High flow nasal cannula combined with non-invasive ventilation *versus* high flow nasal cannula alone in patients with acute hypoxemic respiratory failure due to pneumonia: a randomized controlled trial

Leonardo Ghezzi,[1] Francesca Graziano,[2] Giulia Bottani,[3] Giulia Marullo,[4] Nicolò Capsoni,[1] Elisa Forni,[1] Fabrizio Vincenti,[1] Paola Rebora,[2] Andrea Bellone[1]

[1]Department of Emergency Medicine, Ospedale Niguarda, Milan; [2]Bicocca Bioinformatics, Biostatistics and Bioimaging Centre (B4), School of Medicine and Surgery, University of Milano-Bicocca, Milan; [3]Department of Emergency Medicine, Ospedale Maggiore, Lodi; [4]Department of Emergency Medicine, Ospedale San Raffaele, Milan, Italy

Correspondence: Leonardo Ghezzi, Department of Emergency Medicine, Ospedale Niguarda, Milan, Italy.
Tel.: +393393507372
E-mail: Leonardo.ghezzi88@gmail.com

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Abstract

Patients with hypoxemic respiratory failure due to community acquired pneumonia are actually treated with a wide range of oxygen devices from nasal cannula to mechanical ventilation. In this monocentric, open label, randomized controlled trial we aimed to compare the efficacy of combined High Flow Nasal Cannula (HFNC) and Non-Invasive Ventilation (NIV) versus HFNC alone in acute Hypoxemic Respiratory Failure (hARF) in patients affected by Community Acquired Pneumonia (CAP). We enrolled 49 patients affected by CAP with hypoxemic respiratory failure (PO2/FiO2 < 300). The patients were randomized into two groups: one has been treated with HFNC alone (group A) while the other received NIV alternated to HFNC every 3 hours (group B). The primary outcome was PO2/FiO2 change from baseline to 21 hours. Secondary outcomes included variation of pH and pCO2, need to continue HFNC or NIV/HFNC after 45 hours, orotracheal intubation, mortality rate, and device comfort. No statistically significant differences between the two arms were shown in PO2/FiO2 change at 21 hours since baseline, in pCO_2 and pH variation, mortality at hospital and at follow-up. Further research is needed to better understand the role of combined HFNC and NIV in hypoxemic respiratory failure in patients with CAP.

Introduction

Patients with hypoxemic respiratory failure due to community acquired pneumonia are usually treated with different devices: nasal cannula, venturi or reservoir masks, Continuous Positive Airway Pressure (CPAP), High Flow Nasal Cannula (HFNC), Non-Invasive Ventilation (NIV) or mechanical ventilation.[1-3]

HFNC has been developed initially for critically ill neonate and infantes,[4,5] however, in the last decade evidence suggested it is effective in diverse underlying conditions, such as hypoxemic respiratory failure, pre and post intubation, exacerbation of Chronic Obstructive Pulmonary Disease (COPD), sleep apnea, acute heart failure, and conditions entailing do-not-intubate orders.[6-8]

HFNC could alleviate symptoms of acute respiratory failure with different mechanisms: deadspace CO_2 washout, reduction of oxygen dilution (ensuring a more precise fraction of inspired oxygen, FiO_2) and produce a moderate positive airway pressure effect when mouth is closed.[9,10] Finally they seem to be very tolerable and comfortable[3] due to the heated and humidified inspired gases.[11]

We also know that non-invasive ventilation has been increas-

ingly used to reduce intubation rate in selected patients with acute respiratory failure. Compared to medical therapy it could improve survival rates and reduce complications associated with mechanical ventilation.[12,13] Nevertheless, in patients with pneumonia, NIV yielded inconsistent benefits with failure rates ranging from 25% and 66%.[14]

Currently, the role of HFNC and NIV in acute respiratory failure is debated.[2,12] NIV is proved as useful in hypercapnic respiratory failure while its efficacy in hypoxemic respiratory failure is uncertain.[3,15]

For this reason, we investigated a selected group of patients, the one with hypoxemic acute respiratory failure, to understand if they could become a specific therapeutic target for HFNC.

In particular, we conducted a randomized controlled trial to compare the efficacy of alternating HFNC and NIV (NIV/HFNC) versus HFNC in hypoxemic acute respiratory failure in patients affected by Community Acquired Pneumonia (CAP).

The primary aim of the study was to compare the growth of PO2/FiO2 (the ratio of arterial oxygen partial pressure expressed in mmHg and the fraction of inspired oxygen expressed as a decimal) in the two groups (NIV/HFNC vs HFNC) from baseline (T_0) to 21 hours. The secondary aims included the comparison between the two groups in term of pH and pCO2 variations, need of orotracheal intubation or to continue the respiratory supports after 45 hours, mortality rate after 30 days, and, finally, the comfort of the devices.

Materials and Methods

Study design and patients

We performed a monocentric, open label, randomized controlled trial (clinicaltrials.gov NCT03758508). We enrolled consecutive adult patients with confirmed CAP admitted at the Emergency Department (ED) of the ASST Grande Ospedale Metropolitano Niguarda between November 2017 and December 2019.

The criteria for eligibility were: ≥18 years, objectively confirmed community acquired pneumonia (CAP) and hypoxemic Acute Respiratory Failure (hARF) defined as the combination of a PO2/FiO2 ratio < 300 after 15 minutes of conventional oxygen delivered with a FiO2 at least of 50%, and a Respiratory Rate (RR) ≥ 25/min.

CAP was defined as the presence of at least two of the following criteria: i) clinical: fever, cough, purulent sputum; ii) laboratory: leukocytosis (WBC > 10 × 10^3/mL), leukopenia (WBC < 4 × 10^3/mL), C-reactive protein (PCR) and/or Procalcitonin (PCT) increase; iii) radiological: positive imaging for parenchymal thickening at Chest X-ray or CT scan.

Patients with one of the following characteristic were excluded: age < 18 years old, hypercapnic ARF (PaCO2 > 60 mmHg), ARF due to other aetiologies [thromboembolism, Acute Respiratory Distress Syndrome (ARDS), pulmonary edema], hemodynamic instability, Glasgow Coma Scale (GCS) < 8, device intolerance or respiratory arrest requiring immediate endotracheal intubation (ETI), immunodepression (congenital or acquired or due recent chemotherapy infusion), nocturnal CPAP use, a do not intubate order, and presence of other NIV contraindications.

The Ethical Committee approval was obtained (Number 03-022018). Written informed consent was obtained according to the local regulation.

Randomization and treatment

Eligible patients were randomly assigned with the use of a randomization tool (excel software) when the experimenter recognize the need of ventilation support for the respiratory failure. We randomized patients in one of the two groups (HFNC – group A or NIV/HFNC, group B) after 15 minutes of oxygenation with reservoir bag with 15 liters.

Patients assigned to group A were treated only with HFNC. Patients assigned to group B received a treatment with NIV alternated to HFNC with time lapses of three hours according to the scheme depicted in Figure 1. In both groups the treatment lasted at least 45 hours.

In both groups, HFNC were set with an initial FiO2 > 50% and a gas flow of 50 L/min than titrated to obtain peripheral oxygen saturation (SpO2) > 90%. The temperature of the humidification chamber was set at 37°C. In group B, NIV parameters (PEEP and PS) were set by the clinician in charge to better adapt the patient to the ventilator, using a target of 6 ml/kg tidal volume, with a minimum PEEP of 5 cmH_2O.

Both oronasal and full face masks were used, chosen according to the patient's anatomy and preference. We used Fisher Paykel nasal cannulas and Monnal T75 or Turbine driven Vela ventilator. The NIV interfaces have been chosen time after time from the experimenter according to the facial features to reduce the leaks.

Data collection and end-point assessment

Data about patients' demographic, comorbidities, pneumonia characteristics (focal, lobar, multifocal, intertitial, associated with pleural effusion), Pneumonia Severity Index (PSI), microbiological samples when performed (nasal swab, haemocultures and urine antigen) and empiric antimicrobial therapy were also collected.

Arterial blood gas analysis was collected in 4 different moments (T_0, T_1, T_{21}, T_{45}) to value the gas exchange over time. Blood tests were collected at T_1 and T_{21} to evaluate WBC count, PCR, PCT, renal and liver functions and assess multiorgan dysfunction.

Information about the need to continue HFNC or NIV/HFNC after 45 hours from the beginning of the treatment, ETI rate, 30 days mortality (evaluated by phone call if the patient was previously discharged) were also collected.

The patient's comfort was evaluated (T_1, T_{21}, T_{45}) using a scale with 5 points (from 1 not tolerated to 5 very well tolerated).

The primary end-point was the change of PO2/FiO2 from T_o to T_{21}. Secondary end-points included: change in PO2/FiO2 up to 45 hours, change in PH, pCO2 after randomization, ICU admission time and inpatient mortality, the weaning time, 30-days overall survival, rehospitalization time and comfort of the device and breathlessness.

Sample size

Assuming a mean value of 150 PO2/FiO2 (at recruitment, T_0), we estimated that a sample size of 56 patients per arm would be able to show a difference of 35 points (standard deviation, sd, 65) in the variation of PO2/FiO2 21 hours after recruitment (T_{21}- T_0) between the groups HFNC and NIV/HFNC with a 80% power (type I error 0.05, two-sided test). Considering a possible lost to follow-up and potential missing values of about 12.5%, we aimed to recruit 64 (56/0.875) patients per arm.

Due to the COVID-19 pandemic we had to interrupt recruitment when a total of 46 patients were randomized (26 were allocated in group A and 20 in group B).

Statistical analysis

Baseline patient's characteristics and clinical outcomes were expressed by mean (standard deviation), median (I-III quartile) and frequency (%), where appropriate.

The primary end-point was assessed by Student's t-test with an intention-to-treat approach. Mean changes of PO2/FiO2 at T_1, T_{21}, T_{45} from T_0 were compared by Student's t-test.

A linear mixed-effect longitudinal model was used to evaluate the trend over time of PO2/FiO2 in the two groups. In particular time was included as a continuous variable and the interaction term between treatment and time was used to evaluate the difference between the two groups. The patient was included as random effect to account for intra-subjects' variability. Similar analyses were performed for the secondary endpoints (PH and PCO_2).

Per protocol analyses including only patients who completed the treatment originally allocated, was also conducted for the primary outcome.

The percentage of patients admitted to ICU or intubated were compared among the two arms using a chi-squared test.

Overall survival was defined as the time between recruitment and death from any cause. Follow-up of all patients was updated 30 days after recruitment. The 30-day mortality in the two arms

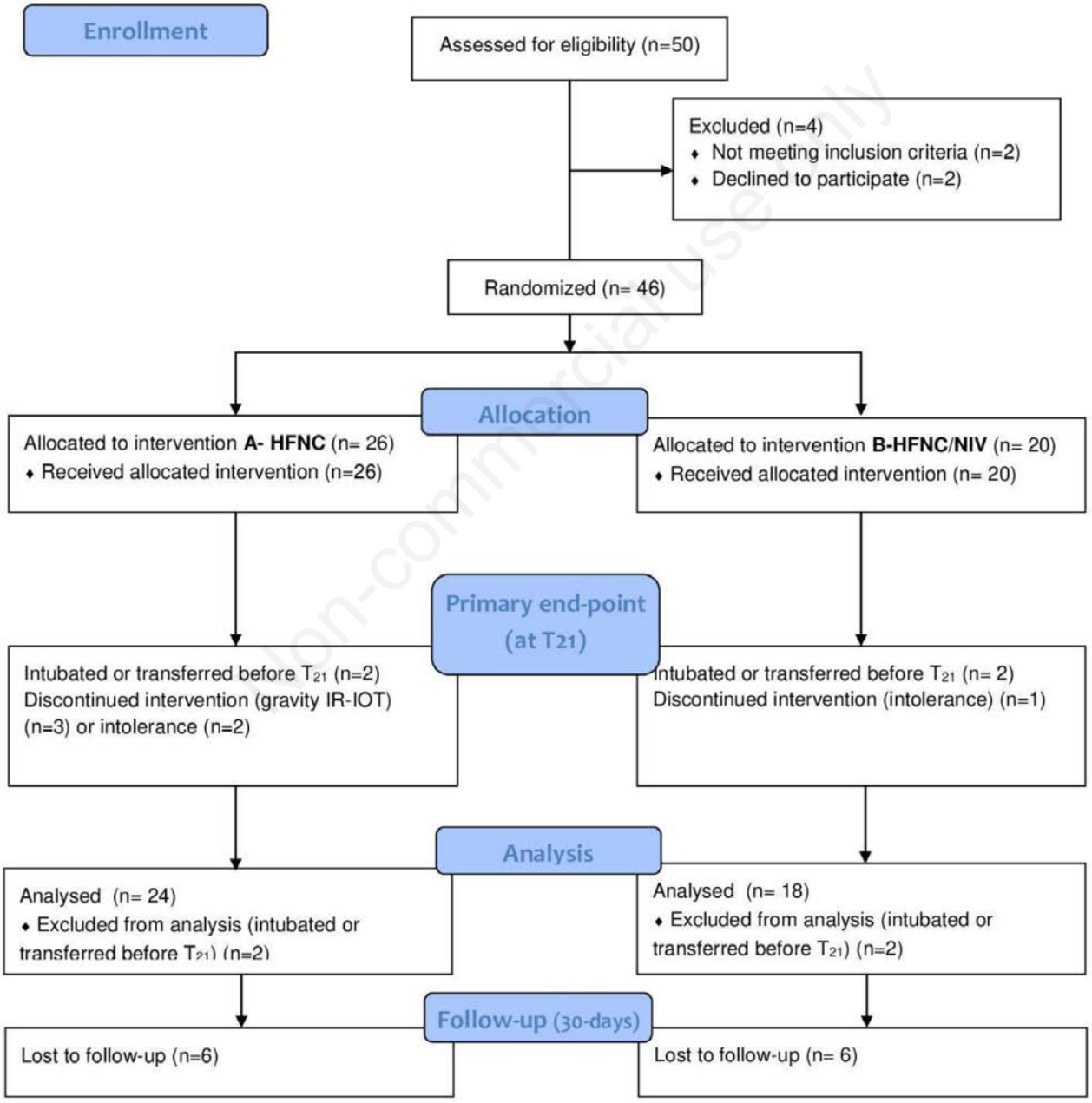

Figure 1. CONSORT flow-chart of the study.

was compared by log-rank test. All analyses were performed using R 3.6.3 (http://www.R-project.org).

Results

Patient characteristics

From November 2017 to December 2019 50 patients with CAP were enrolled at the Emergency Department (ED). Four patients have been excluded and the reasons for excluding them were lack of informed consent, and failure to meet inclusion criteria. Finally, 46 patients have been randomized in the two arms: 26 patients were allocated to arm A (HFNC) and 20 to arm B (HFNC/NIV). The CONSORT flow-chart is reported in Figure 1.

The median age was 73.5 years (min-max: 50-90 years old), and 50% were male. The major comorbidities were diabetes (12 patients, 26.1%), health failure (17.4%) and about 19% had a previous myocardial infarction (Table 1). As shown in Table 1, the study groups had similar characteristics at baseline.

Baseline pneumonia features, vital signs and emogas blood sample

The majority of patients presented a community acquired pneumonia (97%) and just one patient has been classified as hospital acquired pneumonia. 19 patients (43.2%) had a multifocal

Table 1. Baseline characteristics of patients.

	A (N=26)	B (N=20)	Total (N=46)
Demographic Characteristics			
Age (Median, I-III Quartile), Year	75 (64.25, 79)	69.50 (63.25, 77.25)	73.5 (64-79)
Gender (Male, N%)	13 (50.0)	10 (50.0)	23 (50.0)
Comorbidities			
Diabetes, N(%)	6 (23)	6 (30)	12 (26.1)
Liver Disfunction, N(%)	4 (15.38)	3 (15)	7 (15.19)
Malignancies, N(%)	2 (7.69)	2 (10.0)	4 (8.69)
Renal Failure, N(%)	4 (15.4)	2 (10.0)	6 (13.0)
Heart Failure, N(%)	2 (7.7)	6 (30.0)	8 (17.4)
Myocardial Infarction, N(%)	5 (19.2)	4 (20.0)	9 (19.6)
Bpco, N(%)	0 (0.0)	1 (5.0)	1 (2.2)
Cerebral Vasculopathy, N(%)	4 (15.4)	1 (5.0)	5 (10.9)
Dementia, N(%)	3 (11.5)	0 (0.0)	3 (6.5)
Cci, Median (I-III Quartiles)	5 (3.25- 6)	4 (4- 5.25)	4.5 (4.0-6.0)
Pulmunary Embolism, N(%)	1 (3.8)	0 (0.0)	1 (2.2)
Emodinamic Instability, N(%)	1 (3.8)	0 (0.0)	1 (2.2)
Immunocompromised, N(%)	0 (0.0)	1 (0.5)	1 (0.25)
Pneumonia Features			
Focal, N(%)	8 (20.0)	13 (36.8)	12 (27.3)
Interstitial, N(%)	4 (16.0)	0 (0.0)	4 (9.1)
Lobar, N(%)	3 (12.0)	6 (31.6)	9 (20.5)
Multifocal, N(%)	13 (52.0)	6 (31.6)	19 (43.2)
Psi Mean (Mean, SD)	129.19 (29.63)	135.70 (22.00)	132.02 (26.51)
Vital Signs			
Sistolic Blood Pressure (Mean, SD), mmHg	120.88 (22.61)	133.15 (30.86)	126.33 (26.98)
Diastolic Blood Pressure (Mean, SD), mmHg	65.00 (11.99)	73.80 (15.26)	68.91 (14.09)
Heart Rate, bpm (Mean, SD)	91.08 (28.03)	107.35 (17.32)	98.31 (25.00)
Respiratory Rate (Mean, SD), brpm	29.32 (5.63)	31.65 (5.91)	30.36 (5.81)
Temperature (Mean, SD)	37.51 (0.97)	37.28 (0.91)	37.43 (0.94)
Emogas blood sample at baseline			
Ph (Median, I-III Quartile)	7.44 (7.41, 7.48)	7.45 (7.42, 7.48)	7.44 (7.42, 7.48)
Pco2mmhg (Median,I-III Quartile)	32 (29, 35.75)	33 (30, 40.30)	32 (30, 39.80)
Hco3 Mmol/L (Median, I-III Quartile)	23 (21, 24)	23 (21, 25)	23 (21, 24.25)
Po2/Fio2 (Mean,SD)	152.77 (51.59)	179.81 (67.24)	164.18 (59.53)

BPCO, chronic obstructive pulmonary disease; PSI, Pneumonia Severity Index; CCI, Charlson Comorbidity Index; SD, standard deviation; mmHg, millimetre of mercury; bpm, beats per minute; brpm, breaths per minute; Mmol/L, millimoles/liter.

pneumonia, 12 (27.3%) a focal pneumonia, 9 (20.5%) a lobar one and 4 (9%) has been found with an interstitial pneumonia. The severity of the pneumonia with the Pneumonia Severity Index (PSI) was respectively 129.2 for the A group and 135.7 in the B group (Table 1). In 30% of the cases patients has a pleural effusion and just 10 patients received the thorax TC scan.

In 44% of cases, we identified pathogens, generally bacteria. In particular, the most frequently isolated germ was *Streptococcus Peumonae* (8 of 45), predominantly found using urinary antigens. Legionella has been identified in 3 patients. Furthermore, they have been one Mycoplasma, one *Pseudmonas Aeruginosa* e one Enterococcus. Other isolation has been Adenoviruses, H1N1 and Type B Respiratory Sincitial Virus.

We did not find relevant variations about the vital signs in the two groups. In particular, both presented with high respiratory rate around 30 records per minute (Table 1).

Both groups had a mild respiratory alkalosis (pH 7.44 vs 7.45) with PaCO2 and HCO3 level similar (Table 1). Finally, the mean of PO2/FiO2 at baseline were 152.8 (group A) vs 179.8 (group B), respectively.

Primary outcome

The Figure 2 (panel A) shows the PO2/FiO2 distribution at the different time points in the two treatment arms. The PO2/FiO2 values were slightly unbalanced at randomization in favor of group B and remained quite stable in the following 21 hours. Among the two groups a similar average growth (T_{21}-T_0) was found (3, sd=70, points in group A vs 2, sd=86, in group B, p-value =0.9792). After 45 hours the PO2/FiO2 differences increased (78 points in group B vs 18 in group A, p-value= 0.0639), but this is based on a lower number of subjects (Table 2).

Per-protocol analysis

A total of 17 (37.0%) patients changed treatment since randomization. Of whom, 6 patients switched group before 21h since randomization: in particular, 5 patients from group A and 1 from group B. The reasons were gravity IR-IOT or intolerance.

When we excluded the 6 patients that switched arm before 21h since randomization, we obtained consistent results (17.8, sd=63.2, points in group A vs 11.8, sd=77.8, in group B, p-value =0.8028).

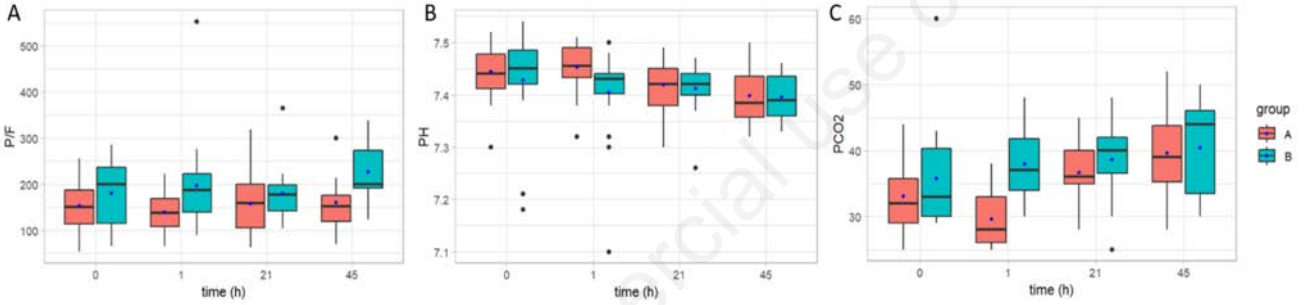

Figure 2. Boxplot of PO2/FiO2 (panel A) and the secondary outcomes (PH and PC02, panel B and C) over time. The upper and lower sides of the box are the I and III quartiles; the horizontal line represents the median and the mean is indicated as a blue dot. Outlier points are defined as those distant more than 1.5*interquartile (III quartile – I quartiles) and plot as a black dot.

Table 2. Results on primary and secondary end-points: PO2/FiO2, PH and PCO2 changes in time among group A and B

Time	N	NA	NB	Group A	Group B	Difference of B-A (95% CI)	p-value
			PO2/FiO2 Mean (SD) of change from baseline (T0)				
T_1- T_0	33[#]	16	17	-6 (47)	17 (93)	23 (-29 to 76)	0.3636
T_{21} – T_0	42	24	18	3 (70)	2 (86)	-0.648 (-51 to 50)	0.9792
T_{45} – T_0	17	10	7	18 (49)	78 (66)	61 (-4 to 126)	0.0639
			Secondary Outcomes Mean (SD) of change from baseline (T0)				
			PH				
Time	N	NA	NB	Group A	Group B	Difference of B-A (95%CI)	p-value
T_1- T_0	33[#]	16	17	0.0063 (0.031)	-0.0129 (0.041)	0.0191 (-0.007 to 0.0449)	0.1385
T_{21} – T_0	33	17	16	-0.0305 (0.0537)	-0.008 (0.068)	-0.0225 (-0.067to 0.0221)	0.3089
T_{45} – T_0	17	10	7	-0.0490 (0.0486)	0.025 (0.088)	-0.0747 (-0.157to 0.0085)	0.0727
			PCO2				
Time	N	NA	NB	Group A	Group B	Difference of B-A (95%CI)	p-value
T_1- T_0	33[#]	16	17	-2.55 (5.68)	1.612 (5.20)	-4.161 (-8.042 to -0.280)	0.03643
T_{21} – T_0	33	17	16	3.135 (6.970)	2.507 (6.83)	0.629 (-4.364 to 5.621)	0.7988
T_{45} – T_0	17	10	7	5.82 (5.93)	-0.514 (7.911)	6.334 (-1.475 to 14.143)	0.1014

[#]one patients had not PO2/FiO2 measure at T0. CI = confidence interval.

Secondary outcomes

PH and PCo2

Regarding the secondary outcomes, distributions of PH and PCo2 over time and between groups were shown in Figure 2, panel B and C. No statistically significant differences between the two arms were shown (Table 3), except for a higher increment of PCO2 in group B (1.612, sd=5.2) versus group A (-2.55, sd=5.68, p-value=0.0364) at T_1 from T_0.

Considering the linear mixed models, the interaction term was significant only for PH (p=0.0133); not significant for PCO_2 outcome (p=0.1042).

Hospitalization and mortality

A total of 8 patients were admitted in ICU (Intensive Care Unit): 4 in each group, among them 2 were intubated in group A and 3 in group B. Approximately 40% of patients need to continue NIV or HFNC for more than 45 hours with no differences between the two groups.

After 30-day follow-up, 5 of 46 patients died (cumulative 30-day incidence 16.7%, 95%CI 2.2-29), of whom 4 patients died in hospital (8.7%). No differences between the two groups were found both in mortality at hospital and at follow-up (Table 3).

Comfort of the device

No difference at each time point was shown between the two groups on the scale of comfort, even when the scale was dichotomized in not and poorly tolerated versus discrete to very well tolerated (Table 2).

Discussion

This is one of the first controlled randomized study evaluating the role of HFNC and NIV in patients with acute respiratory failure due to pneumonia.

Unfortunately, the COVID-19 pandemic had an impact on this clinical trial. The recruitment was interrupted, and the study failed to reach the estimated sample size of 112 patients. In this randomized, open-label trial, no statistically differences were found in the variation of PO_2/FiO_2 ratio after 21 hours from baseline between the two groups.

Considering the PO_2/FiO_2 ratio at 45 hours from baseline, the mean of change showed a difference in favor of group B.

We have found that both treatments were well tolerated; on the opposite, we showed a switch of six patients of group B towards to group A because of a face-mask poor tolerance. These preliminary results elicit that HFNC is a strategy providing good comfort through warmed and humidified gas flow delivered via nasal prongs.[10,11,16] The better modality of improving oxygenation is oxygen itself but severe hypoxemia due to pneumonia is mainly secondary to a shunt effect whereas oxygen is often not useful.[17] It is well known that HFNC can generate a low level of PEEP by a high flow of gas.[18,19] Moreover, the level of PEEP generated by HFNC could be reduced by the nasal prongs diameter and when patients open their mouth.[18] It's very likely that in severe pneumonia the need of PEEP level could be higher than 5 cmH_2O. According to our daily experience we can speculate that the ideal PEEP is between 8 to 12 cmH_2O in order to optimize alveolar recruitment and to increase functional residual capacity.[7,20] In addition to PEEP, ventilatory support through Pressure Support (PS) can increase lung volumes, prevent atelectatic/consolidated units and can be applied when venous admixture exceed 30%. These physiological assumptions, at the basis of our study, are well shown by previous results.[21]

In our experience the severity of pneumonia and respiratory failure can differentiate the use of HFNC: in severe acute respiratory failure with respiratory distress, it is reasonable to apply HFNC during rest time from recurrent NIV cycles; conversely, HFNC only can be used when respiratory failure is less severe. This modality to integrate NIV with HFNC may represent the best possible treatment because it takes advantage of the benefits of both techniques: PS and ideal PEEP through NIV and the best tolerance through HFNC. However, this is drawn from bedside experience but more research is needed to assess this matter.

In a previous paper of Frat *et al.*,[22] intubation rate was similar in the HFNC group compared with noninvasive ventilation group but there was a significant difference in favor of high-flow oxygen in 90-day mortality compared with noninvasive ventilation in acute hypoxemic respiratory failure patients. In that study the level of pressure-support was of 8 cmH20 and PEEP was of 5 cm H_20. Even in our study we did not find differences in intubation rate in the two groups.

The limits of our study are many. The first limit was the need to interrupt enrollment because of the beginning of COVID-19 pandemic. We had to modify our organization and change the mission of our emergency medicine ward in order to treat acute COVID patients. Given the small size of the sample compared to the estimated one, it was not possible to obtain robust results. Secondly our study was monocentric.

In conclusion, despite the limits of the study, the results could be very interesting since they focus attention on the need of HFNC alone or the combination of HFNC with NIV in severe respiratory failure due to pneumonia. Our data suggest the importance of com-

Table 3. Hospitalization and mortality.

n At hospital	Overall 46	Group A 26	Group B 20	p-value
Admitted to the intensive care unit (ICU), n (%)	8 (19.5)	4 (17.4)	4 (22.2)	1.000
Need of orotracheal Intubation in ICU	5 (62.5)	2 (50.0)	3 (75.0)	1.000
NIMV or HFNC more than 45h, n (%)	18 (43.9)	11 (47.8)	7 (38.9)	0.799
At hospital mortality, n (%)	4 (8.7)	4 (15.4)	0 (0.0)	0.191
At follow-up (30 days)	**30**	**18**	**12**	
Mortality at follow-up (30 days) since randomization, n (%)	5 (16.7)	4 (22.2)	1 (8.3)	0.300
Hospitalization, n (%)	3 (10.0)	1 (5.6)	2 (16.7)	0.709

bined HFNC with NIV as a first step for severe pneumonia treatment whereas HFNC might represent as the first step treatment in less severe patients and during the NIV intervals.

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