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Effect of Prone Position on Clinical Outcomes of Non-Intubated Patients with Covid-19: A Randomized Clinical Trial

Running Head. The Effect of Prone Position on Patients with Covid-19

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Abstract

Background. Prone positioning (PP) is a well-known respiratory support approach. Limited data are available for the use of PP in non-intubated patients with COVID-19.

Aim. This study aims to investigate the effect of PP on the clinical outcomes of patients with COVID-19 pneumonia.

Methods. In This clinical trial, the participants in the PP group (n=41) were asked to lie comfortably in a prone position for 90 minutes. In the supine position (SP) group (n=41), the participants were asked to lie comfortably in a supine position for 90 minutes. Clinical data such as oxygen saturation, respiratory rate, the severity of dyspnea, mean arterial pressure, and pulse rate were assessed at 0 (immediately before), 30, 60, 90 minutes after the start of the intervention and 30 min after resuming the supine position. The participants in the PP group were then asked to intermittently stay in a prone position for a total of eight hours per 24 hours of hospitalization. The participants in the control group were asked to remain in their

usual positions during the hospital stay. Finally, the length of hospital stay, intubation rate, and survival assessed.

Findings. Prone positioning was associated with significant improvement in oxygen saturation (P = 0.001), respiratory rate (P=0.004), the severity of dyspnea (P=0.014), and mean arterial pressure (P=0.027). There was no significant difference between the two groups in terms of pulse rate (P=0.890), hospital stay (P=0.994), intubation rate (P=0.324), and survival (P=0.091).

Discussion. Our results demonstrated that prone positioning showed marked improvement in some short-term clinical outcomes in non-intubated patients with COVID-19.

Conclusion. Prone positioning can be considered an inexpensive, accessible, and simple measure in awake non-intubated patients with COVID-19.

Keywords: Acute respiratory distress syndrome; Coronavirus; Covid-19; Prone Position

Summary of Relevance

Problem or Issue

Lack of specific treatment for COVID-19 pneumonia has led to increased efforts by nurses to find methods for caring.

What is Already Known?

Some quasi-experimental studies have suggested that prone positioning may improve oxygenation in patients with COVID-19 pneumonia.

What Does This Paper Adds?

This study is one of the few clinical trials investigating the effect of prone positioning on disease outcome in non-intubated patients with COVID-19 pneumonia.

Introduction

In late 2019, Coronavirus Disease 2019 (COVID-19) quickly spread worldwide and led to a high mortality rate (Ghelichkhani & Esmaeili, 2020). COVID-19 pulmonary involvement leads to pneumonia and Acute Respiratory Distress Syndrome (ARDS) (Galehdar et al., 2021). The prevalence of ARDS in patients with COVID-19 has been reported to be up to 17% (Chen et al., 2020). The COVID-19 pandemic led to a rapid increase in the number of patients requiring mechanical ventilation support for ARDS, followed by overload in intensive care Units (ICU). Hence, clinicians have to employ creative ideas to limit the need for respiratory support, including awake-prone positioning (PP) (Touchon et al., 2021).

The studies have found that PP effectively improves the oxygenation of the patients affected by ARDS or severe acute respiratory syndrome (SARS) (Aguirre-Bermeo et al., 2018; Chiumello et al., 2018; Joynt & Yap, 2004). A controlled trial showed that PP resulted in increased ventilator-free days, decreased extubation time, and mortality in the patients with ARDS (Guérin et al., 2013). The lung inflation exerted this effect, increased lung volumes (for example, increased residual volume and end-expiratory volume), improved pulmonary perfusion and gas exchange, homogenized pulmonary ventilation, reduced

pulmonary arterial pressure, and an increase of the posterior pulmonary alveolar recruitment. In addition, the PP has beneficial effects on lung protection and hemodynamic maintenance as it distributes the pressure in the lungs and reduces the pressure on the right ventricle (Chiumello et al., 2018; Joynt & Yap, 2004). The use of PP in non-intubated COVID-19 patients has been newly suggested by several notable organizations to avoid intubation and potentially improve patient-oriented outcomes (Bamford et al., 2020; Weatherald et al., 2021). Also, other studies are offering the experiential use of PP in patients with COVID-19 to improve oxygenation. This intervention, accompanied by other treatments, can be used in supportive care for the COVID-19 patients (Meng et al., 2020).

Lack of particular treatment for COVID-19 pneumonia has led to increased efforts by nurses to find methods for caring. However, the novel nature of the disease and subsequent shortage of evidence-based studies have led to confusion in the healthcare providers, debilitating them in providing suitable healthcare methods (Galehdar et al., 2020; Galehdar et al., 2021). Therefore, according to the above, the PP may be effective on the clinical outcomes of patients with COVID-19 pneumonia. In case of promising results, this method can be used as a beneficial care strategy for these patients due to no need for special tools or equipment and cost-effectiveness. Therefore, this study aimed to evaluate the effect of PP on the clinical outcomes of patients with COVID-19 pneumonia. Clinical outcomes include SpO_2, Respiratory Rate (RR), Heart Rate (HR), Mean Arterial pressure (MAP), and severity of dyspnea measures.

In addition, this study aims to evaluate the effects of self-prone positioning on other outcomes such as hospital stay, intubation rate, and survival among awake-non intubated patients with COVID-19.

Methods

Trial Design

This randomized controlled clinical trial was conducted between August 2020 and April 2021.

Participants

The study population included all patients with COVID-19 who were admitted to the COVID-19 ward, Shohaday Ashayer hospital, located in Khorramabad, Iran. The diagnosis of COVID-19 was based on clinical symptoms and signs, Computed Tomography (CT) of chest findings compatible with the COVID-19 pneumonia pattern, and Polymerase Chain Reaction (PCR) test. The inclusion criteria consisted of an age range of 35-70 years; lack of supportive ventilation; lack of Chronic Obstructive Pulmonary Disease (COPD) or asthma; lack of orthopedic and spine disorders; no history of thoracic surgery during the last six months. Exclusion criteria were unable to tolerate PP (Kordestani-Moghadam et al., 2020), severe

cough, nausea, and vomiting during positioning, sudden changes in vital signs to a level greater than 20% of the baseline, and unwillingness to continue to participate.

Blinding

Due to logistical reasons, only the data analyst and principal investigators were blinded to group assignment.

Sample Size Estimation

Some information was needed to estimate the sample size, such as Standard Deviation (SD) of variables and interpersonal correlation coefficient of data. For this purpose, a pilot study was performed on five volunteer patients with supine positions. Patients' respiratory rate and hemodynamic changes (MAP and PR) were assessed for 90 minutes. Consequently, based on a respiratory rate and taking into account; 1-β=0.90, α=0.05, D1 (difference|H1) =3, M (number of time points) =5, covariance type=compound symmetry, σ (SD of a single observation) =4.8, ρ (autocorrelation)=0.6 with using the PASS-15, the primary sample size was estimated as 37 per group. Then, considering a possible attrition rate of 10%, the final sample size was enlarged to 41 people per group.

Randomization

The participants were allocated to the intervention, prone position (PP) (n=41) and control, supine position (SP) (n=41) groups using a table of random numbers and the stratified random allocation sequence. According to baseline oxygen saturation (SPO2), gender, and age 16 strata were first created. Then, within each stratum, using permuted block randomization with block-size two and an allocation ratio of 1:1, the participants were allocated to groups PP and SP (0-4 for PP-SP sequence and numbers 5-9 for SP-PP sequence). A biostatistician designed the random allocation and enrolled the participants.

Instruments

A checklist consisting of two parts was prepared. The first part contained of 12 variables, including; sex, age, Body Mass Index (BMI), marital status, educational qualifications, occupation, previous disease history, percentage of Fraction of Inspired Oxygen (FIO_2) during the intervention, clinical signs at the

beginning of hospitalization and the duration between hospitalization and intervention, which were obtained through interviews with the participants and their medical records. The second part of the checklist included the SPO_2, RR, MAP, HR, the severity of dyspnea (from the beginning of the study) duration of hospitalization, intubation rate, and survival (from the time of ward admission (willingness to participate in the study) to discharge, transfer to the ICU or, patient's death). Visual analog scale (VAS) measures the severity of dyspnea from the scale of zero (no dyspnea) to 10 (the most severe of dyspnea ever experienced).

Primary Outcome Measures:

SPO_2, RR (bpm), HR) (bpm), MAP (mmHg), the severity of dyspnea (Visual Analogue Scale) [Time Frame: These outcomes were collected at immediately before (0), 30, 60, 90 and 120 minutes after the start of the intervention]

Secondary Outcome Measures:

Hospital stays, intubation rate, and survival. [Time Frame: These outcomes were collected at the time of patient discharge to home/house spice, transfer to the ICU or, patient's death].

Intervention

In this study, immediately after admission to the ward, having inclusion criteria and willingness to participate in the study, the participants in the PP group were asked to lie comfortably in a prone positioning for 90 min and then resume to supine. The participants in the SP group were asked to lie comfortably in a supine position at an angle of 30°for 90 min. Participants in both groups could be connected to a 21-60% FIO_2 using a simple mask during intervention. The outcomes of this phase included the assessment of SPO_2, RR, MAP, PR at 0 (immediately before), 30, 60, 90 minutes after the

start of the intervention and 30 min after resuming the supine position. All of these parameters were measured using a GE Dash 4000 Patient Monitor.

The severity of dyspnea is also measured using VAS at 0 (immediately before), 30, 60, 90 minutes after the start of the intervention and 30 min after resuming the supine position.

At the end of the 90 minutes, the participants in the PP group were free to resume the supine position or maintain the PP. Still, they were asked to intermittently stay in a PP for a total of eight hours during the 24 hours of hospitalization. The participants in the SP group were asked to remain in their usual positions (other than the PP) during the hospital stay. We did not collect data during these additional prone positioning sessions as for the first session. Just a total length of time in prone position was recorded.

If patients requested to resume the supine position before the 90 minutes was complete, the prone position was considered unfeasible, and the reason was reported. Other criteria to stop a given proning session were: distress, discomfort, dyspnea, use of accessory respiratory muscles, musculoskeletal pain, hypotension SBP≤90 mmHg, immediate need for intubation, transition to high flow nasal cannula respiratory oxygen desaturation SPO_2≤70%, vomiting, aspiration, and facial edema.

Then the secondary outcomes were collected at the time of the discharge from the study participation to home/house spice, transfer to the ICU or, patient's death.

Patients were followed-up until hospital discharge for the occurrence of intubation, time to intubation, and death. We did not collect data on any prespecified adverse events.

Statistical methods

Data were analyzed by Intention-to-Treat (ITT) approach. The normality of variables was assessed using the Kolmogorov-Smirnov test. Data of both groups were described using the frequency distribution table, the indices of the mean and SD, and line plots. The study groups were compared with basic and demographic variables using univariate tests such as the Monte Carlo Chi-square, Mann-Whitney, and Fisher's exact test. Categorical variables were compared by Chi-square or Fisher' exact test, while continuous variables were compared with independent t-test or Mann-Whitney. If the P-value in

univariate analyses was less than 0.25, the effect of that variable was adjusted to multivariable analyses. For within groups and between-group comparisons of respiratory status and hemodynamics, a combination of analysis of covariance (ANCOVA) and repeated-measures ANOVA was used at a significant level of 0.05 by adjusting the effects of other underlying variables and baseline values (Shih & Aisner, 2022). The length of hospital stay from the beginning of the intervention was compared using a Generalized Linear Model with the identity link function. The firth logistic regression model was used to compare survival. The logistic regression model was used to compare intubation rate (Rossi, 2022). The statistical analyses were done by SPSS version 21 and SAS version 9.2 software.

Ethical Consideration

This clinical trial study was conducted in line with the current guidelines of the Declaration of Helsinki. The Ethics Committee approved the trial protocol of the Lorestan University of Medical Sciences (IR.LUMS.REC.1399.059). In addition, the trial protocol was approved by the Iranian Registry of Clinical Trials (IRCT20160126026217N4).

Written informed consent was obtained from all the participants. The subjects were allowed to either participate in the trial or quit at any phase. They were assured of confidentiality in conducting the trial and keeping the data secret. Permissions were obtained from the Shohaday Ashayer hospital authorities.

Results

Five participants in the intervention group withdrew from the study because of intolerance to the PP. Still, the data of these patients were analyzed by the Last Observation Carried Forward (LOCF) imputation method (Figure 1). The results showed that the mean age of participants in this study was 53 ± 71 years. The number of people with hypertension was significantly higher in the PP group than in the control group (P = 0.002). However, no statistically significant differences were observed between the groups regarding other baseline and demographic characteristics and symptoms of COVID-19 pneumonia. Nonetheless, the effects of the variables of education level, hypertension, other underlying diseases, cough, and other symptoms of COVID-19 were adjusted as confounding variables in statistical models (P < 0.25) (Table 1 and Table 2).

After adjusting for the effect of confounders variables, the mean duration of hospitalization in the PP group (14.970 ± 0.854 days) was 0.008 days less than that of the SP group (14.978 ± 1.104 days). Still, this difference was not statistically significant (P = 0.994).

There was no significant difference between the two groups in survival by firth logistic regression model (P = 0.994, 95% CI for Adjusted Odds Ratio: 0.965-1.608). Also, the logistic regression model showed that the odd ratio for intubation decreased by 60.8%, which was not statistically significant (P = 0.324, 95% CI for Adjusted Odds Ratio: 0.061-2.520) (Table 3).

Table 4 shows the respiratory and hemodynamics measures in two groups in the study's times. After the Greenhouse-Geisser correction, the repeated measures ANOVA test results showed that the interaction effect of the group and the time factor was statistically significant on the mean changes of SPO2 (P=0.001, F=20.60, DF=1), RR (P=0.004, F=8.71, DF=1), dyspnea (P = 0.014, F=6.27, DF=1), and MAP (P = 0.027, F=5.08, DF=1). Furthermore, the results of this test showed that the interaction effect of the group and time factor (P=0.89, F=0.165, DF=2.48), the main effect of the time factor (P = 0.64, F=0.50, DF=2.48), and the main effect of the group (P=0.458, F=55, DF=1) were not statistically significant on the mean PR change.

As we see in Figure 2, the most considerable difference of SPO2 was related to time points of 120 and 90 minutes, which increased by 2.20 and 1.53 units, respectively, in the PP group compared to the SP group. In the RR measures, the difference between the two groups was initially increasing and then decreasing trend over time. The most considerable difference was related to time points of 60 and 90 minutes, which fell by 0.91 and 0.86 units, respectively, in the PP group compared to the SP group. In the case of dyspnea, the difference between the two groups had a decreasing trend over time. The most considerable difference was related to time points of 120 and 90 minutes, which decreased by 0.68 and 0.33 units, respectively, in the PP group compared to the SP group.

In the case of MAP measures, the difference between the two groups was first increasing and then decreasing and increasing again over time. The most considerable difference was related to time points of 60 and 120 minutes, which increased by 1.37 and 0.75 units, respectively, in the PP group compared to the SP group. Finally in the case of PR The most considerable difference was related to time points of 60 and 120 minutes, which increased by 0.80 and 0.63 units, respectively, in the PP group compared to the SP group.

Discussion

The present clinical trial results showed that the PP in patients with COVID-19 could improve the short-term clinical outcome such as SPO2, MAP, RR, and the severity of dyspnea. However, this position did not affect PR, the length of hospital stay, the intubation rate, and survival.

It was observed that SPO2 levels had statistically significant increase in the PP group compared to the SP group. Moreover, the participants in the PP group experienced less RR and dyspnea, which is clinically in line with SPO2 results and indicates oxygenation. The results of this study are in line with other studies examining the effects of PP on COVID-19 patients(Coppo et al., 2020; Elharrar et al., 2020; Sartini et al., 2020; Telias et al., 2020). A feasibility study showed that PP was applicable in COVID-19 pneumonia patients and could improve oxygenation(Coppo et al., 2020). Another study showed that PP could decrease RR and improve oxygenation in patients with noninvasive ventilation outside the ICU (Sartini et al., 2020).

Moreover, Scaravilli et al. reported that the PP improved Partial Pressure of Oxygen (PO2) in non-intubated patients and PO2 levels remained high for up to 6 hours after repositioning (Scaravilli et al.,

2015). Consistent with these findings, the present study showed that the SPO2 level in the PP group was better than that in the SP group for 30 min after repositioning; it should be noted that the follow-up lasted only for 30 min, while it should have continued for a more extended period. In the PP, the lung is less compressed, and the trans-pulmonary pressure becomes homogeneous (Touchon et al., 2021). Improved respiratory status and oxygenation can reduce FIO_2 levels and consequently the risk of reabsorption atelectasis. The results also showed a significant decrease in dyspnea, which could be in line with the hypothesis that self-induced lung injury decreases by a PP, which requires more extensive studies.

The results showed that the mean of MAP in both groups had a downward trend. However, the patients in the PP group had higher MAP levels. Ouchi et al. (2006) stated that PP could lead to enhanced neural activity in the posterior brain region, the forebrain, the amygdala, and especially the precuneus networks. These reactions may improve parasympathetic tone in the brain and thus create a state of relaxation and lower blood pressure. The results showed there was no difference in PR between the two groups. Similarly, Ruste et al. (2018) observed a higher MAP level in the PP group while no changes were observed in PR . A similar result was found by Liu et al. (2021), who showed that the PP did not affect PR in patients with COVID-19. The PP can increase the cardiac index, and consequently MAP, and prevent tachycardia by improving the emptying of the right ventricle and increasing the preload. Moreover, the improvement in MAP indicates improved tissue perfusion, including the lung tissue, which can improve ventilation and produce noticeable clinical effects.

The present study showed that applying a PP reduced the relative intubation odds of patients by 60.8%, but this reduction was not statistically significant compared to the control group. Previous studies have reported conflicting results; a prospective study reported that a PP with high flow nasal oxygen; did not reduce the intubation rate (Ferrando et al., 2020). Similar results were observed in other studies (Coppo et al., 2020; Padrão et al., 2020). However, a retrospective study showed that the PP reduced the intubation rate by 69% (Jagan et al., 2020). Further controlled clinical trials with higher sample sizes are needed to evaluate the intubation rate in the PP.

More favorable clinical results were obtained in the PP group; however, the length of hospitalization did not differ between the two groups. Contrary to these results, it was observed in the study of Liu et al. (2021) that daily PP for six hours would lead to improved oxygenation and decreased hospital stay among COVID-19 patients (20). This difference could be due to similar medication courses in both groups in the present study necessary for the patients.

According to our findings, the survival in the PP group was better than in the SP group. So that survival in the PP group was 100% while in the SP group was 92.7%. However, there was no statistically significant difference between the two groups. In intubated patients with mild to severe ARDS, the PP is effective in survival, supported by clinical trials and meta-analyses (Guérin et al., 2013; Munshi et al., 2017; Sud et al., 2014). Although the PP improves oxygenation in many intubated patients, these changes are not directly related to survival, and survival benefits are most likely achieved by reducing intubation-induced lung injury (Bernard et al., 1994). The effect of improved oxygenation is not clear on clinical outcomes, such as survival, in non-intubated patients. Such patients are not at risk for ventilator-induced lung injury. Thus, potential clinical benefits of the PP in this group of patients may be due to improved oxygen delivery, reduced respiratory function, and a reduced relative risk of intubation. In the present study, non-intubated patients were in a PP for eight hours a day, which improved their survival rate. In some studies, on the other hand, improved survival was seen in intubated patients with ARDS if the patient remained in this position for 12 hours and more(Munshi et al., 2017; Sud et al., 2014). Overall, comparing the study results, it can be seen that the PP can be more effective for short-term outcomes.

In a recent meta-analysis on 35 studies, Chua et al. demonstrated that PP improved SpO_2 than SP in COVID-19 patients (Chua et al., 2021). In another survey of 28 studies, PP was associated with improved oxygenation parameters and reduced mortality and intubation rate in COVID-19 related respiratory failure (Behesht Aeen et al., 2021). In another systematic review and meta-analysis on 14 studies, lower mortality was found in the group placed in the PP, but the tracheal intubation rate was unchanged (Fazzini et al., 2022). In all these studies, the authors have stated that given the limitations such as a limited number of studies with small sample size, and cohort studies, substantial heterogeneity

of measured outcomes, randomized controlled studies are warranted before conclusions are made about safety, and further studies are warranted to standardize the regime of PP to improve the certainty of evidence.

Limitations

The present study is one of the few clinical trials investigating the effect of the PP on disease outcome in non-intubated patients with COVID-19 pneumonia. In this study, the effect of confounding variables was adjusted and minimized by stratified randomization and statistical models to discern the actual effect of the intervention. However, there were limitations to the study, including no examination of lung CT scans and blood tests to determine the severity of the disease. Another limitation of the study was the short follow-up time after 90 min in the PP; hence, the follow-up time should be increased in future studies. Future studies are suggested to assess lung involvement and consider its effects on the statistical analysis. A more considerable number of experimental groups are recommended in future studies to compare the efficacy of multiple lengths of time in the PP. Moreover, a higher sample size should be considered for a more detailed examination of outcomes with relatively lower incidence, such as intubation and survival. Although, no significant adverse events related to PP were observed, five patients did not tolerate long durations of the PP.

Conclusion

The PP can be considered an inexpensive, accessible, and uncomplicated procedure in awake non-intubated patients with COVID-19 to improve short-term clinical outcomes such as respiratory and hemodynamic status.

Registration

This trial was registered at the Iranian Registry of Clinical Trials (IRCT20160126026217N4) on 2020-06-08.

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CRediT authorship contribution statement

Made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;SY, FE, FM, TC, ME, Involved in drafting the manuscript or revising it critically for important intellectual content;SY, FE, FM, TC, Given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content;SY, FE, FM, TC, ME, Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SY, FE, FM

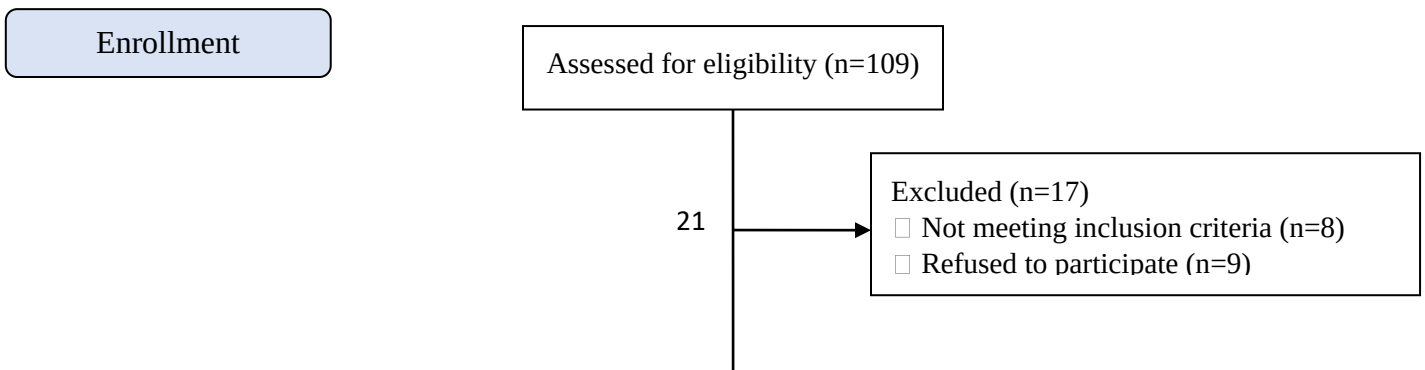
Conflict of Interest

The authors confirm that there is no conflict of interests.

Ethical Consideration

This clinical trial study was conducted in line with the current guidelines of the Declaration of Helsinki. The Ethics Committee approved the trial protocol of the Lorestan University of Medical Sciences (IR.LUMS.REC.1399.059) on 2020-05-06. In addition, the trial protocol was approved by the Iranian Registry of Clinical Trials (IRCT20160126026217N4) on 2020-06-08.

Written informed consent was obtained from all the participants. The subjects were allowed to either participate in the trial or quit at any phase. They were assured of confidentiality in conducting the trial and keeping the data secret. Permissions were obtained from the Shohaday Ashayer hospital authorities.



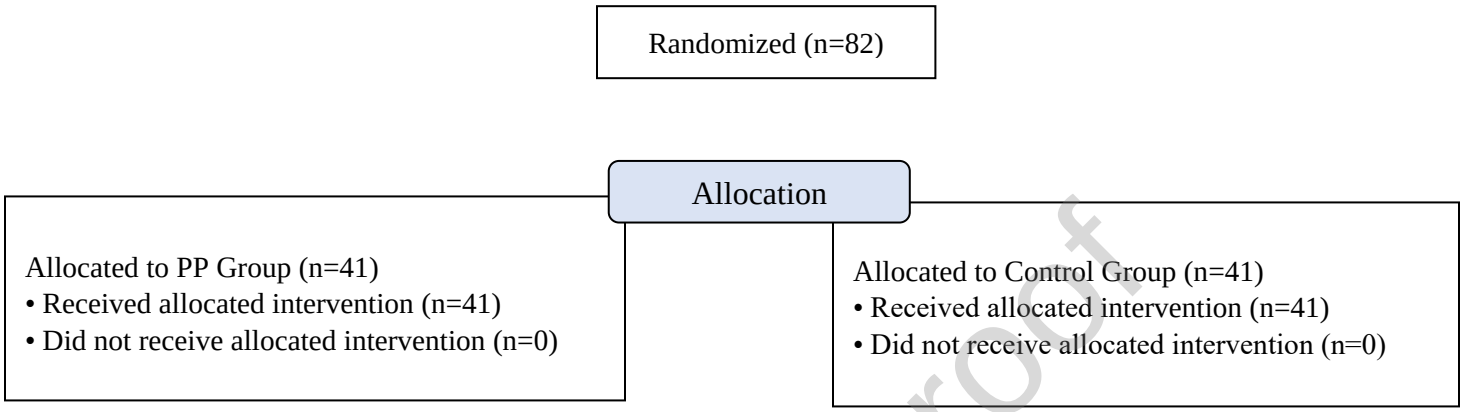


Figure 1. Study flow diagram

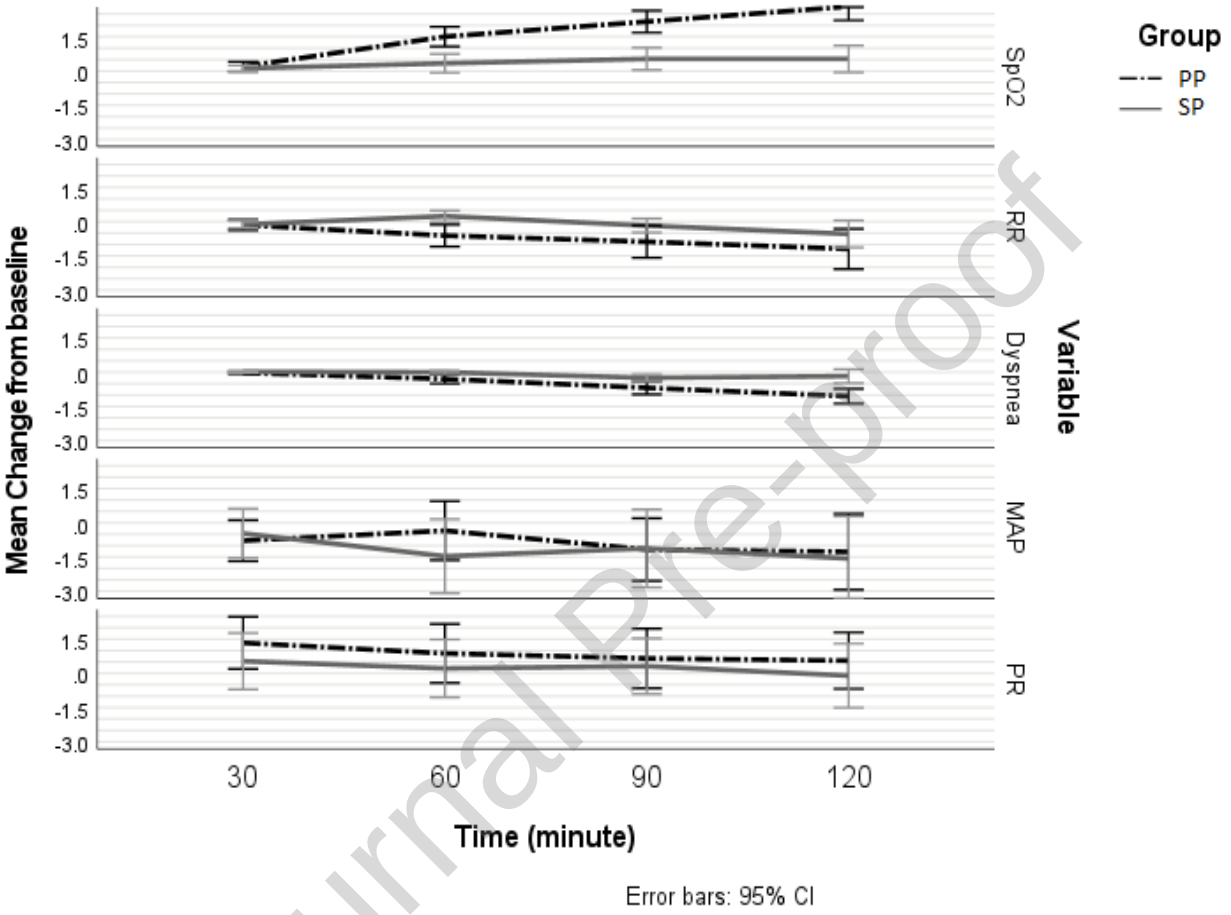


Figure 2. Mean changes of respiratory and hemodynamics measures from baseline in the PP and SP groups

Table1. Baseline and demographic characteristics 19 between the PP and SP groups

Variables	PP Group (N=41)	SP Group (N=41)	P-value

Age N (%)			
<50	16(39.00)	16(39.00)	> **0.999**[a]
≥50	25(61.00)	25(61.00)	
Gender N (%)			
Male	18(43.90)	18(43.90)	> **0.999**[a]
Female	23(56.10)	23(56.10)	
Marital Status N (%)			
Single	5(12.20)	2(4.90)	**0.578**[b]
Married	32(78.00)	35(85.40)	
Widow/ divorced	4(9.80)	4(9.80)	
Job Status N (%)			
Housewife	17(41.50)	16(39)	
Unemployed	4(9.80)	0(0.00)	**0.332**[b]
Worker/Farmer/Rancher	4(9.80)	4(9.80)	
Employed/Military/Teacher	4(9.80)	9(22)	
Health Worker	2(4.90)	2(4.90)	
Other	10(24.40)	10(24.40)	
Education N (%)			**0.230**[b]
Illiterate	14(34.10)	11(26.80)	
Primary/High school	9(22.00)	10(24.40)	
Diploma	12(29.30)	7(17.10)	
Higher education	6(14.60)	13(31.70)	
Cancer N (%)			
Yes	2(4.90)	5(12.20)	**0.423**[a]
No	39(95.10)	36(87.80)	
Diabetes N (%)			
Yes	10(24.40)	9(22.00)	> **0.999**[a]
No	31(75.60)	32(78.00)	
Hypertension N (%)			
Yes	21(51.20)	7(17.100)	**0.002**[a]
No	20(48.80)	34(82.90)	
Chronic Liver Disease N (%)			
Yes	1(2.40)	1(2.4)	> **0.999**[a]
No	40(97.60)	40(97.60)	
Chronic Renal Failure N (%)			
Yes	3(7.30)	2(4.90)	> **0.999**[a]
No	38(92.70)	39(95.10)	
Other Diseases N (%)			
Yes	9(22.00)	3(7.30)	**0.116**[a]
No	32(78.00)	38(92.70)	
FIO_2 Mean(SD)	23.49 (5.44)	23.80(5.39)	**0.663**[c]
BMI Mean(SD)	24.98(2.45)	24.44(2.50)	**0.446**[c]
Time gap between onset of symptoms and intervention Mean(SD)	1.61(0.92)	1.49(0.75)	**0.667**[c]

[a] Fishers exact test
[b] Chi-Square test with Monte Carlo simulation
[c] Mann-Whitney test

Table2. Symptoms of COVID-19 between the PP and SP groups

Variables	PP Group (N=41)	SP Group (N=41)	P-value [a]
Fever N (%)	29(70.70)	25(61.00)	**0.485**
Yes	12(29.30)	16(39.00)	
No			
Cough N (%)	26(63.40)	33(80.50)	**0.139**
Yes	15(36.60)	8(19.50)	

No			
Dyspnea N (%)	30(73.20)	31(75.60)	> **0.999**
Yes	11(26.80)	10(24.40)	
No			
Runny Nose N (%)	4(9.80)	4(9.80)	> **0.999**
Yes	37(90.20)	37(90.20)	
No			
Fatigue N (%)	14(34.10)	10(24.40)	**0.467**
Yes	27(65.90)	31(75.60)	
No			
Confusion N (%)	23(56.10)	22(53.70)	> **0.999**
Yes	18(43.90)	19(46.30)	
No			
General Weakness N (%)	14(34.10)	19(46.30)	**0.368**
Yes	27(65.90)	22(53.70)	
No			
Decreased of Sense Smell or Taste N (%)	10(24.40)	11(26.80)	> **0.999**
Yes	31(75.60)	30(73.20)	
No			
Redness of Eyes N (%)	3(7.30)	2(4.90)	> **0.999**
Yes	38(92.70)	39(95.10)	
No			
Other symptoms N (%)	15(36.60)	8(19.50)	**0.139**
Yes	26(63.40)	33(80.50)	
No			

[a] Fishers exact test

Table 3. Intubation and survival rates between the PP and SP groups

Variable	PP Group N (%)	SP Group N (%)	Adjusted Odds Ratio	P-Value	95% CI for Adjusted Odds Ratio
Intubation	3(7.30)	8(19.50)	0.392	0.324 [a]	0.061-2.520
survival	41(100.00)	37(92.70)	1.246	0.091[b]	0.965-1.608

[a] Logistic regression

[b] Firth logistic regression

Table 4. Respiratory and hemodynamics measures between the PP and SP groups in the study's times

Variable	Time				
	Before	**30 min**	**60min**	**90min**	**120 min**
SPO_2					
PP	84.95(4.18)	85.15 (4.41)	86.46(4.76)	87.12(4.72)	87.78(4.95)
SP	84.41(3.54)	84.54(3.70)	84.76(3.60)	84.95(3.84)	84.95(4.15)
RR					
PP	19.32(3.87)	19.17(3.73)	18.71(3.05)	18.44(2.80)	18.12(2.58)
SP	19.29(3.66)	19.17(3.76)	19.54(3.78)	19.12(3.38)	18.76(3.85)
Dyspnea					
PP	6.05(3.09)	6.02(3.11)	5.76(3.08)	5.37(3.02)	5.00(2.86)
SP	4.54(3.44)	4.56(3.46)	4.54(3.45)	4.29(3.32)	4.37(3.20)
MAP					
PP	93.85(13.77)	93.07(14.27)	93.51(13.70)	92.68(14.04)	92.59(13.60)
SP	91.56(10.00)	91.10(10.46)	90.10(10.71)	90.44(10.62)	90.00(10.64)
PR					
PP	81.37(9.85)	82.71(9.21)	82.24(9.28)	82.02(9.20)	81.93(9.09)
SP	79.27(12.17)	79.80(12.38)	79.49(12.39)	79.59(12.13)	79.17(11.89)

Table 5. Respiratory and hemodynamics measures difference between the PP and SP groups

Variable	Time				P-value				
	30 min	**60min**	**90min**	**120 min**	**Time*Group interaction**	**Time main effect**	**Group main effect**	**F**	**D**
SPO_2									
PP	0.19(0.67)	1.51(1.36)	2.17(1.53)	2.82(1.90)	0.001	0.977	0.001	22.600	1
SP	0.12(0.39)	0.34(1.29)	0.53(1.55)	0.53(1.85)					
RR									
PP	-0.14(0.72)	-0.60(1.53)	-0.87(2.23)	-1.19(2.80)	0.004	0.126	0.025	8.712	1
SP	-0.12(0.50)	0.24(0.76)	-0.17(0.97)	-0.53(1.87)					
Dyspnea									
PP	-0.02(0.15)	-0.29(0.64)	-0.68(0.90)	-1.04(1.02)	0.014	0.680	0.005	6.274	1
SP	0.02(0.15)	0.00(0.22)	-0.24(0.48)	-0.17(0.97)					
MAP									
PP	-0.78(2.85)	-0.34(4.09)	-1.17(4.34)	-1.26(5.27)	0.027	0.673	0.597	5.081	1
SP	-0.46(3.42)	-1.46(5.14)	-1.12(5.41)	-1.56(5.82)					
PR									
PP	1.34(3.62)	0.87(4.08)	0.65(4.13)	0.56(3.91)	0.890	0.647	0.458	0.013	1
SP	0.53(3.94)	0.21(4.02)	0.31(3.86)	-0.09(4.44)					