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Research Article

Use of the high-flow helmet CPAP non-invasive ventilation device designed in Peru in patients with severe acute respiratory syndrome (COVID-19): A prospective multicenter study

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Abstract

High-flow non-invasive ventilation (NIV) devices reduce the morbidity and mortality of COVID-19. The objective was to evaluate the use of the non-invasive ventilation device with high-flow helmet CPAP designed in Peru in patients with severe acute respiratory syndrome (COVID-19) hospitalized in the emergency services of five hospitals. Prospective multicenter and cross-sectional observational study from five hospitals from July to August 2020. 19 patients were recruited and divided into two groups (G-1 n = 10; G-2 n = 9) applying clinical and gasometric parameters as indicators of disease evolution upon hospital admission and within 24 hours. A progressive increase in these parameters was observed in those patients who used the NIV CPAP helmet within the first 24 hours. In G-01, improvement was evident in 90% (n = 9/10): PaO_2 (range 48–137; average: 82.49 ± 8.07; p-value = 0.008), CO_2 (25.2–51.0; 36.62 ± 2.62; p-value p = 0.327), and the PaO_2/FiO_2 coefficient (87–318; 191.5 ± 18.68). 10% of patients did not progress optimally, being subjected to endotracheal intubation and invasive mechanical ventilation. In G-02 the values were $\%SatO_2$ (range 92–98;

96 ± 0.76) and the SaO_2/FiO_2 coefficient (214–228; 223.2 ± 1.80), indicating significant improvement within 24 hours ($p < 0.001$). It is concluded that the use of the CPAP helmet non-invasive ventilation (NIV) device contributes to improving gasometric values and clinical condition. Being an alternative to recover typical cases of COVID-19 in all hospitals in Peru.

Keywords

COVID-19, respiratory failure, CPAP helmet, high-flow ventilation, ventilatory support

Introduction

Severe acute respiratory syndrome (COVID-19) is an inflammatory process of the pulmonary capillary endothelium, with a decrease in the capillary lumen due to endothelial thickening and angiogenesis in response to severe local tissue hypoxia (Ackermann et al. 2020; Varga et al. 2020); additionally, endothelial inflammation of arterioles and capillaries-venules of the heart and necrosis of cardiac myocytes is observed (Agyeman et al. 2020; Fox et al. 2020; Bartra et al. 2021). The causal agent of COVID-19 is the type 2 coronavirus (SARS-CoV-2), made up of an outer membrane with accessory glycoproteins (protein E and M) and the main spike protein (S), inside which is located a nucleocapsid and single-stranded genomic RNA (Ackermann et al. 2020; Carsana et al. 2020; Liu et al. 2020). The spike protein has been described to bind to the angiotensin-converting enzyme 2 (ACE-2) receptor and to the immunoglobulin family proteins basigin (EMMPRIN) and CD147 on erythrocytes.

The Spike (S) protein binds to ACE-2, then the transmembrane protease serine 2 (TMPRSS2, which is located near ACE-2) cleaves the spike protein to form the dimeric Spike/ACE-2 complex that enters the cytoplasm (Hoffmann et al. 2020) and promotes the activation of metalloproteinase 17 (ADAM17), which is responsible for removing ACE-2 from the surface of vessels and epithelia (Fig. 1A) (Cumhur Cure et al. 2020; Kreutz et al. 2020). Additionally, ADAM17 activates macrophages, which release tumor necrosis factor (TNF-α) and leukocytes, including granulocytes (neutrophils, eosinophils, and basophils), monocytes (CD14+ and CD16+), and lymphocytes, responsible for releasing IL-1β, IL-7, IL-8, IL-9, IL-10, FGFb, CSF-G, CSF-GM, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, and VEGF; these cytokines are detected in plasma at high concentrations and are associated with the cytokine storm (Kreutz et al. 2020; Parra-Izquierdo et al. 2020).

Angiotensin II levels increase and bind to angiotensin II type 1 receptors (AT1R), coupling to the Gqα/11 protein, this activates phospholipase C (PLC) which cleaves phosphatidylinositol 4,5-bisphosphate (PIP_2), generating second messengers inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG), responsible for activating protein kinase C (PKC), which activate myosin light chain kinase (MLCK), and these phosphorylate myosin to couple with actin, generating arteriolar vasoconstriction that leads to the elimination of nitric oxide (NO) derived from the endothelium, generating platelet aggregation, coagulation, microvascular thrombosis in pulmonary and heart vessels (Klok et al. 2020; Kreutz et al. 2020; Mehta et al. 2020); At the same time, mitogen-activated protein kinases (MAPK) and ERK are activated, releasing transforming growth factor-beta (TGF-β); additionally, heat shock protein 27 (HSP-27) and plasminogen activator inhibitor type 1 (PAI-1) are expressed, respectively. TGF-β increases collagen 1 and fibronectin, which are responsible for fibrosis, growth, and cell migration of vessels and heart (Fig. 1B) (Klok et al. 2020; Mehta et al. 2020). The cytokine storm, the high concentration of angiotensin II, the elimination and dysfunction of the ACE-2 receptor induce oxidative stress of the mitochondrial membrane and the cytoplasm, causing the elimination of nitric oxide (NO) derived from the endothelium, all of which generates the symptoms of COVID-19 (Klok et al. 2020; Kreutz et al. 2020; Mehta et al. 2020). Fig. 1 shows the entry of coronavirus type 2 (SARS-CoV-2) and the molecular mechanism of action of the disease.

To improve acute respiratory failure in patients with COVID-19, a non-invasive ventilation (NIV) device is used (Antonelli et al. 1998; Antonelli et al. 2007; Ferreyro et al. 2020), due to its easy handling and because it does not generate the complications of a conventional mechanical ventilator (Antonelli et al. 2007). A systematic review with meta-analysis concluded that timely use of NIV in adult patients with acute hypoxemic respiratory failure is associated with a lower risk of requiring mechanical ventilation and death compared to standard oxygen therapy (Garpestad and Hill 2006). Indications for NIV include chronic obstructive pulmonary disease (COPD), cardiogenic shock, and acute respiratory distress syndrome (ARDS) (Antonelli et al. 2007; Lazzeri et al. 2020).

In the context of the COVID-19 pandemic, the use of the NIV device has increased and represents a treatment alternative with a good response in European and American countries, since its use guarantees a lower rate of complications than invasive mechanical ventilation (IMV) (Lazzeri et al. 2020). NIV includes continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) mode, which can be delivered at different interfaces. The CPAP modality has the benefit of increasing the functional residual capacity of the lung, thus reducing both the work of breathing and the risk of opening and closing of the airways. Furthermore, the application of PEEP recruits non-aerated alveoli in dependent lung regions, stabilizing the airways; this modality is included in the recommendations for the treatment of mild to moderate ARDS by the WHO (World Health Organization 2020). The most used NIV devices are the facial or nasal mask and the helmet,

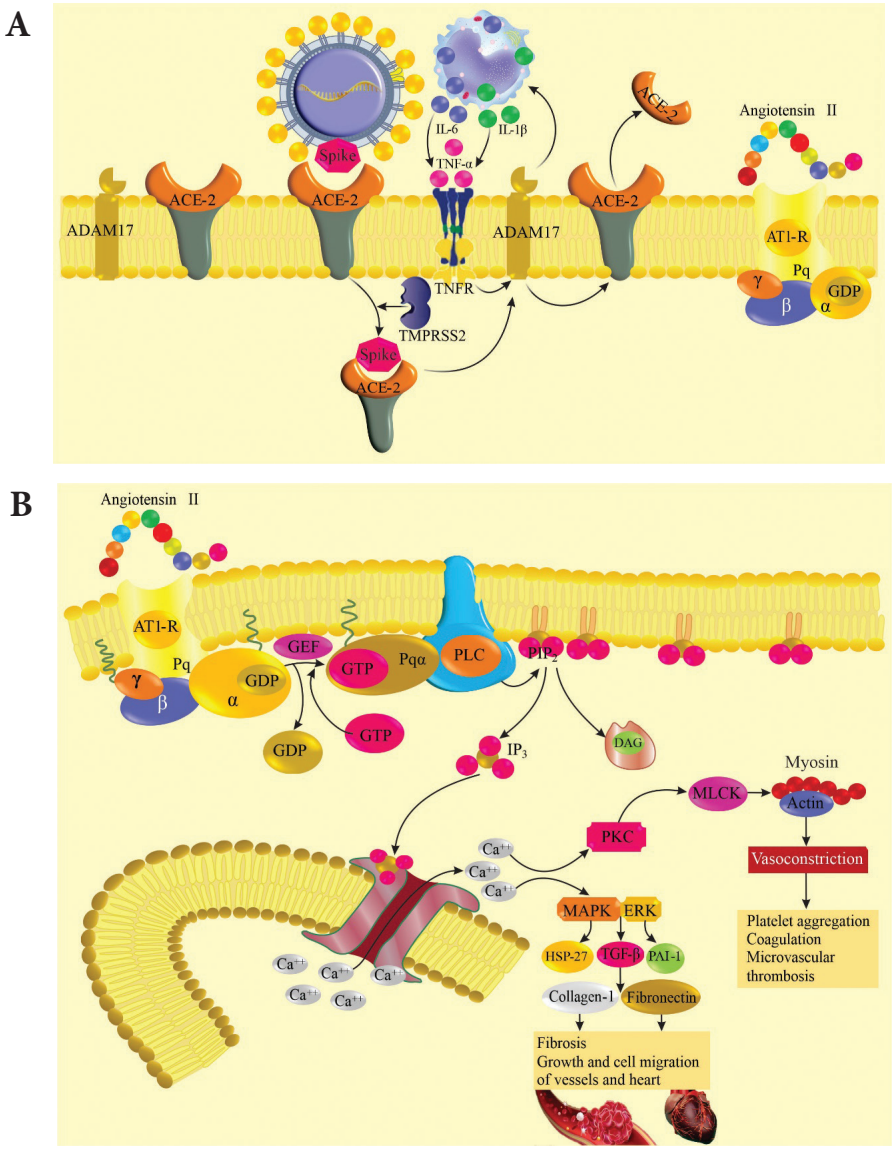

Figure 1. Mechanism of destruction and elimination of the ACE-2 receptor and the molecular mechanism of action of COVID-19.

which is the interface of choice. The selection of one of them is based on a risk/benefit analysis for both the patient and the healthcare staff, and helmets are recommended, as they have a lower range of aerosol dispersion, reducing the risk of contagion of COVID-19 (Ing et al. 2020). Given the need and shortage of non-invasive oxygen therapy alternatives in Peruvian hospitals, engineers from the National University of Engineering (UNI) designed, patented, and obtained permission to manufacture a "Helmet CPAP" helmet, which was called the "CONI CPAP helmet"; this device was inspired by and reproduced from Italian models and other European countries. Fig. 2 shows the correct use of the CPAP helmet non-invasive ventilation (NIV) device in two patients diagnosed with atypical pneumonia and COVID-19 infection.

The SciELO database of Peru, PubMed-NCBI and ScienceDirect were searched for published designs and studies of non-invasive ventilation (NIV) CPAP helmet devices in patients diagnosed with atypical pneumonia and COVID-19 infection in Peru, and it is evidenced that these studies are limited or scarce, in this sense, it is justified to carry out NIV CPAP helmet studies designed by the authors for four reasons: First, to generate scientific evidence of the advantages of using the helmet CPAP device designed by the authors, such as lower risk of gas leaks and therefore lower risk of disease transmission (Whittle et al. 2020), lower mortality compared to standard oxygen therapy, decreased intubation rate, easy use, and better patient tolerance compared to face mask (Amirfarzan et al. 2021); Second, it shortens the length of stay in the Intensive Care Unit (ICU), and therefore, less risk of acquiring other hospital-acquired diseases; Third, demonstrate that its use is not only for atypical pneumonia and COVID-19 but could also be used in other respiratory diseases that require oxygen therapy, such as chronic obstructive pulmonary disease (COPD), cardiogenic shock, and acute respiratory distress syndrome (ARDS). Fourth, by demonstrating their usefulness with greater advantages over invasive devices, health authorities will make these devices available to hospitals in the Andean and jungle regions of the country, making them accessible to patients with low economic resources. Therefore, the objective was to evaluate the use of the non-invasive ventilation device with high-

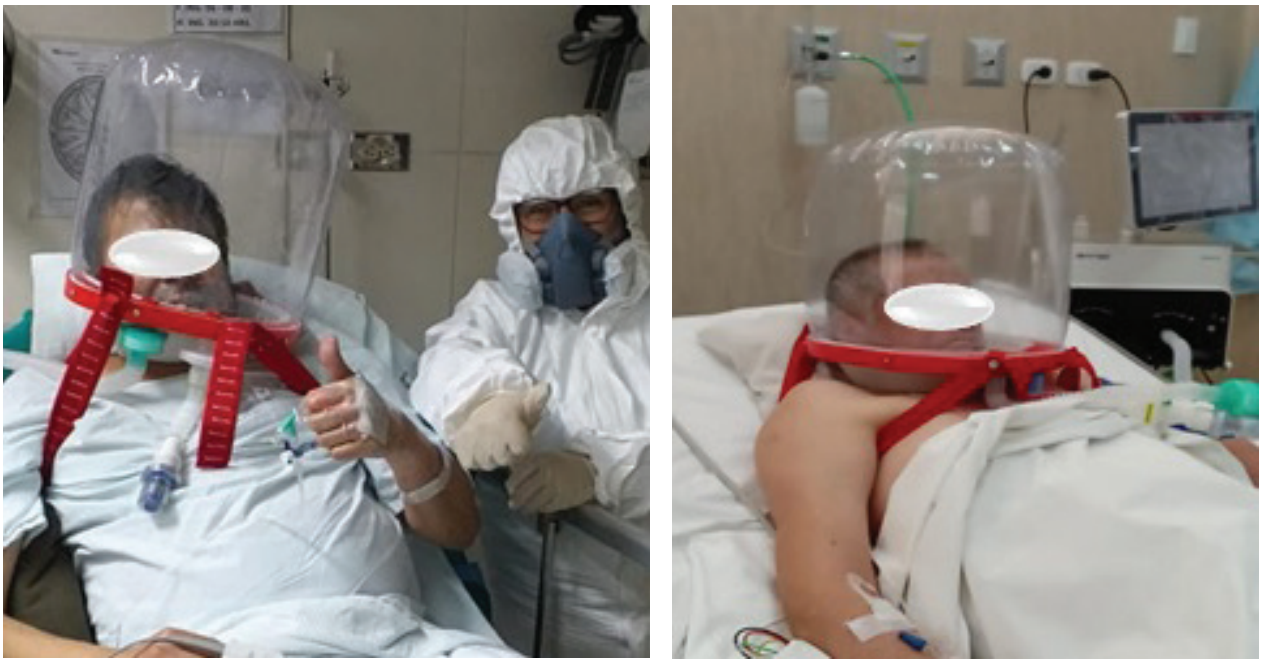

Figure 2. Use of the CPAP helmet non-invasive ventilation (NIV) device in patients with a diagnosis of atypical pneumonia and COVID-19 infection.

flow helmet CPAP designed in Peru in patients with severe acute respiratory syndrome (COVID-19) hospitalized in the emergency services of five hospitals, evaluated in the first 24 hours, applying clinical and gasometric parameters as indicators of disease evolution.

Materials and methods

Design and type of study

Prospective multicenter and cross-sectional observational study.

Population and study sample

The study population was patients diagnosed with COVID-19 who presented with acute respiratory failure and who used the non-invasive ventilation (NIV) device called CPAP helmet during their hospitalization and who met the selection criteria. Data were collected from 19 patients (sample) from five hospitals (Guillermo Almenara Irigoyen National Hospital in Lima, Rezola Hospital in Cañete-Lima, Honorio Delgado Hospital in Arequipa, Carlos Seguín Escobedo National Hospital in Arequipa, and Hermilio Valdizán Medrano Regional Hospital in Huánuco); the study period being July to August 2020. The data collection technique was carried out using a collection instrument designed by the researchers and validated by expert judgment.

Selection criteria

The selection criteria for follow-up were the coefficient of alveolar partial pressure of O_2/inspired fraction of O_2 (PaO_2/FiO_2), percentage of arterial oxygen saturation ($\%SatO_2$), and $\%SatO_2/FiO_2$ coefficient measured at admission and within the first 24 hours of treatment. The FiO_2 value of 0.43 was considered as an indicator of good response measured in a laboratory using oxygen concentration equipment, and patients diagnosed with COVID-19 were treated in five hospitals in Peru.

Operational definition

Successful NIV with helmet CPAP is defined as a patient with acute respiratory failure due to COVID-19 who does not require mechanical ventilation and who achieves improvement in gasometric parameters. Failure of NIV with helmet CPAP is defined as the need for mechanical ventilation or no improvement in arterial gasometric parameters or death.

Ethical aspects

The study was carried out in strict compliance with the ethical standards and criteria of the Belmont Report and the Declaration of Helsinki with the current revision. A code was assigned to each patient document to ensure confidentiality and anonymity.

Statistical analysis

The data obtained from the collection instrument (cards) were entered as they were collected, structuring a database in an Excel spreadsheet. Once the database was correctly constructed, it was exported to the STATA 14 statistical program, where coding and statistical analysis were carried out. A value of $p < 0.05$ was considered statistically significant.

Results and discussion

Data were collected from 19 patients in five COVID-19 hospitals according to the operational definition and data selection criteria. Hospitalized patients were over 18 years of age, male, with comorbidities such as type 2 diabetes mellitus and obesity in 40% of patients (4/10), who were between day 1 and day 10 of hospitalization (mean: 4 ± 3.19), receiving 90% (9/10) ventilatory support with the reservoir mask and 10% (1/10) with a binasal cannula at 5 L/min (Table 1).

Table 1. Clinical and sociodemographic characteristics of the patients.

Characteristics	Number/mean	Percentage (%)	Range
Number of patients (n)	19	100	
Age (years)	57.1 ± 8.21		36–75
Male sex	19	100	
Female sex	0	0	
Comorbidities:	4	21	
• DM2	2	10.5	
• Obesity	2	10.5	
Hospitalization (days)	2.57		1–10
Pretreatment using:	10	52.6	
• Reservoir mask	9	47.3	
• Binasal cannula	1	5.3	

DM2: Diabetes Mellitus type 2.

The analysis of clinical and laboratory parameters will be analyzed in two groups, due to the affinity of the variables collected. Group 1 included patients with a diagnosis of atypical pneumonia and COVID-19 infection who used the helmet CPAP non-invasive ventilation device, and arterial gasometric and clinical condition were used as a method of monitoring and evolution of the patients, one being taken at baseline and the other 24 hours after treatment (Table 2). Under baseline conditions, it was observed that patients presented moderate to severe hypoxemia with PaO_2 in a range of 38.1–80 (mean: 57.49 ± 14.33) and CO_2 in a range of 25.1–42.3 (mean: 33.5 ± 4.99), with PaO_2 coefficient/FiO_2 between 45–164 (mean: 76.5 ± 34.94), all with Glasgow 15, conscious, oriented in time, space, and person. During follow-up and monitoring within the first 24 hours with the NIV device with a CPAP helmet as ventilatory support, improvement was observed in hypoxemia levels, achieving mild hypoxemia values or reaching normal values. PaO_2 values were found in a range of 48–137 (mean: 82.49 ± 8.07), indicating significant improvement ($p = 0.008$); CO_2 values were between 25.2–51 (mean: 36.62 ± 2.62), not statistically significant ($p = 0.327$); and the value of the PaO_2/FiO_2 coefficient was from 87 to 318 (mean: 191.5 ± 18.68), indicating that the degree of respiratory failure was reversed from severe to moderate.

In this sense, based on the operational definition and the values of the gasometric parameters, the results indicate success of NIV with a CPAP helmet (90%; n = 9/10). Only 10% of patients did not progress optimally, being subjected to endotracheal intubation and invasive mechanical ventilation. No deaths were observed during the follow-up and monitoring of the present study.

Table 2. Gasometric parameters of patients with a CPAP helmet non-invasive ventilation device.

Gasometric parameters	At the beginning of NIV with helmet CPAP	Within 24 hours with CPAP helmet	p-value	Size
% $SatO_2$	85.47 ± 3.23	90.13 ± 4.78	0.374	0.296
PaO_2	57.49 ± 4.54	82.49 ± 8.07	0.008	1.080
PCO_2	33.59 ± 1.57	36.62 ± 2.62	0.327	0.328
FiO_2	0.85	0.43	< 0.001	3.098
PaO_2/FiO_2	76.5 ± 11.04	191.5 ± 18.68		

The PaO_2/FiO_2 coefficient indirectly measures lung injury, while the percentage of normal hemoglobin saturation with oxygen (%$SatO_2$) indicates what percentage of the hemoglobin in the blood is loaded with oxygen molecules, which must be higher at 95% breathing room air (FiO_2 0.21) at sea level (1 atm or 760 mmHg). With normal pulmonary ventilation (12 breaths/min, moving 500 mL of air in each cycle) and a normal dead space (ventilation not used for exchange), alveolar ventilation greater than 4 L/min is delivered, achieving an alveolar PO_2 (PAO_2) and arterial (PaO_2) of about 100 mmHg (Mateos 2020).

The comparison of the PaO_2/FiO_2 coefficient between baseline and follow-up is represented in Fig. 3.

Table 3 reports the comparative parameters of the $SatO_2$ percentage of the patients with the NIV CPAP helmet device and the p-values from the beginning, during the follow-up, monitoring, and end of the experiment corresponding to group 2, which was made up of 9 patients of different sexes, male (age range 45–55 years) with a diagnosis of atypical pneumonia and COVID-19 infection, without comorbidity, and who were hospitalized for at least 1 day. In this group, the percentage of oxygen saturation (%$SatO_2$) was used as a monitoring method; for this, a baseline was carried out at the first and then at the second hour, and during the experiment it was measured at 12 and 24 hours. Under baseline conditions, gasometric and clinical parameters such as $SatO_2$ percentage were between 80–93 (mean: 87.6 ± 1.73), all with Glasgow 15, conscious, oriented in time, space, and person.

Table 3. $SatO_2$ percentage parameters of patients with a non-invasive helmet CPAP ventilation device.

Parameters	At the beginning of NIV with helmet CPAP	Within 24 hours with a CPAP helmet	p-value	Size
% $SatO_2$	87.66 ± 1.73	96 ± 0.76	0.001	1.611
FiO_2	0.85	0.43		
$SatO_2/FiO_2$	215.66 ± 2.08	223.2 ± 1.80	< 0.001	1.699
Glasgow Scale	15	15		

At the first 2 hours of follow-up with the NIV CPAP helmet used as ventilatory support, $SatO_2$ percentage values between 87–96 (mean: 92.6 ± 0.76) were evident, indicating that the degree of desaturation is improving, reaching mild levels, while the %$SatO_2/FiO_2$ coefficient was observed in a range of 202 to 223 (mean: 215.6 ± 2.08). In the first 24 hours of using the NIV helmet CPAP as ventilatory support, $SatO_2$ values were observed between 92–98

(mean: 96 ± 0.76) and the SaO_2/FiO_2 coefficient in a range of 214–228 (mean: 223.2 ± 1.80), indicating significant improvement within 24 hours ($p < 0.001$).

The comparison of the $SatO_2$ percentage between baseline and follow-up values is seen in Fig. 4.

The results of the present study are consistent with various prospective observational studies that have been previously published, such as the study by Aliberti et al. (2020), who reported that hypoxemia improved in 52% of patients who used CPAP, with the values of the PaO_2/FIO_2 ratio at the beginning of oxygen therapy being 142.9 (range: 96.7–203.2), without a helmet, and after 6 h of using the CPAP helmet, it was 205.6 (range: 140.0–271.1; $p < 0.0001$). The mean duration of helmet CPAP treatment was 6 (3–10) days. Only four patients discontinued helmet CPAP due to intolerance. CPAP failure was observed in 70 patients (44.6%): 34 (21.7%) were intubated, and 36 (22.9%) died during the ICU stay. A total of 87 patients (55.4%) improved during their stay in the ICU, were transferred to oxygen therapy, and were transferred to the general ward. Amirfarzan et al. (2021) indicate that the CPAP device is not intended to replace endotracheal intubation and mechanical ventilation in patients with acute respiratory failure due to COVID-19; however, it deserves to be considered for use during a pandemic. It is proposed that to discontinue the use of the CPAP device, one must first decrease PEEP and FiO_2, increase CPAP-free time, achieve improvement in respiratory distress, and have an ability to maintain $SpO_2 > 96\%$ and $FiO_2 \leq 40\%$. Mateos-Rodríguez et al. (2021) observed a progressive increase in oxygen saturation (range 98–99%) in patients who used a CPAP device as an alternative after 30 and 60 min, although this change was not significant ($p = 0.058$ and $p = 0.122$, respectively). A statistically significant improvement was observed in the $SatO_2/FiO_2$ variable ($p = 0.040$). Liu et al. (2020) have shown that the use of NIV CPAP mode is safe and effective for the treatment of patients with mild to moderate acute respiratory failure. The need for ventilatory support is based on reducing respiratory work, and this is favored with the CPAP helmet because it acts as a positive pressure system that prevents the collapse of non-oxygenated alveoli; therefore, high FiO_2 is not required in the early stages of the disease and thus avoids lameness of the respiratory system.

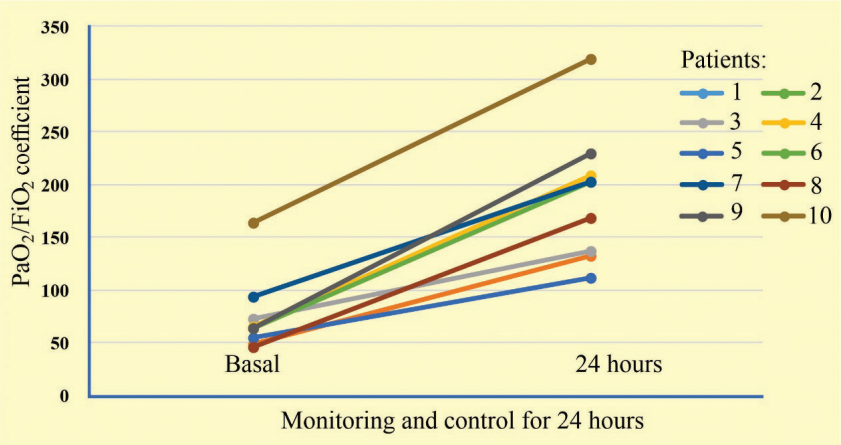

Figure 3. Comparison of the PaO_2/FiO_2 coefficient between baseline and follow-up in relation to the use of the CPAP helmet non-invasive ventilation device.

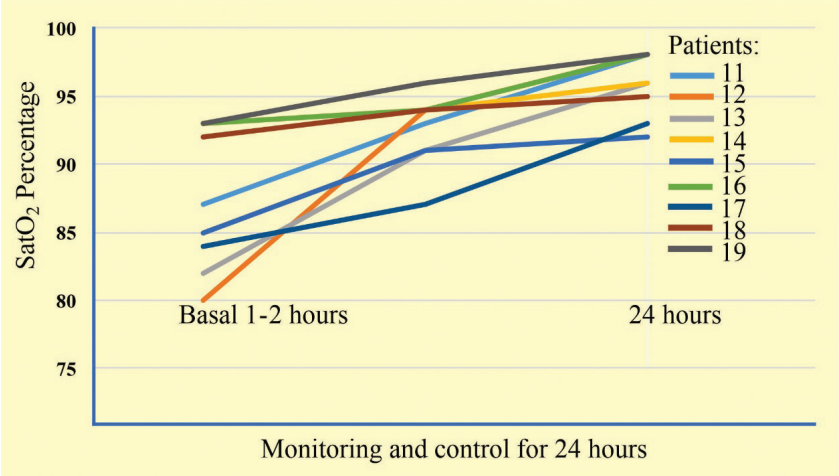

Figure 4. Comparison of the $SatO_2$ percentage between baseline and follow-up values obtained from patients who used the CPAP helmet non-invasive ventilation device.

Clinical pharmacists and medical specialists participated in the study process, controlling the blood gas parameters (% $SatO_2$, PaO_2, PCO_2, FiO_2, and PaO_2/FiO_2). Additionally, the pharmacists provided personalized pharmaceutical care on the ingestion of the medication with 200 mL of water, drug administration interval considering the maximum plasma time (t_{max}) and the half-life time ($t_{1/2}$) to avoid interactions, and exercising pharmacovigilance to detect, report, and prevent adverse reactions to medications and vaccines used in COVID-19.

The results of this study must be considered in the context of several limitations. One of them is the number of patients included (n = 19); the results cannot be extrapolated, and the cases must be analyzed individually. The collapse of hospital centers and health personnel cannot cope with personalized monitoring of patients, which is why we do not have clinical parameters that could help support the information. Other biases that can lead to confusion are the inequity of the Peruvian health system, given that many hospitals do not have basic laboratory tests to adequately monitor patients, as was evident in this study since the Hospital de Huánuco does not have AGA available, not allowing adequate monitoring; therefore, the health team decided to monitor the patient with non-invasive methods such as pulse oximeters, which give us approximate values of the patient's oxygenation. However, this is the first study that evaluates the use of a non-invasive high-flow helmet CPAP ventilation device designed by Peruvian researchers in patients with severe acute respiratory syndrome (COVID-19) in a multicenter prospective study that may be used in other respiratory diseases.

Conclusion

Based on the results, it is concluded that the use of the non-invasive ventilation (NIV) CPAP helmet device contributes to improving the values of PaO_2, $SatO_2$, and SaO_2/FiO_2, which is considered useful and should be an alternative to recover typical cases of COVID-19 in all hospitals in Peru.

Recommendations

Doctors, pharmacists, and other health professionals must take an active role in addressing inequalities in access to medical services; the first step is to supply medical equipment and instruments to provide equal and quality medical care at the four levels of hospital care in Peru (Level I made up of health centers and health posts; Level II made up of local hospitals; Level III made up of regional hospitals; Level IV made up of highly specialized hospitals). At all levels of care, prevention, diagnosis, and timely treatment must be provided in the three geographic regions (coast, Andes, and jungle), without considering socioeconomic conditions, age, sex, ethnicity, and/or religion, which will allow progress towards universal health.

The second step is to promote the implementation of 4P medicine (predictive, preventive, personalized and participatory), that is, the medical consultation should not focus on the symptoms, but rather, through predictive medicine, genes and allelic variants that predict chronic diseases would be identified; through preventive medicine, foods that activate these genes would be avoided; and if medication is required, personalized pharmacological treatment would be initiated based on the metabolic genotype/phenotype (personalized or precision medicine); and with the participation of biochemists, pharmacists, nurses, patient and treating doctor (participatory medicine) adherence to the prevention and treatment of the disease would be achieved (Alonso et al. 2019; Slim et al. 2021). The third step is to carry out relative bioavailability studies of generic and similar medicines (medicines manufactured by different laboratories with commercial names) to obtain bioequivalent medicines and in clinical practice demonstrate therapeutic interchangeability. With this, we ensure medications that fulfill their social good, of high quality, efficacy, safety, and accessibility in hospitals for people with low economic resources (Alvarado et al. 2021a, 2021b; Alvarado et al. 2022). Likewise, the non-invasive ventilation device with a high-flow helmet CPAP that has been designed, manufactured, patented, and used with permission from the General Directorate of Medicines, Supplies, and Drugs (DIGEMID) of Peru should be available at all four levels of hospitalization and available for patients with chronic obstructive pulmonary disease (COPD), cardiogenic shock, and acute respiratory distress syndrome (ARDS).

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Data availability

All of the data that support the findings of this study are available in the main text.

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