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Research Article

Early Use of Non-invasive Mechanical Ventilation and Invasive Mechanical Ventilation in Severe Influenza Virus Pneumonia in an Intensive Care Unit: Period 2009-2018

Alberto Belenguer-Muncharaz[1,2]*, Irina Hermosilla-Semikina[1] and Francisco Bernal-Julián[1]

[1]*Intensive Care Unit, Hospital General Universitario de Castelló, Castellón, Spain*

[2]*Pre-Departmental Unit of Medicine, School of Health Sciences, Jaume I University (UJI), Spain*

***Corresponding Author:** Alberto Belenguer-Muncharaz, Intensive Care Unit, Doctor Peset Alberto Belenguer-Muncharaz, Intensive Care Unit, Doctor Peset University Hospital, Valencia, Spain.

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Abstract

Introduction: In hypoxaemic acute respiratory failure (ARF) due to influenza viral pneumonia, a high percentage of subjects admitted to the intensive care unit (ICU) require ventilatory support. Invasive mechanical ventilation (IMV) is the most commonly used ventilatory intervention, compared to non-invasive ventilation (NIV). NIV is not indicated in patients with hypoxaemic ARF.

Aim: To analyse the benefit of the use of NIV and IMV, determining mortality and complications such as the need for tracheotomy, duration of ventilatory support, length of stay at the ICU and in hospital, and mortality at the ICU, in hospital and after 6 months. Within the NIV group, we analysed the need for intubation, side effects associated with NIV, and NIV failure related factors.

Patients and Methods: Cohort of subjects admitted during the period 2009 - 2018 to a medical-surgical ICU for Influenza virus pneumonia. Thirty-three (92%) received NIV (continuous positive airway pressure and NIV) and three (8%) received IMV.

Results: Applying propensity score, IMV showed no negative influence on mortality with respect to NIV [OR 4.6 (IC 95% 0.059 - 358.320, p = 0.492)]. The NIV failure rate was 10 (31%) subjects. The main side effects observed during NIV were noise, claustrophobia and dryness of mucosa. In the NIV failure, the SAPS 3 and SOFA on admission and 5-day were higher to the NIV success [60 ± 14 vs 44 ± 13, p < 0.01], [4 (4 - 5) vs 3 (3 - 4), p = 0.001] and [8 (7 - 10) vs 4 (3 - 5), p = 0.001], respectively. Meanwhile, the lenght of stay at ICU and hospital, and mortality were higher in the NIV failure group. The main related factor to the failure of NIV was SOFA at admission > 5 [OR 1.9 (CI 95% 1.270 - 2.870), p = 0.005]. There was no contagion in the healthcare staff.

Conclusion: NIV was widely used with a high success rate. Mortality was not increased by IMV. Organ failure upon admission should make us consider the need for direct use of IMV.

Keywords: *Influenza Virus; Pneumonia; Acute Respiratory Failure; Non-Invasive Ventilation; Invasive Mechanical Ventilation*

Introduction

From the 2009 Influenza A (H1N1) virus outbreak [1-6] to the recent coronavirus epidemic in China [7], viral infections are a challenge for health systems. In the H1N1 Influenza epidemic in 2009, between 10 and 30% of hospitalized patients required admission to Intensive Care Unit (ICU) [8]. The main cause of admission was severe hypoxemic acute respiratory failure (ARF), due to a required need for ventilatory support (between 71.8% to 93%) [1,3-6]. Invasive mechanical ventilation (IMV) was the most commonly used as a ventilatory support technique (76.2%) [1-3,5,9,10].

Furthermore non-invasive ventilation (NIV) is not indicated in hypoxemic ARF [11]. Specifically, in the outbreak due to Influenza A H1N1 virus, a recommendation for non-use of NIV was established by various scientific societies, given the limited benefit of NIV in patients with acute respiratory distress syndrome (ARDS) and the risk of infection of healthcare workers with the aerosolization of these devices [6,12]. In this regard, in different series published, the use of NIV was scarce and with high failure rate (between 60% to 85%) [1,3,4,6,9]. Only small series showed rates of NIV failure lower than those published [13-15]. In a review, the authors concluded that NIV was useful in the early phase of ARF for influenza A infection; although, its use was not recommended in case of development of ARDS [16].

In the present study we analyzed the benefit of using NIV and IMV during the period 2009 - 2018, in our cohort of patients admitted to ICU with hypoxemic ARF due to influenza virus pneumonia. The primary outcome was to compare mortality between NIV and IMV. As secondary outocomes, we analyzed complications such as need for tracheotomy, duration of ventilatory support, ICU and hospital stay, mortality in ICU, hospital and at 6 month. Within the NIV group we also analyzed: need for intubation, side effects associated with NIV, as well as factors related to NIV failure.

Material and Methods

A retrospective study was conducted in a medical-surgical ICU of a third level hospital, following a previous study [13]. The study was approved by the Clinical Research Ethics Committee of the research center and, given the characteristics of the study, informed consent was not requested.

Subjects aged 18 years or older admitted to the unit from 2009 to 2018 with suspected severe Influenza virus pneumonia were included [17]. Initially the study focused on subjects with influenza A H1N1 infection, but given the variation in the different types of influenza virus causing pneumonia (A, A H1N1, B, A/B) and the technical impossibility of the Microbiology laboratory to identify the different subtypes of the virus, the objective of the study was extended to all subjects with severe Influenza virus pneumonia. Patients with fever (> 38ºC) accompanied by flu-like symptoms (cough, myalgia, sore throat) along with hypoxemic ARF, estimated by the need for inspired oxygen fraction (FiO_2) ≥ 0.5 through venturi type mask to achieve transcutaneous oxygen saturation (SaO_2) ≥ 92%, were admitted to the ICU. On admission, nasalpharyngeal-swab were collected (for antigen determination) and subsequent determination of polymerase chain reaction (PCR), in case of negative results and high diagnostic suspicion [4]. Primary viral pneumonia was defined as Influenza virus infection accompanied by ARF and the presence of alveolar opacification in the chest x-ray and negative bacterial cultures. Secondary bacterial pneumonia (coinfection) was defined as Influenza virus infection along with clinical signs of bacterial infection (fever, cough, purulent sputum and positive bacterial cultures (respiratory, blood or urine antigens). Pneumonia was considered as severe if it met the criteria established by the ATS/IDSA [18]. Subjects with chronic respiratory disease (exacerbation of chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, hypoventilation-obesity disease) [9,12] or those with previous prolonged hospital stay (>15 days) for another pathology and no criteria at ICU admission of primary or secondary pneumonia were excluded from the study.

Monitoring

On subject admission, arterial and central venous catheter were used for hemodynamic monitoring. Respiratory monitoring consisted of determining respiratory rate (RR) and SaO^2 through the Nellcor II D-25 Pulse Oximeter (Nellcor® Puritan BennetInc, Decasanton, CA, USA). Arterial gas blood samples were processed in ABL560 cooximeter (Radiometer MedicalA/S®, Copenhagen, Denmark).

The sputum, urine (antigen for *Pneumococcus* and *Legionella*) and blood culture samples were processed to identify infections causing pneumonia. Also demographic data, comorbidities, date of hospital and ICU admission, hemodynamic, respiratory and gasometrical parameters, number of affected quadrants on chest x-ray, and type of ventilatory support applied were collected. Number of organ failure through the Sequential Organ Failure Assessment (SOFA) score upon admission, and mortality estimation through Simplified Acute Phisiology Score (SAPS) 3 during the first 24 hours, were calculated. Complications produced during the stay in the unit were collected, such as: orotracheal intubation, reintubation, need for trachetomy, 5-day organ failure (measured by SOFA scale), cardiorespiratory

arrest, evolution to acute respiratory distress syndrome (ARDS) [19], transfer to extracorporeal membrane oxygenation (ECMO) center and mortality (in ICU, hospital and at 6 months). The duration of mechanical ventilation, the length of stay in the ICU and the hospital were calculated. The side effects associated with the use of NIV (claustrophobia, aerophagia, insomnia, headache, environmental noise, otitis) and the possibility of transmission of the infection to healthcare workers were recorded. And finallly, ICU, hospital and 6-moth mortality were registred.

Non-invasive ventilation protocol. Continuous positive airway pressure (CPAP) systems and BiPAP Vision and V60 (Respironics Inc®, Pennsylvania, USA) were used. The procedure was explained to the patient while in a semi-recumbent position. The interface was selected according to the patient's anatomy and subsequent adjustment by straps by members of the staff. The CPAP systems used were the CPAP-Whisperflow™ (Caradyne, Ireland) and the CPAP-Boussignac™ (Vygon, Ecouen, France.). The CPAP-WhisperFlow™ (Caradyne, Ireland) is a device capable of delivering a flow of 140 L/min. The interface used was a Dimar™ Helmet (Medolla, Italy) where was connected a positive end-expiratory pressure (PEEP) resistor valve (RespironicsInc™, Pennsylvania, USA).

CPAP-Boussignac™ (Vygon, Ecouen, France) produces a virtual PEEP (like a turbine), generated by the confluence of four high-flow oxygen and air jets. In both CPAP systems, the levels of the inspired fraction of oxygen (FiO_2) and PEEP varied, between 0.5 - 1.0 and 5 - 20 cmH_20, respectively. The BiPAP Vision and BiPAP V60 (Respironics™Inc, Pennsylvania, USA) were connected to heated humidification system (MR850, Fischer and Payckel, Auckland, New Zealand) through circuit tubing.

Oronasal masks (RespironicsInc., Murrysville, PA, USA), or facial masks (Total Face® and Perfor Max®) (RespironicsInc., Murrysville, PA, USA), respectively, were used throughout the ventilatory process. Once adapted, the mask was fitted to the patient with straps. The ventilatory procedure [20] consisted of the initial setting of an inspiratory positive airway pressure level (IPAP) of 10 - 15 cmH_20 and an expiratory positive airway pressure (EPAP) of 5 - 6 cmH_20, respectively, with the aim of achieving volumes of 5 - 7 ml/kg, RR of 25 - 28 breaths/minute and clinical improvement (decrease in dyspnea, respiratory and heart rate and improvement in patient-respiratory synchrony). Minimum FiO_2 was applied to achieve a SaO_2 of 92 - 94%. NIV was continuously maintained except for hygiene or hydration. Once these objectives were obtained, and the process leading to ARF was being resolved, the support was gradually reduced until it was completely removed, changing to a venturi type mask with FiO_2 0.4 - 0.5 or a high flow oxygen therapy (HFOT). NIV failure was considered, and intubation was performed, if any of the following conditions were present [20]: intolerance to NIV, agitation, lack of clinical improvement (RR > 40 breaths/minute, use of accessory muscles, thoraco-abdominal asyncrony) or worsening of oxygenation (decrease in paO_2/FiO_2), hemodynamic instability (dopamine > 15 µgr/kg/min or noradrenaline > 0.4 µgr/kg/min), increased $paCO_2$ or decreased pH, and finally, the need for urgent intubation to isolate the airway. NIV success was considered to the absence of the need for intubation in view of the patient's clinical-gasometric improvement.

Invasive mechanical ventilation

Subjects were sedated with propofol or midazolam and analgesiated with morphine prior to intubation, along with muscle relaxants, in case of poor adaptation to the ventilator. Initial ventilatory settings were [21]: volume-assisted mode, tidal volume (Vt) of 8 - 10 ml/kg, RR of 12 - 14 breaths/min, minimum initial PEEP of 5 cmH_20, to obtain a plateau pressure of < 30 cmH_20. FiO_2 and PEEP were adjusted to obtain SaO_2 between 92 - 94%. The ventilatory settings were modified in case of evolution to ARDS [22]: Vt < 6 - 7 ml/kg, Plateau pressure < 30cmH_20. PEEP and FiO_2 parameters were adjusted to achieve a SaO_2 of 92 - 94%. The weaning process of the IMV was carried out after clinical and gasometric stabilization of the subject, and improvement of the process that led to IMV. Extubation was perfomed after a successful spontaneous breathing trial using a T-tube. All changes made to the types of ventilation, the intubation process, or withdrawal of mechanical ventilation and subsequent extubation were carried out by the attending physician.

Once the subject was admitted to the unit, he or she was isolated in closed boxes, and all healthcare workers in charge entered the box with the isolation measures established by the Hospital Committee for the Control of the Epidemic (gloves, gown, cap and N95 mask). Data on admitted subjects were included in the National Influenza A Registry promoted by the Infectious Diseases Working Group (GTEI) of SEMICYUC [6,9].

Statistical analysis

T-Student or U-Mann Whitney was used to compare the groups in terms of quantitative variables, according to parametric or non-parametric distribution. For qualitative variables the Chi-square test was used (with Fisher's exact test). Given the retrospective characteristics of the study and in order to avoid biases produced by the inclusion of subjects in the NIV or IMV group, propensity score was applied by means of multiple regression for mortality analysis between NIV and IMV. Considering the small number of subjects, the covariate included in the multiple regression (enter method) to create the propensity score was SAPS 3 > 70, which was significant in univariate analysis. For the determination of factors related to NIV failure by OR at 95% confidence interval (95% CI), we selected SOFA > 5 [10], which was also significant in univariate analysis. It was considered statistically significant when $p < 0.05$. The statistical package SPSS 22.0 was used for the analysis.

Results

Of a total of 238 subjects admitted to the hospital for viral pneumonia, 62 were admitted to the ICU (Figure 1), with three clearly established incident peaks and winter predominance (Figure 2). After excluding subjects with decompensated chronic pulmonary disease or long hospital stays due to another illness, an analysis was performed on 36 subjects with hypoxaemic ARF due to viral pneumonia, and who required ventilatory support (33 in NIV and 3 in IMV). Overall, they were middle-aged men with low levels of comorbidity, mostly from the Emergency Department, with primary viral pneumonia. Upon admission, they presented with organ failure estimated by SOFA score [4 (3 - 5)], in which respiratory failure predominated, as can be seen in the high percentage of subjects with significant radiological involvement (36% had radiological involvement in ¾ quadrants in chest x-ray) and the level of hypoxaemia (Table 1).

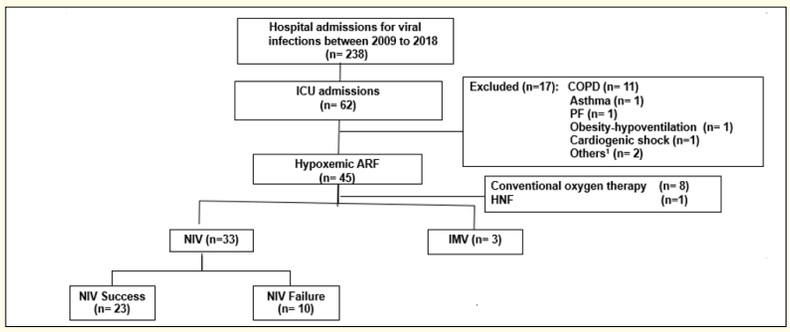

Figure 1*: Flow Diagram*

1: Previous hospital admission (> 15 length of stay at hospital) days because of bacteraemia in a haematological subject and decompensated in a liver cirrhosis subject

ARF: Acute Respiratory Failure; ICU: Intensive Care Unit; COPD: Chronic Obstructive Pulmonary Disease; PF: Pulmonary fibrosis; HNF: High-Oxygen Nasal Flow; NIV: Non-Invasive Ventilation; IMV: Invasive Mechanical Ventilation.

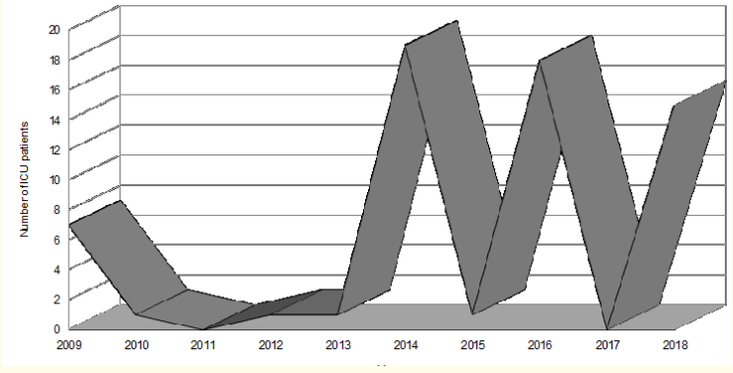

Figure 2: *Evolution of ICU admissions.*

	Global (n = 36)	NIV (n = 33)	NIV success (n = 23)	NIV failure (n = 10)	IMV (n = 3)
Sex, male n (%)	20 (56)	20 (61)	15 (65)	5 (50)	0 (0)
Age, years	56 ± 15	54 ± 15	55 ± 17	52 ± 14	70 ± 11
BMI, kg/m^2	29 ± 4	29 ± 4	29 ± 4	28 ± 3	30 ± 0.2
SAPS 3	51 ± 16	49 ± 15	44 ± 13	60 ± 14[c]	72 ± 22[a]
SOFA at ICU admission[e]	4 (3 - 5)	4 (3 - 4)	3 (3 - 4)	4 (4 - 5) [d]	5 (4 - 6)
SOFA 5-day after admission[e]	4 (3 - 8)	4 (3 - 8)	4 (3 - 5)	8 (7 -10) [d]	10 (7- 11)
Comorbidities					
Hypertension, n (%)	12 (33)	11 (33)	9 (39)	2 (20)	1 (33.3)
Diabetes mellitus, n (%)	6 (17)	5 (15)	3 (13)	2 (20)	1 (33.3)
Haematological disease, n (%)	4 (11)	4 (12)	2 (9)	2 (20)	0 (0)
Alcoholism, n (%)	1 (3)	1 (6)	0 (0)	1 (10)	0 (0)
Smoking, n (%)	12 (33)	12 (36)	8 (35)	4 (40)	0 (0)
Setting					
Emergency Room, n (%)	22 (61)	19 (58)	15 (65)	4 (40)	3 (100)
Ward, n (%)	11 (31)	11 (33)	6 (26)	5 (50)	0 (0)
Other Hospital, n (%)	3 (8)	3 (9)	2 (9)	1 (10)	0 (0)
Number of Rx quadrants, n (%)					
1/4	9 (25)	8 (24)	7 (30)	1 (10)	1 (33.3)
2/4	7 (19)	7 (21)	3 (13)	4 (40)	0 (0)
3/4	13 (36)	12 (36)	8 (35)	4 (40)	1 (33.3)
4/4	7 (19)	6 (18)	5 (22)	1 (10)	1 (33.3)
Cause of pneumonia					
Primary viral pneumonia[f]	29 (81)	27 (82)	19 (83)	8 (80)	2 (67)
Secondary pneumococcial pneumonia[g]	7 (19)	6 (18)	4 (17)	2 (20)	1 (33)
Hospital to ICU admission[e], h	4 (2 - 36)	4 (2 -37)	3 (2 -36)	7 (3 -82)	2 (1 -2)
Time from hospital admission to start of NIV[e], h	-	7 (3 - 38)	5 (3 - 37)	16 (4 - 82)	-
Time from ARF to onset of NIV[e], h	-	7 (3 - 25)	5 (2 - 10)	25 (6 - 44) [h]	-
Parameters at ICU admission					
Median blood pressure, mmHg	89 ± 17	89 ± 15	91 ± 16	86 ± 14	90 ± 19
Heart Rate, bpm	107 ± 20	106 ± 21	104 ± 22	110 ± 18	121 ± 14
Respiratory Rate, bpm	33 ± 8	33 ± 8	32 ± 10	34 ± 4	32 ± 3
pH, mmHg	7.43 ± 0.07	7.43 ± 0.07	7.43 ± 0.07	7.43 ± 0.06	7.41 ± 0.11
PaO_2/FiO_2	94 ± 59	96 ± 61	106 ± 72	75 ± 18	67 ± 32
$PaCO_2$, mmHg	39 ± 14	40 ± 14	43 ± 16	33 ± 7	32 ± 3
Lactate, mmol/l	2 ± 2	1 ± 1	2 ± 1	1 ± 0.2	6 ± 2[b]
Type of NIV					
CPAP, n (%)	-	21 (64)	14 (61)	7 (70)	-
NIV, n (%)	-	7 (21)	5 (22)	2 (20)	-

Both (CPAP and NIV), n (%)	-	5 (15)	4 (17)	1 (10)	-
Interface					
Full-face mask		19 (58)	12 (52)	7 (70)	-
Helmet		13 (39)	10 (43)	3 (30)	-
Both Full-face mask and helmet		1 (3)	1 (4)	0 (0)	-
Inspitatory airway pressure 1st hour, cmH_20	-	16 ± 2	17 ± 2	16 ± 2	-
Expiratory airway pressure 1st hour, cmH_20	-	8 ± 2	7 ± 3	10 ± 1	-
PEEP 1st hour, cmH_20		12 ± 6	12 ± 6	13 ± 5	-
Fraction of inspired oxygen	-	0.7 ± 0.19	0.7 ± 0.19	0.8 ± 0.17	-

Table 1: *Characteristics of groups at intensive care unit admission.*
[a]: Comparing NIV vs IMV (p < 0.05).

[b]: Comparing NIV vs IMV (p < 0.001).

[c]: Comparing NIV success with NIV failure (p < 0.01).

[d]: Comparing NIV success with NIV failure (p < 0.001).

[e]: Median and interquartile range, the rest mean and standard deviation.

[f]: In NIV group: Influenza A H1N1 (n = 17), Influenza B (n = 5), Influenza A (n = 2), Influenza A/B (n = 1), 2 cases unknown; In IMV group: Influenza A H1N1 (n = 2).

[g]: In NIV group: Influenza A H1N1 (n = 3), Influenza A (n = 2), Influenza B (n = 1); In IMV group: Influenza A H1N1 (n = 1).

[h]: Comparing NIV success with NIV failure (p=0.05).

NIV: Noninvasive Ventilation; BMI: Body Mass Index; SOFA: Sequential Organ Failure Assessment; ICU: Intensive Care Unit; SAPS: Simplified Acute Phisiology Score; COPD: Chronic Obstructive Pulmonary Disease; ARF: Acute Respiratory Failure.

In most cases, 33 (92%) subjects received NIV as the first therapeutic option. Only 3 (8%) subjects undergoing IMV had a higher risk of death from SAPS 3 [72 ± 2 vs 49 ± 15, p < 0.05] and higher lactate level [6 ± 2 vs 1 ± 1, p = 0.001] than the NIV group (Table 1). Crude mortality was higher in the IMV group [2 (68%) vs 3 (9%) in the NIV group, OR 20 (95% CI 1,374-291,067), p = 0.028]. The subsequent analysis of mortality applying the propensity score showed an absence of negative influence of IMV on mortality [OR 4.6 (95% CI 0.059-358.320, p = 0.492)].

In the NIV group, tachypnoea (33 ± 8 bpm) and hypoxaemia (PaO_2/FiO_2 = 96 ± 61) were prevalent among the subjects who were admitted to the ICU. The most frequently used device was WhisperFlow-CPAP™ (Caradyne, Ireland) and Boussignac-CPAP (Vygon™, Ecouen, France), and the most used interface was oronasal (58%) (Table 1). The side effects mainly observed during NIV were noise, claustrophobia and dryness of mucosa (Table 2). No transmission of the infection to healthcare staff was found.

NIV problems	n = 20
Noise[1], n(%)	10 (71)
Claustrophobia, n(%)	6 (30)
Dryness of mucous membranes, n (%)	5 (25)
Conjunctivitis[1] n (%)	2 (14)
Gastric distension n (%)	2 (10)
Otitis, n (%)	2 (10)

Table 2: *NIV problems. [1]: n = 14 subjects.*

The NIV failure rate was 10 (31%) subjects. In the comparative analysis (Table 1), SAPS 3 was higher in the NIV failure [60 ± 14 vs 44 ± 13 in the NIV success group, p < 0.01]. Meanwhile, this group recorded the highest organ failure estimated by SOFA on admission and on 5-day SOFA [4 (4 - 5) vs 3 (3 - 4) in the NIV success, p < 0.001] and [8 (7 -10) vs 4 (3 - 5) in the NIV success, p = 0.001], respectively. There was also a greater delay in admission to the ICU in the failure group, as well as at the onset of the NIV, although this did not reach a significant difference. Likewise, the pO_2/FiO_2 ratio on admission to the ICU was lower in the failure group (75 ± 18 vs 106 ± 72 in the NIV success, p = 0.08). As for the secondary objectives of the study (Table 3), the NIV failure group presented a higher rate of organ failure (as reflected in the 5-day SOFA), together with a longer stay in the ICU [20 (8 - 29) vs 7 (3 - 9) in the NIV success, p = 0.002], hospitalisation [24 (11 - 52) vs 13 (8 - 18) in the NIV success group, p = 0.048], just as in higher mortality in the ICU [3 (30%) vs 0 (0%) in the NIV success, p = 0.022]. The main factor related to the NIV failure was the SOFA at admission > 5 [10 (100%) in the NIV failure vs 11(48%) of the NIV success, OR 1.9 (CI 95% 1.270 - 2.870), p = 0.005].

Physiological parameters	Global (n = 33)	NIV success (n = 23)	NIV failure (n = 10)	p*
Reintubation, n (%)	1 (3)	0 (0)	1 (10)	0.303[a]
Tracheostomy, n (%)	2 (6)	0 (0)	2 (20)	0.085[a]
Respìratory arrest after intubation, n (%)	2 (6)	0 (0)	2 (20)	0.085[a]
Transfer ECMO center	1 (3)	0 (0)	1 (10)	0.303[a]
Cardiovascular failure, n (%) n = 32	15 (45)	7 (35)	8 (80)	0.050[a]
Renal failure, n (%) n = 32	10 (30)	5 (25)	5 (50)	0.231[a]
Hepatic failure, n (%) n = 32	4 (12)	3 (15)	1 (10)	1.000[a]
Haematological failure, n (%) n = 32	8 (25)	6 (27)	2 (20)	1.000[a]
Type of ARDS, n (%) (n = 28)				
Mild	4 (14)	4 (21)	0 (0)	0.183
Moderate	15 (53)	10 (53)	5 (56)	0.183
Severe	7 (25)	3 (16)	4 (44)	0.183
Duration of NIV[b], hours	92 (27 - 136)	121 (50 - 158)	24 (5 - 111)	0.011
Overall duration of ventilation[b,c], days	6 (3 -15)	5 (2 - 6)	16 (7 - 26)	0.724
ICU LOS[b], days	8 (4 -17)	7 (3 - 9)	20 (8 - 29)	0.002
Hospital LOS[b], days	14 (9 -24)	13 (8 -18)	24 (11 - 52)	0.048
ICU Mortality, n (%)	3 (9)	0 (0)	3 (30)[d]	0.022[a]
Hospital Mortality, n (%)	3 (9)	2 (9)	3 (30)	0.149[a]
6-month Mortality, n (%)	6 (18)	3 (13)	3 (30)	0.245[a]

Table 3: *Outcomes, duration of ventilation, length of stay and mortality at ICU and hospital.*

**: Compating NIV success with NIV failure.*

[a]: Fisher exact test.

[b]: Median and interquartile range.

[c]: Adding noninvasive ventilation and invasive mechanical ventilation.

[d]: Death reasons: multiorgan failure (two cases), ARDS (one case).

NIV: Noninvasive Ventilation; ECMO: Extracorporal Membrane Oxygenation; ARDS: Acute Respiratory Distress Syndrome; ICU: Intensive Care Unit; LOS, Length of Stay.

Discussion

Since the outbreak of 2009, in the analysis of our sample we have been able to observe a considerable increase in recent years of viral pneumonia, although in an irregular way, with some years of an almost absence of reported cases. Meanwhile, we have observed a change in the behaviour of the type of infection, shifting from a predominance of primary viral pneumonia in the oubreak 2009 [8,13], as was notified [8], to an increase in the bacterial coinfection rate [23]. We were also able to detect changes in the types of influenza, all of them with a similar behaviour.

NIV was the most commonly used type of ventilatory support in our sample, with 92% use. This result is far from the rates of use of NIV according to National Registry (47.4% in the 2013 - 2015 period) [23], which indicates a clear commitment to the use of NIV as the first therapeutic option, despite the non-recommendation for the use of NIV in patients with hypoxaemia, except at centres with experience [24].

Mortality in the IMV group was very high (68%), probably due to the higher use of NIV, and with a use of IMV in more severe subjects, as can be seen in the level of organ failure and the higher SAPS 3 score. Despite this, the propensity analysis showed no increase in mortality due to the use of IMV as the first option, in line with published studies [9]. A secondary analysis of a prospective multicentre study reported a lower crude mortality in the NIV group (24.6% vs. 31.3% in IMV, $p < 0.001$), but higher in the NIV failure group. In a later adjusted analysis of mortality, a higher mortality in the NIV failure group was observed (HR 1.19 95% CI 0.99-1.44, $p = 0.07$) [10]. Either way, the need for IMV is a clear mortality related factor. In a multicentre observational study which analysed two epidemic periods, the need for IMV was decisive in mortality [OR 6.8 (2.3 - 19.7), $p < 0.001$] and [OR 3.9 (1.4 - 10.7), $p = 0.01$], respectively [23].

As for the analysis of the NIV group, the failure rate occurred in 10 (31%) subjects, clearly lower compared to other studies (around 55 to 85%) [3,4,9,10]. According with our results, a multicentre study showed a failure rate of 21.7% [15]. Factors which could have influenced the good results obtained included the use of specific NIV respirators and interfaces (face masks or helmets), which are better tolerated by the subjects. In any case, NIV was not exempt from side effects, with noise, claustrophobia and dryness of mucosa being the most frequent. Another factor which could have positively influenced was the application of high pressure levels (IPAP 16 ± 2 cmH_20, EPAP 8 ± 2 cmH_20 and CPAP 12 ± 6 cmH_20) capable of improving oxygenation, and providing rest to the respiratory muscles and which are within the recommended pressure levels [25]. A relevant fact is the wide use of CPAP systems with helmet interfaces, which particularly occurred in the first outbreak of Influenza A [13]. Despite being a closed transparent polyvinyl system, like a diving helmet, which may produce intense noise and feelings of claustrophobia, it is more comfortable than other types of interfaces, just as it shares the benefits of NIV [26]. Several publications have demonstrated a success of the helmet device in subjects with hypoxaemic ARF [26-28]. Therefore, this device could be beneficial in early use, in subjects who do not present with the work of breathing despite the significant degree of hypoxaemia, and who, due to the absence of signs of ARF, give us the false image of stability [8].

The NIV failure group had worse SAPS 3, as well as greater organ failure (both on admission and after five days), compared to the success group. This state of higher organ failure estimated by SOFA, between 5 - 7, was also analysed in other studies [9,10,15,29]. The higher level of severity in the NIV failure could suggest the underlying presence of more organ failures due to a state of oxygen deficit, and which would only be manifested by the overload of the respiratory system through a persistent tachypnoea that would lead to intubation [25]. Another important result is the delay in the ICU admission, as well as the delay in the start of NIV in the NIV failure group, although none of these results was of statistical significance. This fact backs up the time window in which the application of NIV can be beneficial and prevent intubation, but beyond that time, the use of NIV is risky [25]. These results would indicate that the delay of both admission and the onset of NIV could have influenced the failure of NIV. As it is logical to expect, the failure of NIV led to a higher rate of complications, prolonged stay in the ICU and hospitalisation, and mortality in the ICU.

Limitation of the Study

The limitations of our study included its retrospective nature and its implementation at a single centre. Another determining factor was the small sample, especially in the IMV group, which determined wide confidence intervals in the mortality risk analysis. Likewise, the

sample size only allowed us to determine a predictive factor of NIV failure, following the recommended rules for determining predictive factors based on the number of results obtained [30]. Despite this, the presence of a high SOFA as a predictor of failure would endorse the results already published [10].

Conclusion

In the light of our results, we can conclude that NIV was widely used in subjects with hypoxaemic ARF due to Influenza virus pneumonia, with a high success rate. In spite of this, factors such as the delay in admission to the ICU, the start of NIV and - above all - organ failure upon admission, should make us consider the need for the direct use of IMV. Overall, the use of IMV did not increase mortality in comparison to NIV.

Conflict of Interest

The authors do not present conflicts of interest.

Bibliography

1. Domínguez-Cherit G., *et al*. "Critically ill Patients with 2009 Influenza A (H1N1) infection in Mexico". *The Journal of the American Medical Association* 302 (2009): 1880-1887.
2. Estenssoro E., *et al*. "Pandemic 2009 Influenza A in Argentina". *The American Journal of Respiratory and Critical Care Medicine* 182 (2010): 41-48.
3. Kumar A., *et al*. "Critically ill Patients with 2009 Influenza A (H1N1) infection in Canada". *The Journal of the American Medical Association* 302 (2009): 1872-1879.
4. Rello J., *et al*. "Intensive Care Adults patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain". *Critical Care* 13 (2009): R148.
5. The ANZIC influenza investigators. "Critical care services and 2009 H1N1 Influenza en Australia and New Zealand". *The New England Journal of Medicine* 361 (2009):1925- 1924.
6. Rodríguez A., *et al*. "Pandemic Influenza A in the ICU: Experience in Spain and Latin America GETGAG/SEMICYUC (Spanish Work Group on Severe Pandemic Influenza/SEMICYUC)". *Medicina Intensiva* 34 (2010): 87-94.
7. Zhu N., *et al*. "A Novel Coronavirus from Patients with Pneumonia in China, 2019". *The New England Journal of Medicine* (2020).
8. Rodriguez A., *et al*. "Gripe A (H1N1)v pandémica en UCI: ¿qué hemos aprendido?" *Archives de Bronconeumologia* 46.3 (2010): 24-31.
9. Masclans JR., *et al*. "Early non-invasive ventilation treatment for severe influenza pneumonia". *Clinical Microbiology and Infection* 19 (2013): 249-256.
10. Rodríguez A., *et al*. "Risk factors for non-invasive ventilation failure in critically ill subjects with confirmed influenza infection". *Respiratory Care* 62 (2017): 1307-1315.
11. Rochwerg B., *et al*. "Official ERS/ATS clinical practice guidelines: non-invasive ventilation for acute respiratory failure". *The European Respiratory Journal* 50 (2017): 1602426.
12. Conti G., *et al*. "On the role of non-invasive (NIV) to treat patients during the H1N1 influenza pandemic".
13. Belenguer-Muncharaz A., *et al*. "Non-invasive ventilation in severe pneumonia due to H1N1 virus". *Medicina Intensiva* 35 (2011): 470-477.

14. Timenetsky KT., *et al*. "High success and low mortality rates with non-invasive ventilation in influenza A H1N1 patients in a tertiary hospital". *BMC Research notes* 4 (2011): 375.

15. Nicolini A., *et al*. "Effectiveness and predictors of success of non-invasive ventilation during H1N1 pandemics: a multicenter study". *Minerva Anestesiologica* 78 (2012): 1333-1340.

16. Esquinas A., *et al*. "Non-invasive mechanical ventilation in high-risk pulmonary infections: a clinical review". *European Respiratory Review* 23 (2014): 427-438.

17. Rodríguez A and Gordo F. "Diagnóstico y tratamiento de los pacientes adultos con insuficiencia respiratoria aguda grave por el nuevo virus de la gripr A (H1N1)" (2020).

18. Mandell LA., *et al*. "Infectious Diseases society of America /American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults". *Clinical Infectious Diseases* 44.2 (2007): S27-72.

19. R anieri VM., *et al*. "Acute respiratory distress syndrome: the Berlin Definition". *The Journal of the American Medical Association* 307 (2012): 2526-2533.

20. Mehta S and Hill N. "Non-invasive Ventilation". *The American Journal of Respiratory and Critical Care Medicine* (2001): 540-577.

21. Tobin MJ. "Mechanical ventilation". *The New England Journal of Medicine* 330 (1994):1056-1060.

22. Ware LB and Matthay MA. 'The Acute Respiratory Distress Syndrome". *The New England Journal of Medicine* 342 (2000): 1335-1349.

23. Marin-Corral J., *et al*. "Patients with influenza A (H1N1) pdm09 admitted to the ICU. Impact of the recommendation of the SEMICYUC". *Medicina Intensiva* 42 (2018): 473-481.

24. Rodríguez A., *et al*. "Recommendations of the Infectious Diseases Work Group (GTEI) of the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC) and the Infections in Critically Ill Patients Study Group (GEIPC) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) for the diagnosis and treatment of influenza A/H1N1 in seriously ill adults admitted to the Intensive Care Unit". *Medicina Intensiva* 36 (2012): 103 -137.

25. Brochard L., *et al*. "Non-invasive Ventilation for Patients with Hypoxemic Acute Respiratory Failure". *Seminars in Respiratory and Critical Care Medicine* 35 (2014): 492–500.

26. Antonelli M., *et al*. "New treatment of acute hypoxemic respiratory failure: Non-invasive pressure support ventilation delivered by helmet- A pilot-controlled trial". *Critical Care Medicine* 30 (2002): 602-608.

27. Principi T., *et al*. "Non-invasive continuous positive airway pressure delivered by helmet in hematological malignancy patients with hypoxemic acute respiratory failure". *Intensive Care Medicine* 30 (2004): 147-150.

28. Patel BK., *et al*. "Effect of non-invasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome". *The Journal of the American Medical Association* 315 (2016): 2435-2441.

29. Hernández Garcés H., *et al*. "Factores de riesgo de fracaso de ventilación no invasiva en neumonía primaria por influenza A en pacientes críticos". *Medicina Intensiva* (2019).

30. Tabachnick BG and Fidell LS. Ratio of cases to Ivs. Chapter 5, Multiple regression. In: Tabachnick BG, Fidell LS, editors. Using multivariate statistics. 6Th de. Boston: Pearson (2013): 123-124.

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