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Variables predictive of outcome in patients with acute hypercapnic respiratory failure treated with noninvasive ventilation

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Abstract

Objective: To assess results with NIV in acute hypercapnic respiratory failure and to identify outcome predictors.

Methods: This was a retrospective observational study on consecutive patients presenting with acute type II respiratory failure and meeting criteria for NIV use over a 5 year period. Patients presenting with haemodynamic instability, inability to protect their airway, malignant arrhythmias and recent oesophageal surgery were excluded. Univariate and Multivariate regression analysis was used to determine the impact on survival. A p value of < 0.05 was considered statistically significant. Software used was SPSS 14.

Results: Total numbers of patients included were 119; 52.9% were males. Mean age was 63.4 ± 11.9 years. Overall Survival to discharge rate was 76.5%, intubation rate was 12.6% and mean length of stay was 11.4 ± 10.9 days. Statistically significant improvements were observed in the pH and PaCO₂ at 24 hours and 48 hours compared to baseline (7.28 v/s 7.37, $p < 0.001$; 74.2 v/s 65, $p < 0.001$). On multivariate regression analysis, sepsis at admission predicted mortality (adjusted Odds ratio 26.4; 95% CI 2.3, 304, $p < 0.009$). A serum HCO₃⁻ > 35 Meq/L (adjusted Odds ratio 0.9; 95% CI 0.83, 0.98, $p < 0.015$) identified those less at risk for intubation.

Conclusion: NIV was found to be both safe and effective in the management of acute hypercapnic respiratory failure. Sepsis and serum HCO₃⁻ at admission identified patients having poor outcomes (JPMA 60:13; 2010).

Introduction

The use of noninvasive ventilation (NIV) in patients with acute hypercapnic respiratory failure has shown to be effective in the relief of dyspnea, the improvement of vital signs and gas exchange, in preventing endotracheal intubation, and improving overall survival.¹⁻⁶ It has now become the standard of care for such patients.^{3,5}

NIV is underused in Pakistan since most pulmonary physicians in practice are either not trained in its usage or have concerns regarding the time commitment that these patients impose on the care process. There is dearth of literature on how well NIV is tolerated in patient populations unique to our region. This fact is especially unfortunate since NIV is a cost-effective intervention; particularly for countries like Pakistan where health care delivery is largely determined by the patients' ability to pay for service. It is estimated in a study from United Kingdom that NIV given on wards reduces the need for intubation by 44% and halves mortality in hospital in patients with chronic obstructive pulmonary disease and mild to moderate acidosis and by preventing intubation, NIV may help to avoid approximately three to nine ICU admissions per year and consequently result in a substantial cost saving for patients.⁷

There are some patients who do not respond to NIV and in these, invasive ventilation becomes essential. Studies

from the West report failure rates of 24% to 50%.^{2,8} Delays in recognizing non-responders can increase hospital morbidity and mortality.⁸ In an effort to optimize outcomes, it is therefore essential to identify non-responders early.

This study was designed to primarily assess the safety and efficacy of NIV in hypercapnic acute respiratory failure in Pakistani patients and additionally to identify prognostic variables for survival, death and endotracheal intubation.

Patients and Methods

This observational cohort study was conducted between 2001 and 2005 at Aga Khan University Hospital, a 450-bedded tertiary care hospital in Karachi, Pakistan. All adult patients (aged 16 years or above) presenting with hypercapnic acute respiratory failure (ARF) and meeting criteria for non-invasive ventilation use were enrolled. The hospital Ethics Committee approved the research protocol.

Hypercapnic ARF was defined as the presence of all the following:

Respiratory rate higher than 25 breaths/minute, arterial pH less than 7.35, and partial pressure of arterial carbon dioxide (PaCO₂) in excess of 45 mmHg.

NIV failure was defined as endotracheal intubation and invasive ventilation after placement on NIV and/or death.

In patients with multiple admissions during the study

period, the first application of NIV was used for analysis. We excluded patients with haemodynamic instability, impending respiratory arrest, inability to protect airway, excessive airway secretions, pneumothorax, acute upper gastrointestinal bleeding, epistaxis, facial deformity/trauma and those with a known hypersensitivity to the mask material.

We applied NIV using BiPAP Vision (Respironics, Murrysville, Pa., USA) in the spontaneous mode with the assistance of pulmonary fellows/ residents and trained nurses. All NIV was initiated in either the Emergency department, Special Care Units or the Intensive Care Unit. As soon as possible, patients on NIV were transferred to a dedicated NIV Special Care Unit. Therapy was initiated with an inspiratory positive airway pressure (IPAP) of 10 cmH₂O and an expiratory positive airway pressure (EPAP) of 5 cmH₂O. This was optimized using continuous pulse oximetry readings (aiming to maintain saturation between 92-95%), arterial blood gas measurements (at 1 hour and periodically thereafter as clinically indicated) and assessment of patient comfort. Three oronasal masks were available to optimize patient comfort: small, medium /small and medium, tightly secured with head straps to minimize leaks. NIV was applied initially for at least 6 hours, lengthening this period according to the patients' requirements.

The discontinuation of NIV was based on clinical judgment and arterial blood gas values.

Patients exhibiting respiratory pauses with loss of alertness or gasping, psychomotor agitation requiring sedation, systolic blood pressure lower than 70 mmHg, pH below 7.26 after 1 hour of NIV or respiratory arrest, were endotracheally intubated.

A pre-designed structured format was used to gather data on demographic features, clinical features, arterial blood gas measurements, duration of NIV and reasons for NIV failure.

The primary outcome variables were endotracheal intubation rate (failure of NIV) and survival to hospital discharge. A secondary study outcome was to identify variables predictive of in-hospital mortality and endotracheal intubation.

The data was analyzed as frequencies for nominal variables and as means \pm standard deviation for continuous variables. Univariate analyses was performed using the chi² test or Fisher's exact test for nominal variables and the t test for means.

To identify factors predictive of mortality whilst using noninvasive ventilation, a univariate analysis was done to compare characteristics in patients surviving to hospital discharge and those that died during hospitalization. Variables with p values less than 0.10 were entered into a forward

stepwise logistic regression analysis using an entry level of 0.05 and a removal level of 0.10. The adjusted odds ratio (OR) was calculated with 95% confidence intervals (95% CI) for all independent predictors of in-hospital mortality. A similar process was used to determine variables predictive of failure of NIV. A p value less than 0.05 was considered statistically significant; all tests were two tailed. SPSS statistical software package (version 14.0) was used for statistical analysis.

Results

One hundred and nineteen patients with hypercapnic ARF were enrolled in the study. Mean age of patients was 63.4

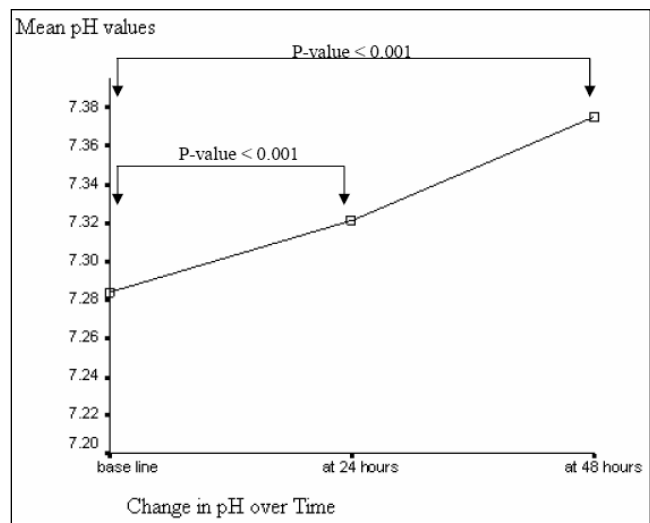


Figure-1: Change in pH after application of noninvasive ventilation.

\pm 11.9 years with 63 (52.9%) males. COPD was the primary cause of hypercapnic respiratory failure in 109 (91.6%) patients, with acute asthma exacerbations accounting for the remainder. All patients were haemodynamically stable at

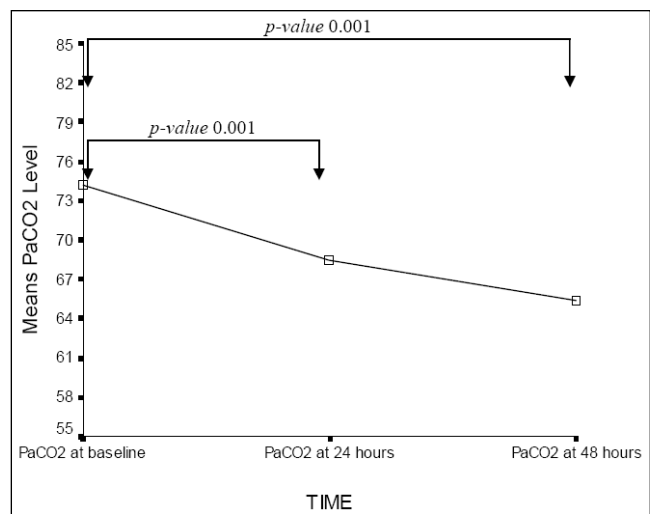


Figure-2: Change in PaCO₂ after application of noninvasive ventilation.

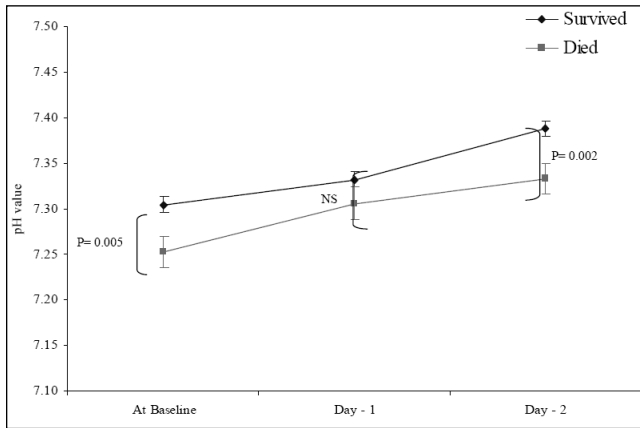


Figure-3: Change in pH on arterial blood gases after application of noninvasive ventilation between survivors compared to nonsurvivors.

presentation; the mean systolic BP was 129 ± 24.5 mmHg, mean heart rate 102.5 ± 21 beats/minute. The mean respiratory rate was 27.7 ± 8.4 breaths/minute. Mental status was reduced (drowsy) in 67 (56.3%) patients. Code status was defined in 93% patients on admission; 59% were full code, whilst 34.5% were not for any resuscitation (DNR).

Table: Factors associated with Survival on univariate analysis of patients placed on noninvasive ventilation.

Factor	Patients who Survived (n=91)	Patients who Died (n=28)	Odds Ratio (95% CI)	P-value
Age (in years)	62.1 ± 12.5	67.8 ± 8.7	0.94 (0.90,0.99)	0.029
Serum Creatinine	1.1 ± 0.5	1.7 ± 0.8	0.3 (0.14,0.61)	0.001
pH at base line	7.31 ± 0.09	7.25 ± 0.09	2.2 (0.8,6.5)	0.005
HCO ₃ (at baseline)	36.1 ± 7.5	32.4 ± 9.3	1.06 (1.0,1.1)	0.032
pH at 48 hours	7.39 ± 0.07	7.33 ± 0.06	3.7 (1.0,13.5)	0.002
Sepsis at admission	1 (1%)	3 (10.7%)	0.38 (0.003,0.43)	0.009
COPD as the Cause of Respiratory failure	2 (20%)	8 (80%)	0.056 (0.01,0.28)	< 0.001

At initiation of NIV, mean pH was 7.28 ± 0.08 , mean PaCO₂ 74.2 ± 20.3 mmHg, mean PaO₂ 84.4 ± 44.2 mmHg and mean HCO₃ 35.2 ± 8 mg/dl. In the succeeding 24 and 48 hour evaluations, there were significant improvements in the PaCO₂ { 68.1 ± 21.7 mmHg, $p < 0.001$ at 24 hrs and 65 mmHg ± 17.22 , $p < 0.001$ at 48 hours} and pH { 7.32 ± 0.08 , $p < 0.001$ at 24 hrs and 7.37 ± 0.7 , $p < 0.001$ at 48 hours} (Figures-1, 2).

No significant changes were observed in serum HCO₃ or PaO₂. Noninvasive ventilation was applied for an average duration of 12.2 ± 5.5 hours on day 1 and then the duration was gradually decreased over succeeding days.

The average length of hospitalization was 11.4 ± 11 days. NIV failure and need for endotracheal intubation was observed in 15 (12.6%) patients. Ninetyone (76.5%) patients survived to hospital discharge and 28 (23.5%) patients died.

Pneumonia, worsening respiratory failure and pulmonary oedema were the most common causes of death. Out of 28 non-survivors, code status of 20 patients was already decided as not for any resuscitation (DNR) considering severity of preexisting disease and other comorbidities. Six (21.42%) patients died after intubation on mechanical ventilation and remaining 22 (79.35%) were on NIV. Complications were nosocomial pneumonia in 20 (16.8%), acute coronary syndrome in 6 (5%) and pneumothorax in 3 (2.5%).

On univariate analysis, factors associated with a higher risk of NIV failure or intubation were; pH less than 7.20 (p 0.011), serum HCO₃ less than 35 meq/L (p 0.015) and serum creatinine greater than 1.5 mg/dl (p 0.001) at admission. On multivariate analysis the only independent predictor of a reduced likelihood of endotracheal intubation was a serum HCO₃ greater than 35 meq/L at admission (Adjusted Odds ratio 0.9; 95% CI 0.83, 0.98, $P < 0.015$).

Univariate analysis of the overall series showed that factors associated with a reduced risk of in-hospital mortality included; a diagnosis of COPD, younger age, the absence of sepsis at admission, higher serum HCO₃ and pH at admission and a higher pH after 48hrs of NIV (Table).

On multivariate analysis the only remaining independent predictor of in-hospital mortality was Sepsis at admission, (adjusted Odds ratio 26.4; 95% CI 2.29, 304.3, $p < 0.009$).

Figure-3 shows the change in pH after application of noninvasive ventilation between survivors and nonsurvivors.

Discussion

This study found that NIV was equally safe and efficacious in Pakistan as reported in patients from more developed health care systems. It was observed that patients presenting with co-existing sepsis and hypercapnic ARF were at a higher risk of dying in the hospital. Patients presenting with serum HCO₃ values less than 35Meq/L were at a greater risk of failing NIV and requiring invasive ventilation.

Though NIV is well accepted and used across the west, there are very few regional descriptions of NIV usage. In 2004, Hussain S.F et al⁹ reported on an overall successful experience with noninvasive ventilation in 69 patients with various causes of acute respiratory failure. Similarly, we reported the benefits of using NIV in COPD patients as an adjunct to post-extubation respiratory failure.¹⁰ In 2006, Singh et al¹¹ from India also reported their favourable experience in 50 patients with all -cause acute respiratory failure. Our's is the largest study reported so far from this region and thus adds strength to the recommendations of using NIV even in poor, underdeveloped health care systems.

In the presented study, a diagnosis other than COPD was a risk factor for mortality. Literature has shown that NIV is most effective in patients with hypercapnic ARF due to COPD.¹² There is little evidence for the efficacy of NIV in hypercapnic ARF due to conditions other than COPD. Although a meta-analysis suggests that NIV is more effective in COPD exacerbations than other conditions⁴ most studies in non-COPD conditions involve hypoxaemic ARF and do not focus on hypercapnic ARF.^{13,14} In our study, majority of patients other than COPD group were asthmatic, with significantly high mortality rates because of failure of intubation. These patients were already decided DNR at the time of admission secondary to multifactorial reasons. It is known that hypercapnic ARF in these patients without intubation has a bad prognosis.

A low pH at presentation has shown an association with increased mortality^{15,16} and the need for intubation¹⁷ in patients admitted with COPD exacerbations. These studies have suggested that no improvement is observed in respiratory acidosis and respiratory rates during the first few hours of NIV and there is a higher likelihood of NIV failure.^{6,18} A fall in PaCO₂^{19,20} and improvement in pH^{2,19-21} have also proved to be protective. Our results are consistent with previously published studies. The findings identified a low pH at admission and failure to improve it for 48 hours, to be highly predictive of mortality in patients initially placed on NIV.

Age was found to be a risk factor for mortality in the presented study. Benhamou et al²² also reported a higher rate of treatment failure in elderly patients while Balami et al²³ opined that NIV can be used successfully in elderly patients admitted with hypercapnic respiratory failure secondary to acute exacerbation of COPD. Their findings of improvement of acidosis, respiratory rate and hypercapnia from the use of NIV are consistent with findings of other randomized trials conducted in a younger population.¹⁻³ Increase failure rate in elderly patients may be due to associated co-morbidities. This has been supported by Seneff et al²⁴ and Morettiet et al.²⁵ Singh et al¹¹ reported that in patients with acute respiratory failure, presence of one or more organ dysfunction was associated with failure

of NIV. Elevated creatinine and concurrent sepsis in our patients was also associated with increase failure rate and mortality which was consistent with finding of these studies. Concurrent sepsis as an independent predictor of mortality in our study has not been identified previously.

The presented study had limitations. There is accumulating evidence regarding improved outcomes with NIV in diverse patient groups with acute renal failure. This has broadened the indications and may have created a selection bias during the study period. The 'NIV service' was introduced at our institution in 2001, and a "learning and experience effect" on the team caring for patients could have had an impact on the outcomes. The retrospective nature of the data acquisition is another limitation. Lastly, the study population was recruited from a single tertiary-care center and this could affect the generalizability of the findings. Despite these reservations, this survey provides valuable information and is useful in demonstrating the value of NIV in a low income country.

In conclusion, to the best of our knowledge, this is the first study from Pakistan that has attempted to identify variables predictive of outcome in patients with acute hypercapnic respiratory failure treated with NIV. It is recommended that NIV should be added to the standard medical therapy for Pakistani patients with acute exacerbations of COPD. The initial pH and PaCO₂ can be used clinically to stratify patients according to their risk of meeting criteria for intubation. Monitoring such patients closely is necessary to evaluate treatment responsiveness and to facilitate endotracheal intubation if NIV fails.

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