

Table 3. Mean ± SD of variables in two groups

Variables		Groups			
		Supine		Prone	
		Mean ± SD	*P* value	Mean ± SD	*P* value
WBC (per µL)	At admission	7666.67 ± 3774.33	<0.001	8135.33 ±3116.39	<0.001
	3 Days later	76.19.33 ± 2807.40		7486.67 ±2846.06	
Neutrophil (per µL)	At admission	5781.67 ± 3136.93	<0.001	5812.60 ± 2542.62	0.027
	3 Days later	5513.20 ± 2290.17		4561.82 ± 2572.53	
Lymphocyte (per µL)	At admission	1283.50 ± 573.45	0.009	1696.20 ± 733.09	0.431
	3 Days later	1433.20 ± 428.58		1738.20 ± 640.47	
NLR	At admission	5.68 ± 5.20	<0.001	4.01± 2.43	0.028
	3 Days later	4.17 ± 2.15		3.29 ± 2.04	
CRP (mg/L)	At admission	14.40 ± 30.78		10.80± 11.16	<0.001
	3 Days later	9.87 ± 12.00		9.27 ± 6.39	
Platelets (per µL)	At admission	188.07 ± 72.06	<0.001	229.20 ± 0.16	0.002
	3 Days later	206.87 ± 79.54		236.73 ± 46.76	
ESR (mm/h)	At admission	39.93 ± 34.50	<0.001	44.80 ± 29.94	<0.001
	3 Days later	42.87 ± 38.83		35.40± 30.88	
LDH (U/L)	At admission	396.40 ± 131.71	0.190	443.87 ± 103.26	0.008
	3 Days later	422.87 ± 147.89		421.47 ± 98.53	
PaO2 (mm Hg)	At admission	52.90 ± 4.36	<0.001	59.13 ± 12.53	<0.001
	3 Days later	56.73 ± 4.80		68.15 ± 17.55	
PA/FiO2 (mm Hg)	At admission	251.90 ± 20.74	<0.001	260.71 ± 34.22	<0.001
	3 Days later	270.17 ± 22.86		297.92 ± 32.96	

Table 4. Difference of variables value between groups (95% CI)

Variables		Difference between groups (95% CI)		*P* value
		Lower	Upper	
WBC (per µL)	At admission	-2120.02	3057.45	0.714
	3 Days later	-2247.01	1981.98	0.899
Neutrophil (per µL)	At admission	-2104.72	2166.69	0.977
	3 Days later	-2773.02	870.22	0.294
Lymphocyte (per µL)	At admission	-79.556	904.96	0.097
	3 Days later	102.586	712.56	0.137
Neutrophil/lymphocyte ratio	At admission	-4.701	1.36	0.270
	3 Days later	2.449	0.695	0.262
CRP (mg/L)	At admission	-5.300	78.66	0.080
	3 Days later	-18.933	29.03	0.220
Platelets (per µL)	At admission	-19.299	18.78	0.683
	3 Days later	-33.702	13.77	0.565
ESR (mm/h)	At admission	-20.917	6.584	0.673
	3 Days later	-7.784	87.577	0.865
LDH (U/L)	At admission	-41.054	135.987	0.281
	3 Days later	-95.390	92.590	0.976
PaO2 (mm Hg)	At admission	-0.787	13.240	0.080
	3 Days later	1.795	21.045	0.022
PA/FiO2 (mm Hg)	At admission	-12.359	29.979	0.401
	3 Days later	6.538	48.969	0.012

and PA/FiO2 during three days after hospitalization in the prone group was significantly higher than the supine group ($P=0.022$ and $P=0.012$, respectively) (Table 4). Other variables did not show a statistically significant difference.

Discussion

ARDS has about 25%-40% mortality even with supportive treatment, which demonstrates the significance of provision of various studies (10). The current study showed that a majority of investigated variables in both

groups had proper and significant improvement after three days after hospitalization, although the comparison of mean showed that the percent of oxygen and PA.FiO2 during three days after hospitalization in prone group was significantly higher than supine group. This finding highlights the role of prone position in breath and oxygenation in patients. In this regard, congruent studies expressed that prone position can increase PaO2/FiO2 up to 35% as well as can decrease the mortality of medium and ARDS, in particular when NMB and ventilation are with low tidal volume (11). Furthermore, various evidence showed that the prone position could prevent lung damage resulted from ventilator (12). Nevertheless, contradictory results have been seen in several studies in which placing the patient in the prone position and then improving them compared to other positions has not been considered. The study by Taccone et al showed that placing patient in the prone position has no remarkable impact on the improvement and mortality of ARDS patients compared to supine statues (14). However, a further meta-analysis of those studies shows a dramatic effect on the recovery of patients with prone position compared to supine position. According to these studies, the mortality rate of patients in prone position was approximately 50% lower than patients in supine position (15). Additionally, if ARDS patients be in the prone position from the beginning days of treatment and most days of hospitalization, they have better symptoms than patients with supine position (13).

In a systematic review conducted by Munshi et al, 2129 patients were considered in which 1093 out of them were placed in the prone position. They found that the mortality of prone group was remarkably less. This study recommended that in order to obtain ideal results, patients should be placed in the prone position for 12 hours per day (16). The study of Schulten et al showed that in patients with acute ARDS, the early prone position remarkably decreases mortality (17).

Our study showed that the amount of oxygen in the prone state increases even more and this is the most significant finding of the study. Guerin et al concluded that placing patients in the prone position significantly improves patients' oxygenation (18). Ding et al expressed that the amount of PaO2/FiO2 in ARDS patients was remarkably high as well as the amount of need to intubation was remarkably less (19). Furthermore, in the study conducted by Haddam et al, 51 patients with PaO2/FiO2 ratio ≤150 who were placed in prone position underwent bedside lung ultrasonography. The findings of lung ultrasonography did not show any pattern in favor of any change in oxygen saturation level in lung tissue; however, some changes in aeration were observed in the prone position (20).

Accordingly Gaudry et al conducted a research on 98 patients suffering from ARDS who underwent abdominal surgery, they approved that placing patients in the prone position not only has not increased post-operative complications but also has accompanied with remarkable improvement of oxygenation in patients. Therefore, it is recommended those patients who underwent abdominal surgery should not be deprived of prone position due to post-operative complications (21).

Overall, the current study demonstrates that prone position had an effect on blood oxygenation and this has been significant in reducing the symptoms and improving the respiratory condition of disease. Even though, in addition to the proposed solutions, the prevention of coronavirus is an important issue. Protecting or reducing transmission in vulnerable populations, including personnel of health care, the elderly, and people at risk is important (23). China and the United States have been taken major preventive and control measurements, including travel screening in order to impose more control on the coronavirus (22). It is hoped that more effective and comprehensive strategies will be provided in developing countries in order to control coronavirus.

Conclusion

The results showed that the arterial partial pressure of oxygen and PA/FiO2 during three days after hospitalization in the prone position group were significantly higher than the supine group and the patients' respiratory functions were improved in the prone position group. In other variables, the two groups had a significant effect within the group, but no significant difference was observed between the two groups. This finding shows the significance of prone position in the therapy process of patients with pneumonia. COVID-19 disease is associated with high mortality and morbidity, and a significant number of patients progress to ARDS and the most vulnerable part of the body, which is affected by COVID-19, is respiratory system. Finally, more attention should be paid to treatment strategies such as improving of the oxygenation status, which can be an important way to reduce patient mortality.

Limitations of the study

One of the limitations of the current study is the investigation of lung morphology and the impacts of subsequent periods, which might be conducted on patients. In addition, another limitation is incidence of specific complications in prone position that has been clinically evident but data gathering was not predicted in this regard.

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Authors' contribution

MM, FM and AG provided technical assistance; MB collected the data and prepared the manuscript. RG acted as a biostatics consultant. MD designed, supervised the study and prepared the final draft of the article.

Conflicts of interest

The authors declare no conflict of interest.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Research Council of Semnan University of Medical Sciences approved this study (IR.SEMUMS.REC.1399.201) and registered at Iranian Registry Clinical Trials (IRCT20151020024625N12; https://www.irct.ir/trial/55690). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from M.D., thesis of Mohammad Bahrami at this university (Thesis#2419). Moreover, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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