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Early View

Research letter

Helmet CPAP treatment in patients with COVID-19 pneumonia: a multicenter, cohort study

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Title

Helmet CPAP treatment in patients with COVID-19 pneumonia: a multicenter, cohort study

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Take Home Message

Helmet CPAP treatment fails in up to 44% of patients with moderate-to-severe hypoxemic acute respiratory failure due to COVID-19 pneumonia

TEXT

Patients with COVID-19 pneumonia can develop hypoxemic acute respiratory failure (hARF) with the need for positive end-expiratory pressure (PEEP). The administration of a continuous positive airway pressure (CPAP) through a helmet improves oxygenation and avoids intubation [1,2]. A European consensus document suggests that helmet CPAP should be the first therapeutic choice for hARF caused by COVID-19 pneumonia, mainly for minimizing aerosol generation [3-5]. However, recommendations are based on experts' opinion and consider only evidence obtained in critically ill COVID-19 patients [3]. The Surviving Sepsis Campaign does not recommend the administration of CPAP for the initial management of severe COVID-19 [6].

In order to evaluate outcomes of COVID-19 patients with pneumonia-related hARF undergoing CPAP treatment, a multicenter, observational, prospective study was conducted between March 7th, 2020 and April 21st, 2020 in three high-dependency units (HDU) at two hospitals in Milan, Italy. Adults (≥18 years) with hARF secondary to community-acquired COVID-19 pneumonia undergoing helmet CPAP treatment were consecutively recruited. Indications for helmet CPAP included all the following: a diagnosis of pneumonia as the only cause of hARF and a partial arterial pressure of oxygen to fraction of inspired oxygen (PaO_2:FiO_2) ratio <300 evaluated during oxygen therapy supplied for at least 30 minutes through either a Venturi mask (FiO_2 of at least 0.50) or reservoir mask. CPAP was delivered through high-flow generators (VitalSigns inc., Totowa, USA; 90–140 L/min; Myo 3133A, Pulmodyne) using a helmet (StarMed, Italy) as interface with a PEEP valve (VitalSigns, USA). The

presence of other causes of hARF were excluded by clinical evaluation. Patients with at least one of the following criteria were excluded: need for immediate intubation, Glasgow Coma Scale <15, respiratory acidosis, systolic blood pressure (SBP) <90 mmHg despite fluid resuscitation and/or use of vasopressors, swallowing disturbance with increasing risk of aspiration pneumonia, and inability to protect the airways. The Ethical Committees of the two hospitals approved the study (No. 345/2020 and No. 17263/2020). Demographic, epidemiological, clinical, and laboratory data were recorded at admission. Arterial blood gas analysis and vital signs were recorded before CPAP, and within 6 hours, on day 3 and day 7 after CPAP initiation. Lung recruitability during CPAP treatment was defined as an increase of PaO_2:FiO_2 ratio of at least 30% from oxygen therapy (baseline) to CPAP treatment (within 6 hours). Severe pneumonia on admission was defined according to latest ATS/IDSA guidelines [7]. Patients were followed up to either 30-days or hospital discharge if still hospitalized at 30 day from HDU admission. The primary outcome was CPAP failure defined as the occurrence of either intubation or death due to any cause during HDU stay. According to local standard operating procedures, indication for intubation included the presence of either ≥1 major or ≥2 minor criteria lasting for ≥1 hour. Major criteria were: respiratory arrest, respiratory pause with unconsciousness, severe hemodynamic instability (i.e., SBP <90 mmHg instead of adequate volume resuscitation), and intolerance to helmet CPAP leading to discontinuation of the device. Minor criteria were: reduction of ≥30% of basal PaO_2:FiO_2 ratio, PaO_2:FiO_2 ratio <100, 20% increase of $PaCO_2$ if basal $PaCO_2$ was ≥40 mmHg, worsening of alertness, new onset or persistent respiratory distress, SpO_2 <90%, and exhaustion. Achievement of the criteria did not automatically imply intubation of the patient, since this decision was based on a multidisciplinary discussion among the attending physician, the senior attending physician and the critical care physician. Secondary outcomes included the weaning from CPAP to oxygen therapy (CPAP success), all-cause in-hospital and 30-day mortality. Do-Not-Intubate (DNI) order was defined as the decision of the attending physician in charge (after discussion with the critical care physician) to withheld intubation and to use CPAP as “ceiling” treatment considering patient’s characteristics (e.g., extremely poor functional

status prior on admission, very low predicted probability of hospital survival, patient's own opinion when reliable, frailty score, and comorbidities). Weaning from helmet CPAP was standardized across the three HDUs. Patients on helmet CPAP who did not show signs of respiratory distress (e.g. RR<25) and maintained a SpO_2>94% with a FiO_2<50% and a PEEP<=5 cmH_2O underwent a weaning trial. Patients maintaining a PaO_2:FiO_2 ratio >250 on Venturi mask with a FiO_2 <40% for at least 24 hours were considered successfully weaned from helmet CPAP. Qualitative and quantitative variables were summarized with frequencies (absolute and relative, percentage) and central tendency (means and medians) and variability (standard deviations, SD, and interquartile ranges, IQR) indicators, depending on their parametric distribution. A chi-squared or Fisher exact test was computed for qualitative variables; Student t test or Mann Whitney was used for quantitative variables with a parametric or non-parametric distribution, respectively. A Cox proportional hazards regression analysis was carried out to assess the relationship between the composite primary outcome and independent variables. No specific computations were carried out. All the individuals potentially fitting the study selection criteria were recruited when admitted at the two hospitals in Milan. A two-tailed p-value less than 0.05 was considered statistically significant. Statistical computations were performed with STATA version 16 (StatsCorp, Texas, USA).

A total of 157 patients [74.5% males; median (IQR) age: 64 (55-75) years] with hARF [median (IQR) PaO_2:FiO_2 ratio of 142.9 (96.7-203.2)] underwent helmet CPAP with an initial median (IQR) FiO_2 of 0.6 (0.5-0.6) and mean (SD) PEEP of 10.8 (2.3) cmH_2O (Table). The most prevalent comorbidities were arterial hypertension (44.0%), diabetes (22.9%), ischemic cardiac disease (17.2%), and chronic arrhythmia (10.8%). Hypoxemia generally improved when CPAP treatment was initiated: median (IQR) values of PaO2:FiO2 ratio at baseline on oxygen therapy [142.9 (96.7-203.2)] significantly improved when helmet CPAP was used after 6 hours [205.6 (140.0-271.1), p <0.0001]. However, an increase of at least 30% in PaO_2:FiO_2 ratio during helmet CPAP application in comparison to oxygen therapy was found only in 52% of the population. Median (IQR) duration of helmet CPAP treatment was 6 (3-10) days. Only 4 patients discontinued helmet CPAP because of intolerance. No patients

were lost during follow-up. CPAP failure was observed in 70 (44.6%) patients: 34 (21.7%) were intubated, and 36 (22.9%) died during the HDU stay. 87 (55.4%) patients improved during the HDU stay, weaned to oxygen therapy and transferred to general ward. No patients were intubated during the first hours after CPAP initiation or under high emergency conditions (e.g. cardiac arrest). Among those who died in HDU, pneumonia-related deaths were detected in 26 patients, while non-pneumonia related in 10 patients, including pulmonary embolisms (5 patients), end-stage renal failure (2 patients), cerebrovascular accident (1 patient), end-stage heart failure (1 patient), and septic shock (1 patient). Among the 34 patients who were intubated in HDU and transferred in the intensive care unit (ICU), 9 (26.5%) died. A total of 65 (41.4%) patients had a DNI status on HDU admission: 36 died and 29 survived. At the multivariable analysis (adjusted for gender, age, severe CAP, IL-6, and a delta of PaO_2:FiO_2 ratio ≥30%), CPAP failure was associated with the severity of pneumonia on admission [HR (95%CI): 2.9 (1.3-6.2); p-value: 0.009] and higher baseline values of IL-6 [HR (95%CI): 1.0 (1.0-1.0); p-value <0.009]. The all-cause in-hospital and 30-day mortality rates were 28.7% and 28.0%, respectively.

The rate of CPAP failure (either intubation or death) in COVID-19 patients seems to be higher in our study compared with the one recently reported in a multicenter, observational study which enrolled non-COVID-19 pneumonia patients with comparable severity of hARF (44.6% VS. 23%) [8]. Both intubation (21.7% VS. 11%) and mortality (22.9% VS. 12%) rates were also higher in COVID-19 pneumonia than non-COVID-19 pneumonia patients [8]. This finding can be explained by the complex phenomena behind the occurrence of the respiratory failure experienced by COVID-19 patients, which is often paralleled by local vascular micro-thrombosis, and, more importantly, by the absence of a treatment of proven efficacy [9]. Nevertheless, the overall mortality rate of our cohort was comparable to that recently reported in ICU patients [10]. A total of 55.4% of our patients with a median PaO_2:FiO_2 ratio of 136 and treated with helmet CPAP avoided intubation, and, then, were successfully weaned to oxygen therapy. Unfortunately, prognostic criteria which can discriminate responders to CPAP therapy at HDU admission are still lacking. Finally, a French study enrolled 38

COVID patients with ARF and suggested that CPAP seems to avoid intubation especially in DNI patients [11]. It is difficult to compare our results with those by Oranger and coworkers for different reasons, including the different intervention (Boussignac and oro-nasal CPAP vs. helmet CPAP), unclear severity of respiratory failure (only PaO_2 was reported), inclusion of patients needing O_2 >6 l/min to maintain an SpO_2 >92%, which represents a selection bias (increase of the number of milder patients), and the absence of a mortality rate reported in the CPAP arm.

The present study has several limitations which can limit the generalizability of our results. Among those, the lack of a control group and different standard operating procedures across the three centers, as well as the lack of important information, including the daily length of CPAP treatment, might reduce the inference. However, this is the first experience which evaluated outcomes in COVID-19 patients undergoing helmet CPAP in a multicenter, prospective study. In conclusion, the application of helmet CPAP in COVID-19 patients should be carefully considered and monitored to prevent a delayed endotracheal intubation.

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TABLE

Table. Baseline characteristics, CPAP treatment and outcomes of the study population according to CPAP failure or success.

	CPAP Success (n= 87)	**CPAP Failure (n= 70)**	**p-value**
Demographics			
Males, n (%)	60 (69.0)	57 (81.4)	0.08
Median (IQR) age	66 (56-75)	60 (51-72)	0.08
Age > 65 years, n (%)	45 (51.7)	26 (27.1)	0.07
Age > 75 years, n (%)	20 (23.0)	15 (21.4)	0.82
Median (IQR) BMI	27.4 (25.1-30.2)	27.5 (23.7-29.3)	0.39
Obesity (BMI ≥30 kg/m^2), n (%)	16 (25.4)	13 (24.1)	0.87
Current/former smoker, n (%)	17 (19.5)	10 (14.3)	0.39
Comorbidities			
Any cardiovascular disease, n (%)	49 (56.3)	32 (45.7)	0.19
Hypertension, n (%)	41 (47.1)	28 (40.0)	0.37
Diabetes, n (%)	24 (27.6)	12 (17.1)	0.12
Ischemic Cardiac Disease, n (%)	19 (21.8)	8 (11.4)	0.09
Chronic Arrhythmias, n (%)	7 (8.1)	10 (14.3)	0.21
Cerebrovascular disease, n (%)	9 (10.3)	4 (5.7)	0.39
Immunosuppression, n (%)	8 (9.2)	3 (4.3)	0.35
COPD, n (%)	7 (8.1)	3 (4.3)	0.51
Chronic Renal Failure, n (%)	6 (6.9)	3 (4.3)	0.73
Liver disease, n (%)	5 (5.8)	4 (5.7)	1.00
Asthma, n (%)	1 (1.29	2 (2.9)	0.59
Radiology			

Consolidation on chest X-ray, n (%)		66 (75.9)	58 (82.3)	0.29
Pleural effusion, n (%)		15 (17.2)	11 (15.7)	0.80
Pharmacological treatment				
Treatment with immunomodulators, n (%)	None	56 (64.4)	42 (60.0)	0.74
	Anakinra	26 (29.9)	22 (31.4)	
	Tocilizumab	5 (5.8)	6 (8.6)	
Hydroxychloroquine, n (%)		84 (96.6)	68 (97.1)	0.83
Lopinavir/ritonavir, n (%)		48 (55.2)	37 (52.9)	0.77
Remdesivir, n (%)		2 (2.3)	3 (4.3)	0.66
Endovenous Steroids, n (%)		37 (42.5)	35 (50.0)	0.42
Antibiotic, n (%)		84 (96.6)	66 (94.3)	0.49
Anticoagulation		24 (27.9)	21 (30.4)	0.73
Disease severity				
Severe pneumonia, n (%)		56 (64.4)	55 (78.6)	0.05
Septic Shock Vasopressor, n (%)		3 (3.5)	2 (2.9)	1.00
Aggressive Fluid resuscitation, n (%)		2 (2.3)	0 (0.0)	0.50
Clinical variables before CPAP treatment				
Confusion, n (%)		7 (8.1)	2 (2.9)	0.30
Mean (SD) temperature (n= 153)		37.3 (1.1)	37.6 (0.9)	0.12
Median (IQR) systolic blood pressure (n= 156)		130 (115-140)	130 (120-140)	0.87
Median (IQR) diastolic blood pressure (n= 156)		75 (70-85)	80 (70-85)	0.69
Mean (SD) heart rate (n= 156)		88.3 (15.6)	86.5 (14.5)	0.47
Median (IQR) respiratory rate (n= 153)		28 (24-32)	25.5 (21-30)	0.09
Respiratory rate ≥30 breaths per minute		37 (43.5)	20 (29.4)	0.07
Median (IQR) SpO_2 (n= 154)		93 (89-97)	95.5 (90-97)	0.41

Blood Gas Analysis before CPAP treatment				
Median (IQR) pH (n= 155)		7.48 (7.45-7.51)	7.47 (7.45-7.50)	0.91
Mean (SD) $PaCO_2$, mmHg (n= 157)		33.0 (5.0)	32.9 (5.9)	0.89
Median (IQR) PaO_2, mmHg (n= 157)		65 (53-83)	75.5 (60-96)	0.009
Median (IQR) PaO2:FiO_2 ratio (n= 157)		136 (95.0-204.8)	152 (100-202)	0.85
PaO_2:FiO_2 ratio Classes	PaO_2:FiO_2 ratio ≤ 100 mm/Hg	23 (26.4)	18 (25.7)	0.90
	(100 <mm/Hg PaO_2:FiO_2 ratio ≤200 mm Hg)	39 (44.8)	34 (48.6)	
	200 <mm/Hg PaO_2:FiO_2 ratio ≤300 mm Hg)	25 (28.7)	18 (25.7)	
Blood tests before CPAP treatment				
Median (IQR) white blood cells, cell/mm^3 (n= 156)		7,060 (5,550-9,630)	8,000 (5,490-10,450	0.45
Median (IQR) platelets, cell/mm^3 (n= 155)		227,00 (169,000-336,000)	199,000 (142,000-264,500)	0.02
Median (IQR) D-Dimer, µg/L (n= 126)		793 (561.0-1,242.5)	1,098 (667-2,444)	0.03
Median (IQR) ferritin, µg/L (n= 123)		1,484 (832-2,732)	1,558.5 (1,049-2,830)	0.54
Median (IQR) IL-6, ng/L (n= 125)		46.6 (19-75)	134 (77.9-266)	<0.0001
Median (IQR) C-reactive protein, mg/dL (n= 157)		13.6 (8.4-44.0)	15.6 (10.8-25.8)	0.49
CPAP Initiation and treatment				
Median (IQR) F_iO_2 % (n= 154)		50 (50-60)	60 (50-70)	<0.0001
Mean (SD) PEEP cmH_2O (n= 154)		10.4 (2.2)	11.4 (2.4)	0.01
An increase of PaO_2:FiO_2 ratio of at least 20% from oxygen therapy to CPAP, n (%)		53 (64.6)	33 (48.5)	0.047
An increase of PaO_2:FiO_2 ratio of at least 30% from oxygen therapy to CPAP, n (%)		51 (62.2)	27 (39.7)	0.006

Median (IQR) days of CPAP treatment (n= 153)	8 (5-14)	4 (3-7)	<0.0001
CPAP complications			
Pneumothorax n (%)	0 (0.0)	1 (1.4)	0.45
Pneumomediastinum, n (%)	0 (0.0)	2 (2.9)	0.20
Hemodynamic instability, n (%)	0 (0.0)	9 (12.9)	0.001
Intolerance*, n (%)	10 (11.5)	11 (15.7)	0.44
Ulcer, n (%)	2 (2.3)	0 (0.0)	0.50
Study Outcomes			
Weaning from CPAP to Oxygen therapy, n (%)	84 (96.6)	6 (8.6)	<0.0001
Median (IQR) days from CPAP initiation to weaning to Oxygen therapy (n= 87)	7 (4-12)	7 (1-8)	0.31
Intubation, n (%)	0 (0.0)	34 (48.6)	<0.0001
Median (IQR) days from CPAP initiation to intubation (n= 34)	-	3 (2-5)	-
Mortality in HDU, n (%)	0 (0.0)	36 (51.4)	<0.0001
Median (IQR) days from CPAP initiation to HDU mortality (n= 36)	-	5 (3-10)	-
Median (IQR) length of hospitalization (n= 138)	18 (14-25.5)	8 (4-22)	<0.0001
In-hospital mortality, n (%)	0 (0.0)	45 (64.3)	<0.0001
Median (IQR) days from CPAP initiation to in-hospital mortality (n= 45)	0 (0-0)	6 (4-11)	-

Footnotes: * Among them, 4 patients discontinued helmet CPAP. CPAP: continuous positive airway pressure; IQR: 25th-75th interquartile range; BMI: body mass index; COPD: chronic obstructive

pulmonary disease; SD: standard deviation; PEEP: positive end-expiratory pressure; PaO2: partial arterial pressure of oxygen; FiO2: fraction of inspired oxygen; HDU: high dependency unit