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Predicting Failure of Non-invasive Ventilation in a Mixed Population

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Abstract

Objective: Non-invasive ventilation (NIV) is widely used as part of the treatment of acute respiratory failure but it is not always successful. The purpose of this study is to determine if NIV failure can be predicted on the basis of information available at the initial point of contact with the patient.

Methods: This is a retrospective study of patients admitted to a six bed non-specialized ICU at Køge University Hospital (Denmark) in the years 2011-2012. Patients were assigned to one of two groups covering successful NIV treatment and NIV failure.

Results: 89 patients were included and the two groups were compared on variables available at the initial point of contact with the patient. Patients in whom NIV treatment failed had higher levels of C-reactive protein (p=0.04). Multivariate analysis showed an odds ratio of 1.13 (95% CI: 1.02-1.25) for NIV failure associated with increased respiratory rate. NIV was less likely to fail in patients with known Chronic Obstructive Pulmonary Disease (p=0.05). The mean duration of NIV before intubation in case of NIV failure was 14.1 hours (SD: 15.0) and was not associated with neither the ICU nor the in-hospital mortality.

Conclusion: In the present study NIV failure was associated with higher levels of C-reactive protein and increased respiratory rates carried an odds ratio of 1.13 (95% CI: 1.02-1.25) for NIV failure.

Keywords: Non-invasive ventilation; Failure; Respiratory failure; Intensive care; Positive pressure ventilation; Endotracheal intubation; Pneumonia

Introduction

Non-invasive ventilation (NIV) is often considered part of the first-line treatment of acute respiratory failure (ARF) in selected patients with preserved respiratory drive [1,2]. It is commonly used both in- and outside of the intensive care unit (ICU). Invasive ventilation requires endotracheal intubation and is associated with ventilator-associated pneumonia and other complications related to prolonged intubation. In some patients NIV is not sufficient and they subsequently require invasive ventilation. Recent research has shown that the duration of NIV before intubation was shorter in survivors than non-survivors [3] among patients not previously diagnosed with cardiac or respiratory illness e.g. chronic obstructive pulmonary disease (COPD).

The purpose of this study is to determine if NIV failure can be predicted on the basis of information available at the initial point of contact with the patient in acute respiratory failure. The variables being compared are those that are typically available when the choice between non-invasive and invasive ventilation has to be made and no distinction was made on the basis of co-existing disease.

Methods

This is a retrospective study of patients in acute respiratory failure admitted to a six bed non-specialized ICU at Køge University Hospital (Denmark) during the years 2011-2012. The hospital has in addition to an emergency department five medical wards with a total of 118 beds and two surgical departments covering general and orthopedic surgery with a total of 146 beds. The patients were admitted to the ICU from all departments of the hospital. Patients were excluded if either non-invasive or invasive ventilation was not an option at the first point of contact with the patient i.e. patients in respiratory arrest or do-not-intubate orders. Patients were also excluded if insufficient data was available. There was no written protocol for selecting between non-invasive and invasive ventilation and the decision was at the discretion of the attending physician. Similarly no written protocol dictated when a patient should be intubated after non-invasive ventilation had been attempted. All patients had a standardized panel of blood samples drawn upon arrival. Samples for C-reactive protein and white blood cell count were drawn from venous blood, while the rest were drawn from arterial blood.

Two groups were defined as follows. Patients treated solely with NIV (NIV success) and patients initially treated with NIV but subsequently required sedation, intubation and invasive ventilation (NIV failure). The primary endpoint was NIV failure and the two groups were compared on variables available at the point of contact in order to determine if it could be predicted that NIV would fail.

The arterial blood gas (ABG) analyses were performed using the Radiometer ABL90 Flex (Radiometer, Brønshøj, Denmark). Systolic blood pressure was measured using non-invasive automatic devices. Temperature measurements were tympanic and respiratory rate and Glasgow Coma Scale score were determined by one of the treating physicians or nurses in the ICU. Both non-invasive and invasive ventilation was done using Hamilton-G5 ventilators (Hamilton Medical, Bonaduz, Switzerland) using pressure regulated modes. The interface for NIV was a total face mask.

Data was analyzed using the two-tailed unpaired t-test except for table 3 in which the paired t-test was used. Mortality and NIV failure rates were compared using χ^2-test. A p-value less than 0.05 was considered statistically significant. Sample size calculation was done

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	NIV success	NIV failure	p-value
Sex (male:female)	22:37	14:16	0.26
Age, mean (range), years	70.5 (38-89)	70.3 (44-85)	0.92

Table 1: Patient characteristics.

	NIV success		NIV failure		
	Mean	SD	Mean	SD	p-value
pH	7.23	0.12	7.23	0.13	0.94
PaO_2 (kPa)	10.10	4.30	11.81	8.05	0.29
$PaCO_2$ (kPa)	11.20	4.40	10.16	4.00	0.27
Lactic acid (mmol/L)	2.0	2.1	1.4	0.9	0.07
Base excess	5.2	8.4	2.3	7.9	0.06
HCO_3^- (mmol/L)	27.3	7.3	24.9	5.9	0.10
C-reactive protein (CRP) (mg/L)	79	91	138	113	0.02*
White Blood cell Count (WBC) (10^9/L)	13.4	5.4	12.3	6.7	0.45
Oxygen saturation	0.89	0.10	0.89	0.08	0.72
Systolic blood pressure (mmHg)	131	36	120	26	0.11
Heart rate (min^{-1})	110	19	107	29	0.60
Respiratory rate (min^{-1})	27	8	30	9	0.06
Temperature (°C)	37.2	0.9	37.3	1.3	0.59
Glasgow Coma Scale score	13	3	13	2	0.40

Table 2: Comparison of patients treated solely with NIV (NIV success) and patients requiring invasive ventilation after NIV was attempted (NIV failure). P-value less than 0.05 is marked with *.

	Initiation of non-invasive ventilation		Initiation of invasive ventilation		
	Mean	SD	Mean	SD	p-value
pH	7.23	0.13	7.23	0.12	0.79
PaO_2 (kPa)	11.81	8.05	12.60	5.59	0.65
$PaCO_2$ (kPa)	10.16	4.00	10.37	3.62	0.44
Lactic acid (mmol/L)	1.4	0.9	2.8	1.3	0.92
Base excess	2.3	7.9	2.9	6.8	0.40
HCO_3^- (mmol/L)	24.9	5.9	25.6	5.3	0.69
Oxygen saturation	0.89	0.08	0.94	0.06	0.01*
Systolic blood pressure (mmHg)	120	26	107	25	0.02*
Heart rate (min^{-1})	107	29	97	25	0.08
Respiratory rate (min^{-1})	30	9	25	10	<0.01*
Temperature (°c)	37.3	1.3	37.1	1.2	0.40
Glasgow Coma Scale score	13	2	13	3	0.40

Table 3: Patients in the NIV failure group at the initiation of NIV and at the initiation of invasive ventilation. P-value less than 0.05 is marked with *.

using a cohen's d of 0.8 with a statistical power of 0.8 and a probability level of 0.05 for a two-tailed hypothesis. Data analysis was performed using Microsoft Excel 2010 (Microsoft Corp., Washington, USA).

Results

A total of 89 patients were included in the study. The patient characteristics of the two groups are shown in table 1. In this study 59 patients were successfully treated with NIV while 30 patients had to be invasively ventilated after NIV failure. The majority of patients (77%) were hypercapnic when admitted with respiratory failure and all patients were given supplemental oxygen via a non-rebreathing mask prior to arterial blood sampling.

To determine if NIV failure could have been predicted at the initial point of contact a comparison between NIV success and NIV failure was made. These variables are shown in table 2 and are presented as mean and the standard deviation of the mean (SD). In patients initially treated with NIV but requiring invasive ventilation there was a trend toward a higher ICU mortality (20.0 vs. 10.2%, p=0.22) and a higher in-hospital mortality (33.3 vs. 15.3%, p=0.08) compared to patients successfully treated with NIV. There was a significantly lower percentage of NIV failure among patients diagnosed with COPD (33 vs. 64%, p=0.005). Multivariate analysis showed an odds ratio (OR) for NIV failure with increased respiratory rate of 1.13 (95% CI: 1.02-1.25) while higher levels of C-reactive protein had an OR: 1.01 (95% CI: 1.00-1.01).

The variables within the NIV failure group were compared at the startup of NIV to the values when the patient was intubated and invasively ventilated to investigate if a worsening was measurable. These results are presented in table 3. Blood samples for CRP and WBC were drawn once a day and since the mean duration of NIV prior to intubation was 14.1 hours (SD: 15.0) these parameters remained unchanged for most of the patients. Among patients intubated after non-invasive ventilation there was no statistically significant difference in the duration of NIV between ICU survivors and non-survivors (13.75 vs. 14.7 hours, p=0.86) or between in-hospital survivors and non-survivors (14.4 vs. 12.7 hours, p=0.80).

As a measure of the severity of disease in patients admitted to an ICU the Simplified Acute Physiology Score (SAPS II) can be calculated. This system uses 15 variables and the final score is calculated from the worst values in the first 24 hours after ICU admission. These numbers are not presented in table 2 because the SAPS II score cannot be calculated at the initial point of contact. SAPS II scoring was not done routinely in our population and is lacking in 32% of the patients in NIV success group and in 20% of the patients in the NIV failure group. The lacking SAPS II scores have not been calculated retrospectively for fear of introducing errors. Among the patients whose SAPS II score had been calculated during the first 24 hours of admission, there was a tendency towards higher scores associated with NIV failure than with successful NIV treatment (52 vs. 45, p=0.10).

Discussion

In the present study NIV failure was associated with increased plasma levels of C-reactive protein. Antonelli et al. [4] found that NIV was more likely to fail (OR: 2.07, 95% CI 1.3-5.4, p=0.005) in patients presenting with community-acquired pneumonia (CAP). As is seen in table 2 none of the other markers typically associated with infection showed statistically significant differences. However in neither group were CRP nor WBC within normal limits, suggesting there were patients in both groups with infection e.g. CAP. Any sign of CAP when using non-invasive ventilation should prompt a high degree of vigilance in order to detect signs of NIV failure as is recommended by Ferrer et al. [5] and the higher CRP in the present study supports this. There was a trend toward higher respiratory rate (RR) being linked to NIV failure and multivariate analysis showed an OR of 1.13 (95% CI: 1.02-1.25). In the multi-center study by Antonelli et al. [4] a respiratory rate ≥ 38 showed an OR for NIV failure of 1.89 (95% CI: 1.06-5.74). An association between Glasgow Coma Scale (GCS) score and NIV failure has been shown by Schettino et al. [6]. The GCS score was included in this study because it is a widely used tool to describe neurological status. Schettino et al took great care in assuring consistent scoring but there is a risk of interobserver variation [7]. Between the two groups there was no significant difference in GCS score and it seems unsuitable as the sole basis for treatment decisions.

A more reliable predictor of NIV failure seems to be a low PaO_2/FiO_2-ratio [4,8]. Carrillo et al. [3] found that among patients with "de novo" ARF i.e. no known previous cardiac or respiratory illness a lower PaO_2/FiO_2-ratio after one hour of NIV treatment independently predicted NIV failure. This ratio has not been investigated here as the present study focuses on the initial point of contact with the patient. This ratio does however stress that patients in acute respiratory failure should continually be reevaluated for treatment failure. In the present study known COPD was related to a lower frequency of NIV failure with numbers matching the study by Carrillo et al. [3] that found that patients with "de-novo" ARF failed more frequently (46 vs. 26%, p=0.007).

Among patients with "de novo" ARF [3] longer duration of NIV prior to intubation was shown to be associated with decreased hospital survival. The duration of NIV that best predicted mortality was ≥ 53 hours with a sensitivity of 69% and a specificity of 83%. In patients with acute lung injury Rana et al. [9] found that non-survivors tended to have a longer delay in the intubation although this was not statistically significant. In the present study neither the ICU nor the in-hospital mortality was associated with the duration of non-invasive ventilation prior to intubation. When comparing the values of the variables at the initiation of NIV to the values at the initiation of invasive ventilation, table 3 shows a significant increase in oxygen saturation and a reduction in the respiratory rate. This would indicate that the patients were in some ways more stable but there was no improvement in gas exchange. In the present study the mean time of non-invasive ventilation prior to intubation was 14.1 hours and a deterioration of the patients was not detected with the selected variables. It seems however, reasonable to assume that further prolonging NIV before intubation would have yielded a measurable worsening and lower survival rates.

The present study found a tendency towards higher SAPS II scores in NIV failure although this was not statistically significant. Multivariate analysis in a previous study [4] revealed SAPS II ≥ 35 as an independent predictor of NIV failure (OR 1.81, 95% CI 1.07-3.06).

This study is of course limited by its retrospective nature and the early administration of supplemental oxygen makes it more difficult to distinguish between hypoxic and hypercapnic respiratory failure. Variables such as GCS and respiratory rate can show interobserver variation as mentioned earlier and when measuring durations of ventilation this was done in one hour intervals and thus carries an inaccuracy.

Conclusions

When dealing with patients with acute respiratory failure a choice between non-invasive and invasive ventilation sometimes has to be made based on the information at hand. This study was designed to investigate if these basic parameters were enough to predict NIV failure. Patients requiring intubation due to NIV failure had higher levels of C-reactive protein and tended to have higher respiratory rates. Multivariate analysis showed an OR of 1.13 (95% CI: 1.02-1.25) associated with increased respiratory rate and there was a lower percentage of NIV failure among patients diagnosed with COPD. The literature shows indications of the detrimental effect of NIV failure and further studies are needed in order to select the right treatment at the initial point of contact in the patient with acute respiratory failure.

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