Awake prone positioning and oxygen therapy in patients with COVID-19 (APRONOX)

Prospective, observational, multicenter study.

Identifiers: **NCT04407468** Unique Protocol ID: **1178/SESEQ-HSGJR/08-05- 20/UTI**
Date: 10/05/2020

APRONOX trial is a retrospective, observational, multicenter study that consists of the main objective, which is to observe the impact of the awake prone, and to see how many patients required intubation, with the additional objectives described in this research

By the APRONOX group

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Theoretical framework

The prone position strategy for patients with acute respiratory distress syndrome (ARDS) is simple and cost-effective since the first description on its use in patients with acute respiratory failure to improve hypoxemia. Different studies have looked for its safety and efficacy in various clinical scenarios, demonstrating that its early use in combination with non-invasive mechanical ventilation (NIV) or high-flow oxygen therapy can reduce intubation rate and mortality in ARDS. In the COVID-19 pandemic, high-value medicine and resource optimization are critical.

Scaravilli et al (1) carried out an analysis of 15 patients admitted presenting acute hypoxemic respiratory failure with spontaneous breathing undergoing a prone position, finding that the strategy had no deleterious effects on PaCO2, pH, respiratory rate, or hemodynamics. For their part, Valter et al (2) reported four cases of patients with respiratory failure where a prone position strategy was used, showing an improvement in oxygenation and good tolerance while awake, avoiding the need for intubation in these patients without significant complications (2).

Ding et al (3) recently published a prospective cohort study of patients with moderate to severe grade ARDS using the prone position combined with non-invasive mechanical ventilation (NIV) or high flow nasal cannula (HFNC), demonstrating the safety and efficiency of the maneuver, finding an improvement in oxygenation and a decrease in the need for intubation. Pérez et al (4) reported a case series of patients with severe non-infectious ARDS where the strategy of early prone and HFNC or NIV, for 2 to 3 hours, improved oxygenation and intubation was avoided in 5 of the 6 cases studied.

Sun et al (5), perform an early intervention strategy in patients with coronavirus-2019 disease (COVID-19) and respiratory failure, supported by NIV or HFNC using the awake prone positioning, reporting a low intubation rate and mortality compared to other regions of China affected by the SARS-CoV-2. Caputo et al (6) evaluated an early awake prone positioning in patients with COVID-19 in an emergency service; describing 50 cases with an oxygen saturation on admission <90%, after the early awake prone strategy for 30-120 minutes, oxygenation improved and intubation was avoided in 64% of patients. Slessarev et al (7), analyzed a patient with COVID-19-associated pneumonia, who was treated with high-flow nasal cannula and awake prone positioning, allowing him to interact with family members and participate in active physiotherapy, the primary result showed an improvement in oxygenation.

There are currently studies in progress to evaluate the benefit of the prone position in patients with COVID-19. The APPROVE-CARE-2020 study is an open, randomized, multicenter controlled study of acute hypoxemic respiratory failure or COVID-19-induced respiratory distress syndrome seeking to determine whether the prone position awake reduces the need for mechanical ventilation (8). The OPTIPRONE clinical trial is recruiting patients with the objective of monitoring the PaO2 / FiO2 ratio with a strategy based on prone position and high-flow oxygen therapy over a period of 2 hours, the current status is awaiting for reporting results (9).

The awake prone position can be combined with a variety of non-invasive oxygenation strategies. The evidence documented so far has shown that it is a safe and effective strategy, and it has been observed that performing it early has been associated with benefit in survival and reduction of the intubation rate in patients with moderate and severe respiratory failure. Another advantage of this technique is that the awake prone position can be performed even in atmospheric air in emergency situations, or in contexts of limited resources. This strategy aims to be a safe, dynamic, practical and free strategy at any level of health care (3). For the diagnosis of COVID-19, reverse transcriptase polymerase chain reaction (RT-PCR) is considered the standard test. However, there are limitations such as the shortage of kits, limitations in sampling and transportation that can give us cases of false negatives in the early stages of the disease. For this reason, imaging studies such as chest tomography (CT) can be a valuable diagnostic method in patients with suspected covid-19 disease, a sensitivity of up to 97% has been observed (10-12).

Shang Wan (11) performed a meta-analysis where 1115 patients were included, where chest tomography images were observed, in which the following characteristics and image patterns were observed:

1. Ground glass opacities and pleural thickening (69%)

2. Peripheral distribution (70%)

3. Consolidation (47%)

4. Air bronchogram (46%)

5. Involvement of the right lower lobe (70%)

6. Involvement of more than 3 lobes (70%)

7. Crazy paving pattern (15%)

In particular, a full understanding of the patterns on tomography as well as the clinical features may be beneficial for an effective diagnosis and treatment in patients with COVID-19 infection (11).

Problem statement

The first case of COVID-19 in Mexico was reported on February 27, 2020, currently our country has 27.2 cases per 100,000 habitants. According to the Ministry of Health, there are currently 36,327 confirmed cases of COVID-19 in the country with a total of 3,573 deaths. The WHO reports in the month of May, Mexico presented a case fatality rate (CFR) of 12%, being one of the highest reported during the SARS-COV 2 pandemic. COVID-19 has a wide range of clinical manifestations, ranging from asymptomatic to severe ARDS that requires invasive mechanical ventilation. According to Chinese reports, not all severe cases of COVID-19 required admission to the ICU, in Italy 12% of positive patients required admission to the critical care unit. In Mexico it has been observed that 56% of the patients who required intubation for severe management of the disease die, on the other hand, in China, 49% of the patients with a severe picture of COVID-19 died. In a multicenter study during the early outbreak in Wuhan 97% of the patients who required invasive mechanical ventilation died, although mortality could be affected by medical practice in each region. It seems important to highlight that several patients who require intubation are in a high risk of dying. There are some comorbidities related to an increased mortality such as hypertension, diabetes, vascular diseases, COPD and cancer, highly prevalent diseases in the Mexican environment. Mortality in patients with mechanical ventilation is striking, it makes us wonder if the ventilatory management *per se* generates complications that lead the patient to death, such as Ventilator-Induced Lung Injury (VILI), hemodynamic repercussion due to positive pressure or the fact that intubated patients are simply more critically ill patients. Another current issue that has been observed internationally is the lack of medical equipment due to the high demand for patients. One of the strategies that have been reproduced internationally is the placement of prone patients early in awake patients without mechanical ventilation, with encouraging preliminary results.

Research question

In patients diagnosed with COVID-19 infection. What is the relationship between the awaken prone position and the need for orotracheal intubation?

Justification

COVID-19 is a pandemic that has significantly challenged health systems worldwide. Due to the large number of infections around the world, the implementation of strategies to reduce the number of intubations and the need for invasive mechanical ventilation becomes important. In addition to the inability of the Mexican health system to respond, patients under invasive ventilation have not had a favorable survival outcome. Up to 97% mortality has been reported in patients requiring intubation. The exact cause of this poor prognosis is not yet known. Early recognition of hypoxemic patients could help with the results. It seems reasonable in these patients to perform procedures to improve the clinical respiratory picture before intubation in less severe cases due to the quoted above. Prone patient placement during invasive mechanical ventilation is a widespread practice in the management of severe ARDS of other etiologies. Currently, few attempts have been made to implement the prone position in patients who spontaneously ventilate with supplemental oxygen, high-flow nasal cannulas, or noninvasive mechanical ventilation. Taking into account that it is a procedure that does not require additional infrastructure within the services and does not represent an additional cost for its implementation, it becomes a valuable tool in the context of COVID-19 where intubation is associated with high mortality, additionally there are mechanical ventilator deficits in most hospitals. This work has feasibility to be carried out because it will be carried out in critical areas that have equipment and trained personnel for it in the different shifts, in addition to having patients diagnosed with COVID-19.

Hypothesis

Null hypothesis (H0): In patients diagnosed with COVID-19 infection, there is no relationship between the awaken prone positioning and orotracheal intubation.

Alternate hypothesis (H1): In patients diagnosed with COVID-19 infection, there is a relationship between the awaken prone positioning and the need for orotracheal intubation.

Objective

Main objective

To analyze the relationship between the awaken prone positioning and the need for orotracheal intubation.

Specific objectives

To explore the impact of the awaken prone positioning on the partial oxygen saturation / inspired oxygen fraction index (SaO_2 / FiO_2).

Determine the free hours without the need for orotracheal intubation of patients in the awaken prone positioning.

To describe the characteristics of the patients in need of orotracheal intubation who were in the awaken prone positioning and those who were not.

Methodology

Study type: Observational, retrospective cohort study.

Study characteristics

- Based on an intervention or not for research purposes: **Observational.**
- For follow up or not of patients over time: **Longitudinal**
- For directionality in obtaining information: **Retrospective**
- By the search or not of associations between two variables: **Comparative**
- By type of population: **Homodemic, multicenter.**

Inclusion criteria

Patient's records with the following characteristics:

- Patients over 18 years of age
- Patients of both genders
- Patients diagnosed with COVID-19 infection
- Patients admitted to hospital
- Complete file

Exclution criteria

- Files not found.
- Patients who do not decide to participate in the study.

Elimination criteria

- Files with incomplete data
- File with a voluntary discharge form or transfer note.

Study population

Patients diagnosed with COVID-19

Variables categorization

The source of collection of the variables will be the clinical file.

Dependent

Variable	Conceptual definition	Operational definition	Type	Measurement scale
Orotracheal intubation	Placing a probe into the trachea through the mouth or nose to connect to a mechanical ventilator.	Performing intubation for any cause or non-intubation during your hospitalization.	Qualitative	Nominal (dichotomous): Yes No

Independent variable

Variable	Conceptual definition	Operational definition	Type	Measurement scale (years)
Age	Time elapsed from the birth of a person to a certain moment.	The age recorded in the clinical record at the patient's admission to the hospital will be considered.	Discrete quantitative	1. 18 a 27 2. 28 a 37 3. 38 a 47 4. 48 a 57 5. 58 a 67 6. 68 a 77 7. 78 a 87 8. 88 a 97 9. >97
Gender	Social concepts of functions, behaviors, activities and attributes for men and women.	Gender that is registered in the clinical record	Qualitative nominal	Male Female
Prone position	What is called the prone position	Record in the record of the placement of the patient in the prone position for a minimum of 2 hours.	Qualitative	Nominal (dichotomous): Yes No
Type of oxygen support supplied	Device used for supplemental oxygen administration.	Record in the clinical record of the type of oxygen supplied.	Qualitative nominal	1. Nasal cannulas 2. High flow nasal cannulas 3. Face mask 4. Other
Partial oxygen saturation index (SpO2) / inspired oxygen fraction (FiO2)	Resulting index for SpO2 / FiO2 ratio	2 index records will be taken at admission and the second after the patient's prone position, recorded in the clinical record.	Discrete quantitative	1. 100 a 150 2. 151 a 200 3. 201 a 250 4. 251 a 300 5. 301 a 350

Confusing variables

Variable	Conceptual definition	Operational definition	Type	Measurement scale
Comorbidities	Presence of one or more disorders in addition to the primary disease or disorder	Registration in the clinical record of any of the comorbidities described.	Qualitative nominal	1.- Diabetes mellitus 2.- Systemic arterial hypertension 3.- Chronic obstructive pulmonary disease 4.- Obesity 5.- Chronic kidney disease 6.- Ischemic heart disease 7.- Other heart diseases 8.- Other diseases
Pharmacotherapy	Drugs given to treat the disease	Registration in the clinical record of the described management.	Qualitative nominal	1. Antivirals 2. Hydroxychloroquine 3. Antibiotics 4. Corticosteroids 5. Immunomodulators 6. Others

Sample size calculation

For the calculation of the sample size, the case of previous studies that explored this same relationship will be taken as the basis, using the following formula:

$n = (N)\,(Z_{\alpha/2})_2\,(p)(q) / (N\text{-}1)\,(E)_2 + (Z_{\alpha/2})_2\,(p)(q)$

Where

- **N** = total infected population in Mexico (8463) Source: SISVER, SINAVE, DGE, SSA, May 12, 2020.
- **$Z_{\alpha/2}$ =** 95% bilateral confidence level (1.96)
- **p** = 50% success rate (0.5)

- **q** = 50% failure rate (0.5)
- **E** = 5% error range (0.05)

Substituting the values

$n = (8463)(1.96)_2 (0.5)(0.5) / (8463 - 1)(0.05)_2 + (1.96)2 (0.5)(0.5)$

n = 368 patients.

Statistical analysis

Descriptive statistics, measures of central tendency, measures of dispersion and standard deviation will be used.

While for the qualitative variable's frequency measures (relative, absolute and percentage) were used. Relative risk will be performed with a 95% confidence interval of significance (95% CI) and contingency tables.

For inferential statistics, the difference in proportions between the dependent (orotracheal intubation) and independent (prone position) variables will first be verified based on the number of expected observations (<5) Fisher's exact test or (> 5) Chi square test, contrasting $H0: \phi = 1$, taking $p < 0.05$ as a statistically significant value.

A multivariate analysis will be used to generate linear regression models with the different variables: prone time, age, gender and orotracheal intubation, $SpO2$ / $FiO2$ index in order to explain their interactions (if the time in prone, age or gender affects the main objective) as well as adopting the best model that matches the observations (best $R2$, AIC) as a predictive model.

The results will be presented in graphs and / or tables as appropriate.

Ethical considerations

This research project will be carried out under the ethical precepts indicated in the General Health Law, Regulation on Health Research, Official Mexican Standard 012. It is an investigation without risk for the research subjects, data will be obtained from the clinical record of patients diagnosed with COVID-19. The group of researchers commits to the confidentiality of the data of the files, as well as to safeguard the identities of the patients and for academic and scientific purposes. Within the scope of this study, it is to favor the implementation of the awaking prone position of the patients with COVID-19 that contributes to improving oxygenation.

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Information gathering instrument

Case	Gender	Age	Comorbidities	Type of oxygen support supplied	Pharmacotherapy	Awake prone position (Yes/no)	Time of Awake prone position (hours)	Initial SaO2/FiO2	SaO2/FiO2 before to the prone position	Prone position (hours)	Intubation Yes/No
