Efficacy of awake prone position to avoid mechanical ventilation for patients with COVID-19

Eficácia do posição prona acordado para evitar ventilação mecânica de pacientes com COVID-19

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Abstract

Background: During the COVID-19 pandemic the application of awake prone position (PP) in subjects has been describing such as a new procedures in combating the acute hypoxemic. **Aim:** Evaluate the efficacy of the awake PP in patients with hypoxemic respiratory failure by COVID-19 to avoid mechanical ventilation (MV). **Methods:** a clinical study. The subjects who were showing signs of hypoxemic respiratory failure were divided into two groups: the intervention group receiving treatment with oxygen therapy plus awake PP, and the control group only oxygen therapy. The primary outcome was the success to avoid the MV, and secondary outcomes were complications, length of stay and mortality rate in the ICU. **Results:** Thirty-two subjects underwent the PP in the Intervention group, and 35 maintained the conventional treatment with the oxygen therapy in the control group. The mean of the clinical variables analyzed did not show difference when comparing the groups. The rate of need of invasive mechanical ventilation (60% vs. 41%, P=0.18) and death rate (29% vs. 13%, P=0.29) was higher in the control group; however statistical diferences not were found. In the Kaplan-Meyer curves, the awake PP presented a tendency of reduction in mortality rate (15%), P=0.29 and presented a tendency of increase (30%) successful to avoid MV, P=0.16. **Conclusion:** The present study despite demonstrating that a simple procedure seems to contribute with a success rate to avoid the mechanical ventilator, however we cannot affirm this result. Lastly, we suggest that news RCT studies be carried out to confirm this find.

Keywords: Mechanical ventilation; Critical care; Respiratory Insufficiency; Prone Position; COVID-19.

Resumo

Introdução: Durante a pandemia de COVID-19 a aplicação do posição prona (PP) em indivíduos acordados vem sendo descrita como um novo procedimento no combate à hipoxemia aguda. **Objetivo:** Avaliar a eficácia da PP em pacientes acordados com insuficiência respiratória hipoxêmica pela COVID-19 para evitar ventilação mecânica (VM). **Métodos:** Estudo clínico, no qual indivíduos que apresentavam sinais de insuficiência respiratória hipoxêmica foram divididos em dois grupos: o grupo intervenção recebendo tratamento com oxigenoterapia mais PP acordado, e o grupo controle apenas com oxigenoterapia. O desfecho primário foi o sucesso em evitar a VM e os desfechos secundários foram: complicações, tempo de internação e mortalidade na UTI. **Resultados:** Trinta e dois sujeitos realizaram o PP no grupo Intervenção e 35 mantiveram o tratamento convencional com oxigenoterapia no grupo controle. A média das variáveis clínicas analisadas não apresentou diferença estatística na comparação dos grupos. A taxa de necessidade de ventilação mecânica invasiva (60% vs.

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41%, P=0,18) e taxa de mortalidade (29% vs. 13%, P=0,29) foram maiores no grupo controle, porém sem diferença estatística. Nas curvas de Kaplan-Meyer, o PP acordado apresentou tendência de redução da mortalidade (15%), P=0,29 e apresentou tendência de aumento (30%) no sucesso para evitar VM, P=0,16, porém ambos, sem diferença estatística significativa. **Conclusão:** O presente estudo apesar de demonstrar que um procedimento simples parece contribuir com uma taxa de sucesso para evitar o uso do ventilador mecânico, contudo não podemos afirmar este resultado. Assim, sugerimos que novos estudos RCT sejam realizados para confirmar esta informação.

Palavras-chave: Ventilação mecânica; Cuidados intensivos; Insuficiência respiratória; Posição prona; COVID-19.

INTRODUCTION

Acute respiratory failure (ARF) is one of the most common causes in the intensive care unit (ICU). Subjects with the acute hypoxemic syndrome are usually treated with intubation and invasive mechanical ventilation (MV). However, their clinical course can often be complicated by the ventilatory assistance itself that induces pulmonary and respiratory muscle injury, in addition to increasing the risk of new cases of pneumonia[1-3].

Thus, it is commonly suggested to avoid intubation and, whenever possible, using non-invasive ventilation (NIV)[3]. However, previous studies and information from experience in the treatment of COVID-19, which point to unsatisfactory results with a high failure rate and a higher risk of spreading the virus in the ICU environment. Nowadays, it is still understood that non-invasive resources, such as CPAP and Bi-Level, are under clinical investigation to be recommended as a ventilatory strategy in treating subjects with COVID-19[1,4,5]. Therefore, the application of PP in adults awake and not intubated can be a fast, simple, and low-cost strategy for this setting.

Previous studies report that subjects diagnosed with COVID-19 generally experience a drop in oxygen saturation (SpO_2 <92%) and tachypnea (respiratory rate> 20 bpm) but do not present significant respiratory difficulties initially, and they often appear to be clinically well. All of them present radiographic findings on computed tomography (CT) with a ground-glass pattern in the pulmonary peripheries or diffusely. However, about 8 to 10% evolve rapidly with hypoxemia refractory to supplemental oxygen (the most severe form of the disease), in which orotracheal intubation is necessary[6]. In this context, conducts, such as the awake prone positioning, can delay the worsening of hypoxemia or avoid orotracheal intubation and mechanical ventilation, and seems to be an option now[7].

Prone positioning (PP) has been used for more than 30 years in acute respiratory distress syndrome (ARDS), contributing to reducing MV duration and mortality rate[8]. On the other hand, there are few studies of the application of PP in adults who were awake and not intubated before the pandemic[3,9-11]. However, during the COVID-19 pandemic, they are limited to demonstrating the effectiveness of the technique[7,12-14]. In this study, we aimed to evaluate the application of awake prone positioning in subjects not intubated with acute hypoxemic, describing the efficacy of avoiding mechanical ventilation in the ICU.

METHODS

The study design was a clinical trial involving four intensive care units with 10 beds each from two hospital centers. The Ethics Committee approved it under number CAAE: 32166620.1.0000.5284 of Universidade Estácio de Sá, nº 4.082.841. Written informed consent was waived, as this is a designated hospital for the treatment of COVID-19 patients.

Initially, all subjects were breathing spontaneously in ICU, showing signs of acute hypoxemic, and they were treated with an oxygen mask with a reservatory bag with 10 L/min to avoid orotracheal intubation and mechanical ventilation, as recommended by the institutional protocol. All subjects admitted to the ICU from March 13th to May 8th, 2020, were screened for the following inclusion criteria: Age greater than or equal to 18 years old; Arterial partial pressure of oxygen (PaO_2) less than 75 mmHg; Drop-in oxygen saturation below 94% when using a nasal catheter or oxygen mask with a reservatory bag with 10 L/min; Confirmation by PCR-TR method or IgM serology for COVID-19 Coronavirus. The exclusion criteria were follow up for terminal condition, pre-existing chronic diseases or immunodeficiency status; Pre-existing hypoxic lung disease, and severe heart failure; advanced age with low life expectancy.

Aiming to reach the hypothesis of the present study that the awake PP can avoid mechanical ventilation of patients with COVID-19, we analyzed the clinical variables: demographic data (gender, age), ICU clinical admission data (arterial blood gases: pH, PaO_2, $PaCO_2$, HCO_3, and SaO_2, CT pattern, D-dimer, Ferritin, C-reactive protein), time of symptom onset, comorbidities, the treatment used in the ICU, and severity on the APACHE II score in the first 24 hours of ICU stay.

The secondary outcomes to the subjects that failed in the initial procedure, and evaluated to invasive mechanical ventilation, also they had the data analyze during of the study: the presence of clinical complications (acute renal failure, shock, and acute respiratory distress syndrome), need for orotracheal intubation and mechanical ventilation (MV), need for pronation in MV, failure in extubation, rate of tracheostomy, length of stay in the ICU, the death rate in the ICU, and discharge rate from the ICU.

Procedure

The prone positioning (PP) only started at the end of March. The groups were selected in agreement with the judgment of the multidisciplinary ICU team; thus, in this period, the awake PP did not make any recommendation to clinical practice for all patients with hypoxemia refractory to use oxygen therapy.

In addition, the ICU's physical therapists provided instructions to patients on how to perform PP properly. They were daily oriented that each session must have had more than 3 hours/day. For patients who did not tolerate awake PP sessions, alternated lateral position only was suggested instead. The control group were the subjects who indeed refused the procedure or were before the initial recommendation period.

This study does not have critically ill patients that used HFNC or NIV support to avoid orotracheal intubation. To evaluate the safety of awake PP, peripheral oxygen saturation, respiratory rate, and hemodynamic parameters (HR and Blood Pressure) were also analyzed before pronation, during, and after the procedure, and if whatever anything was unstable, the procedure was canceled.

Statistical analysis

Continuous variables were expressed as mean and standard deviation in the case of normal or median distribution and internal quartiles; categorical ones were expressed frequently. The T-test for independent samples or Mann-Whitney was to assess differences between groups, as appropriate. Values of $P<0.05$ were considered significant. Kaplan-Meier curve was used to analyze survival probability and procedures successful in avoiding mechanical ventilation with Log-rank Test. The statistical analysis performed used the MedCalc statistical software version 19.2.6.

RESULTS

From March 13th to May 8th, 2020, 658 individuals initially suspected of being infected with the new Coronavirus (COVID-19) were selected in two centers. Three hundred and thirty-three individuals confirmed COVID-19 by PCR-TR or IgM serology. Eighty-eight of them were referred to the intensive care unit due to persistent hypoxemia after receiving oxygen therapy. Thirty-five subjects (intervention group) were instructed and helped to perform the awake PP, in addition to supplemental oxygen with a 10 L/min reservatory bag, and the fifty-six individuals in the cohort followed only with supplemental oxygen with a 10 L/min bag reservatory (control group). Figure 1 shows the flowchart of the participants and the reasons for exclusions throughout the study.

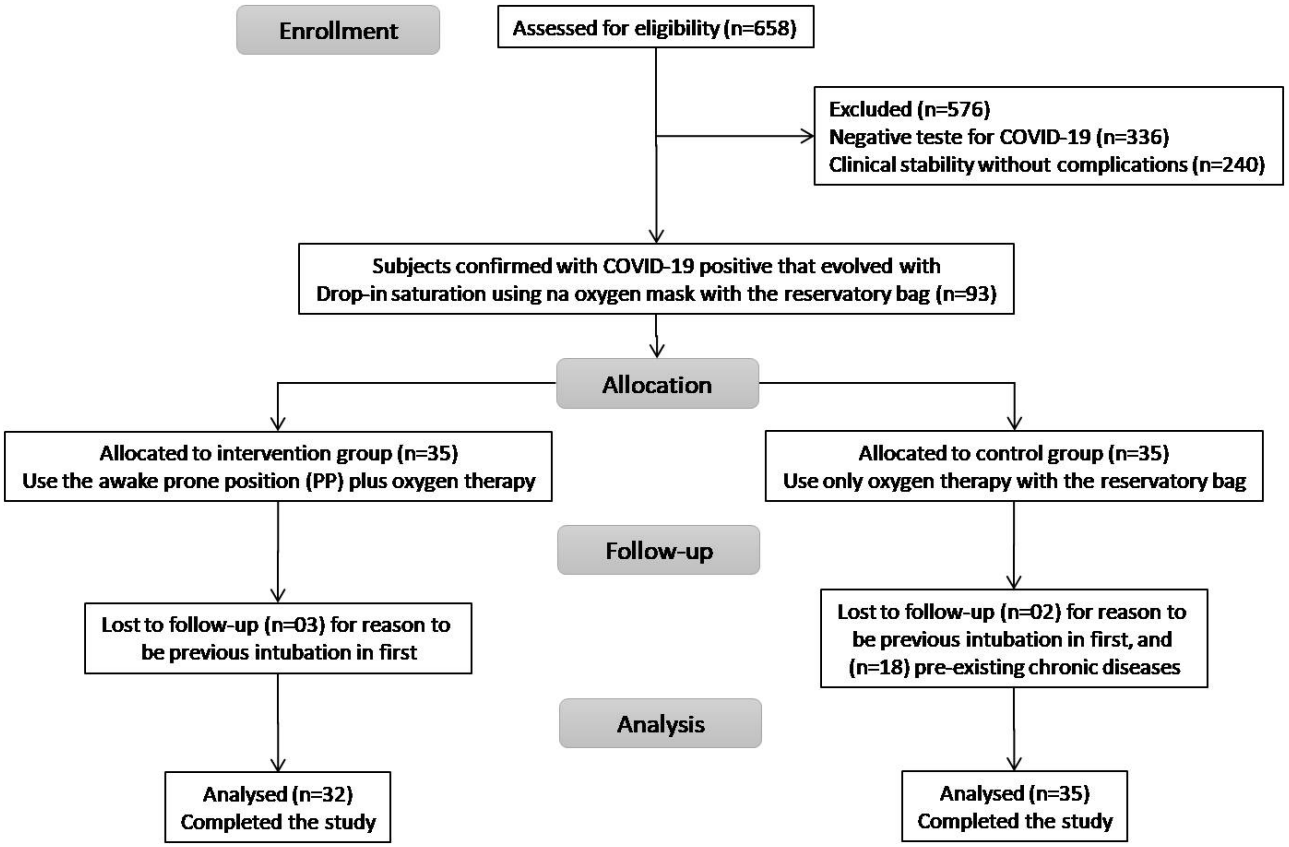

Figure 1. Flowchart of the study participants. Six hundred and fifty-eight subjects were assessed for eligibility and, after applying the exclusion criteria, 93 were selected. The final analysis was performed with thirty-two and thirty-five subjects in the intervention and control group, respectively.

In the intervention group (N=32), 11 subjects who remained on awake PP for about 30 to 120 minutes, even with improved oxygenation (SpO_2>90%) during the intervention, however, did not achieve clinical stability to avoid orotracheal intubation, two subjects did not respond to the procedure (SpO_2<90%) and were also intubated in the same day. The other 19 subjects, who managed to tolerate PP between 3 to 6 hours a day, by three days consecutively, progressed satisfactorily, in which the procedure was maintained until discharge from the unit.

Among the 35 subjects in the control group, twenty-one subjects evolved with worsening hypoxemia were intubated and coupled ventilation, and the other 14 subjects maintained the condition until discharge from the unit.

The general characteristics of all subjects who completed the study and the differences between the groups are shown below in Table 1. Regarding the co-morbidities observed, the number of subjects without comorbidities was the same between the groups. In addition to those identified as the most prevalent in the pandemic scenario: obesity, arterial hypertension, diabetes, also to be shown in Table 1.

The mean of the clinical variables analyzed: D-dimer, Ferritin, C-reactive protein, ground glass percentage on the entry CT, pH, PaO_2, $PaCO_2$, HCO_3, and SaO_2 did not show a statistical difference when compared between the groups, Table 1.

Secondary outcomes were analyzed by the following variables in Table 2: the presence of clinical complications (acute renal failure, shock, and acute respiratory distress syndrome), need for orotracheal intubation and mechanical ventilation (MV), need for pronation in MV, failure in extubation, rate of tracheostomy, length of stay in the ICU, the death rate in the ICU, and discharge rate from the ICU. However, the statistical difference has not been found about all variables. Besides, the control group had a higher rate of orotracheal intubation requiring invasive mechanical ventilation (60% vs 41%, P=0.18), the death rate (29% vs 13%, P=0.29) and the discharge rate (71% vs 88%,

Table 1. General characteristics of the studied subjects (N = 67).

Variables	Control (35)	Intervention (32)	P Values
Demographic data			
Gender M/F, n (%)	23 (66) / 12 (34)	21 (66) / 11 (34)	0.99
Age, years	59 ± 16	52 ± 13	0.06
Symptom onset, days	7 ± 3	8 ± 2	0.12
APACHE II score (%)	24.6 ± 15.2	24.8 ± 14.1	0.71
ICU time, days	12 ± 9	10 ± 7	0.36
Clinical variables			
D-dimer (ug/mL)	1.80 ± 2.29	1.47 ± 2.47	0.57
Ferritin (ng/mL)	995.9 ± 895.2	1243.6 ± 976.9	0.28
C-reactive protein (mg/dL)	12.67 ± 10.17	13.41 ± 10.35	0.76
CT pattern (%)	35.17 ± 18.44	37.83 ± 18.69	0.56
pH	7.40 ± 0.06	7.41 ± 0.04	0.33
PaO_2 (mmHg)	67.98 ± 13.71	65.29 ± 10.77	0.27
$PaCO_2$ (mmHg)	40.21 ± 7.99	37.24 ± 4.60	0.07
HCO_3 (mmol/L)	23.50 ± 5.30	23.12 ± 3.66	0.48
SaO_2 (%)	91.48 ± 6.29	91.46 ± 4.35	1.00
Comorbidities			
No comorbidities	10	10	0.98
Obesity (BMI>30 kg/m^2)	11	14	0.43
Systemic arterial hypertension	13	12	0.82
Type II diabetes	6	8	0.62
Others diseases	5	3	0.81

Mean ± standard deviation; M: male; F: female; APACHE: Acute Physiology and Chronic Health Evaluation; ICU: Intensive Care Unit; CRP: C-reactive protein; pH: hydrogen potential; SaO_2: Arterial oxygen saturation; BMI: body mass index.

Table 2. Secondary outcomes and complications in the ICU during the study.

Variables	Control (35)	Intervention (32)	P Values*
Outcomes in the ICU			
Use of the ventilator, n (%)	21 (60)	13 (41)	0.18
Death in the ICU, n (%)	10 (29)	4 (13)	0.19
Discharges in the ICU, n (%)	25 (71)	28 (88)	0.19
Complications and treatments during the study			
Acute renal failure, n (%)	19 (54)	15 (47)	0.72
Shock, n (%)	18 (51)	13 (41)	0.52
ARDS, n (%)	10 (29)	7 (22)	0.73
HC+AZ, n (%)	34 (97)	32 (100)	0.96
Corticosteroid, n (%)	25 (71)	24 (75)	0.96
Anticoagulant, n (%)	26 (74)	28 (88)	0.29

* Q-square test, Control vs Intervention; MV: mechanical ventilation; ICU: intensive care unit; ARDS: Acute respiratory distress syndrome; HC + AZ: Hydroxochloroquine with Azithromycin.

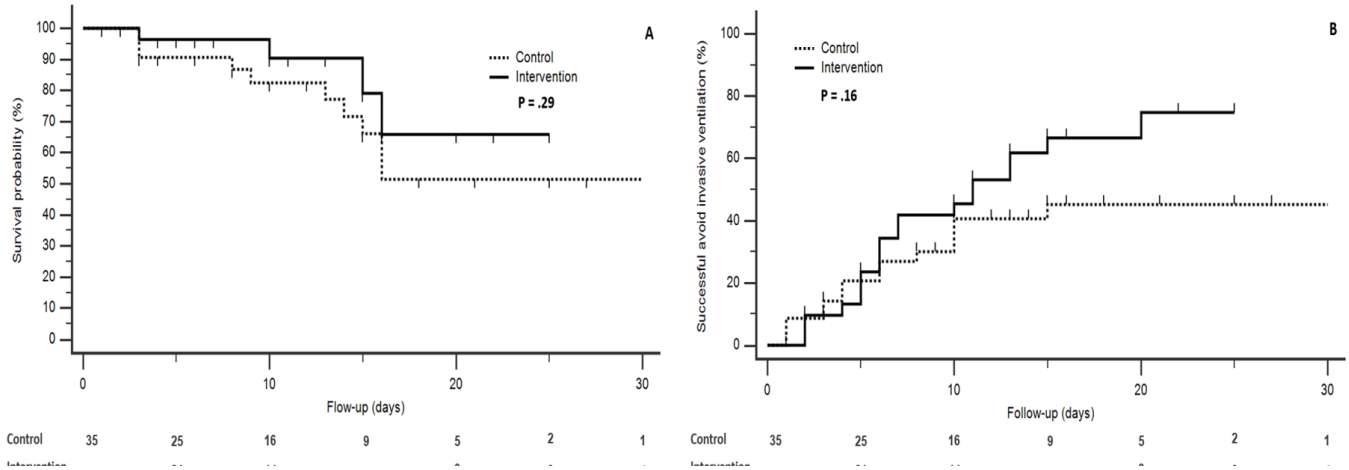

Figure 2. Kaplan-Meier curves showing ICU survival (panel A) and the probability of avoiding mechanical ventilation (panel B).

P=0.16), although the data is favorable to the intervention group, it found no statistical difference confirmed by the Q-square test.

We also compared the patterns treatments with Hydroxychloroquine and Azithromycin, the use of venous corticoids, and anticoagulants between the groups. None variables showed differences between groups (Table 2).

ICU survival and effectiveness in preventing mechanical ventilation in the intervention group and the control group are described in Figure 2. There was a tendency to reduce mortality rate (15%) in favor of the intervention group (66% vs 51%, P=0.29), panel A. The success rate to avoid mechanical ventilation also presented a tendency to increase (30%) in the intervention group (75% vs 45%, P=0.16), panel B. However, no statistical difference was found in both analyses.

DISCUSSION

In Brazil, at the beginning of March 2020, the patients diagnosed with Covid-19 hospitalized at ICU followed the guidance to proceed with orotracheal intubation without previous using non-invasive resources. However, in the end of the month the use of prone position awake subjects started your recommendation during the 2020 COVID-19 pandemic as an alternative to improve oxygenation and prevent orotracheal intubation with effectiveness around 50%. It also proved to be a simple, safe procedure, free of cost, and that mainly does not generate aerosols[7,12-14]. The present study despite to show higher effectiveness in preventing orotracheal intubation around 59%, we could not affirm with a retrospective study design such condition.

Since the beginning of this pandemic, risk factors are being tracked, and the prevalence of the most severe form of the disease appears to be associated with obesity (BMI>

30 kg/m^2), high blood pressure, type 2 diabetes, and the prevalence of the average age between 50-60 years[1,4,5]. The main characteristic observed in the present study for the group that did not receive the prone position intervention was advanced age (64 years), the early symptoms (6 days), and the greater presence of chronic diseases compared to the intervention group. These factors are probably associated with the lack of indication of the prone positioning due to the greater limitation and difficulty in actively performing the procedure and tolerating remaining in the position for several hours.

Other studies point to the increased possibility of inflammatory complications, thromboembolic events, and reduced oxygen affinity with hemoglobin in the most severe forms of the disease[1,4,5,15]. Thus, markers such as CRP, D-dimer, and Ferritin are part of this patient's laboratory routine, in addition to arterial blood gases. However, our findings did not detect statistical differences in these markers between groups, and these variables also did not show any association with mortality in logistic regression.

Computed tomography (CT) is being widely used to characterize the presence and initial severity of the disease, in which patterns of peripheral or diffuse lesions are being described, as well as the percentage of involvement of the lung parenchyma[6]. The study by Dong et al., 2020, in a sample of only 25 subjects, demonstrated through CT that the typical ground-glass and consolidation pattern reduced from 42% to 29% after the prone position procedure on average for 3.6 hours[13]. Our sample found no statistical differences in the percentage of CT lesions between groups, and there was also no association with mortality.

Among the articles already published, the gasometric pattern was the most relevant question regarding the answer before, during, and after the procedure. All the evidence shows an improvement in oxygenation minutes after the installation of the awake prone position; however, after resupination, there is no significant support for this improvement[7,12-14]. Elharrar et al., 2020, pointed out in a sample of 24 subjects that 63% tolerated the procedure for more than 3 hours, but only 25% showed significant improvement during and after the maneuver[14]. Only two subjects had a paradoxical response in our sample, and 11 others did not support clinical improvement. Of these 13 subjects who failed the intervention, the average age was 53 years old, APACHE II was 30%, seven were male, the mean of 7 days symptoms onset, five had more than 50% of the peripheral pulmonary injury by CT.

Until now, the survival of subjects who used the prone position in awake subjects has not been indicated[7,12-14]. In our study, it was possible to observe a 15% reduction in mortality in subjects where this procedure was performed compared to those who did not use the awake prone position. However, there was no found statistical difference. Thus, it is necessary a randomized controlled trial (RCT) study to confirm such result.

It is worth mentioning that the logistic regression pointed to two characteristics that significantly influenced the outcome with mortality: date of onset of symptoms, and days of ICU. None of the recent publications on the subject has an analysis of survival and risk factors[7,12-14]. It is worth noting that the present study found the same reports, as in other publications on COVID-19, which an earlier period of manifestation of symptoms prolongs hospitalization and favor a higher rate of risks and secondary complications during the recovery period, and these are undoubtedly the criteria that deserve to be highlighted in this scenario.

Surprisingly, APACHE II and complications such as acute renal failure, sepsis, and ARDS were not associated to better explain mortality, which may demonstrate their inability to assess prognosis in these subjects with this specific disease. Perhaps the development of specific prognostic indexes, such as the recent severity index for COVID-19, is essential to identify the most serious cases[16].

The present study had limitations due to the non-competing clinical study and the small sample of subjects under the intended intervention. However, we leave relevant and optimistic information for the intensive care teams, who can be easily trained to change the course of this pandemic. We hope that a new study randomized clinical trial can corroborate our findings and achieve answers about the length of stay in PP and the best association with other techniques, such as the use of CPAP, Bi-Level, and high flow nasal cannula (HFNC) in the search for better results.

CONCLUSION

The present study despite demonstrating that a simple procedure seems to contribute with a success rate to avoid the use of invasive mechanical ventilator, however we cannot affirm this result. Lastly, we suggest that news randomized clinical trials (RCT) studies be carried out to confirm this finds.

FUNDING

Nothing to declare.

CONFLICT OF INTEREST

Nothing to declare.

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