Non-invasive ventilation for acute hypercapnic respiratory failure unrelated to chronic obstructive pulmonary disease (COPD)

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Abstract

Background and objectives: Non-invasive ventilation (NIV) is increasingly used for patients presenting with acute hypercapnic respiratory failure (AHRF), however although studies have demonstrated clear benefit in patients with COPD there is little evidence to guide treatment for AHRF unrelated to COPD, particularly outside of the critical care unit. The current survey reports the use of NIV, predominantly delivered in a dedicated NIV unit, in patients with AHRF unrelated to COPD.

Methods: Patients were included in this retrospective cohort survey if they had AHRF (pre-NIV pH<7.35 and $PaCO_2$>6.0 kPa) unrelated to COPD and were managed with NIV. The primary outcome measure was survival to discharge with secondary outcomes of survival to 30, 90 and 365 days.

Results: From 132 patient episodes requiring NIV, 79.55% survived to discharge, which is greater than previously reported outcomes for the use of NIV in COPD. Survival was independently associated with age but not pre-NIV pH, O_2 or diagnosis.

Conclusions: NIV is a safe and effective treatment and can be considered for use in patients with AHRF unrelated to COPD in specialist NIV units. Further prospective studies are required to identify further important prognostic features in this group of patients.

Introduction

Non-invasive ventilation (NIV) began to be widely used in the critical care unit for the management of acute hypercapnic respiratory failure (AHRF) in the 1980s, and in this setting several randomised controlled trials (RCT) demonstrated NIV reduced the mortality rate, length of hospital stay and need for endotracheal intubation in patients experiencing acute exacerbations of COPD which spread outside critical care over the last 20 years [1]. An important RCT set up on a medical ward demonstrated symptomatic and mortality benefits, and also a reduction in the need for invasive mechanical ventilation, in patients admitted with an acute exacerbation of COPD with a pH of 7.25 to 7.35 and PCO_2>6 kPa who were treated with NIV on a general medical ward [2]. The evidence supporting the delivery of NIV outside of the critical care unit supported the spread of acute NIV across the world.

Domiciliary NIV is now an established therapy for *chronic* ventilatory insufficiency unrelated to COPD including obesity related respiratory failure (incorporating 3 separate groups: hypercapnic obstructive sleep apnoea (OSA), combined OSA and obesity hypoventilation syndrome (OSA–OHS) and lone OHS [3]); thoracic cage structural abnormalities; progressive neuromuscular conditions; and rarer myopathic and neuropathic disorders [4,5] and its introduction before the development of daytime hypercapnia has been shown to improve long term outcomes [6-8]. However, the effectiveness of NIV in the *acute* setting for the management of AHRF unrelated to

COPD is not clearly established, [9-12] particularly outside of critical care units where its use is more pragmatic, and the published evidence base is limited to 2 critical care based studies in patients with obesity hypoventilation [13,14]. Nevertheless, NIV is increasingly used in the management of AHRF unrelated to COPD, and we therefore conducted a retrospective cohort survey in these patients in a dedicated NIV unit, which is part of a specialized respiratory ward in a large UK teaching hospital. The primary outcome measure was survival to discharge with the standard of care determined by previously reported outcomes from a National audit for NIV in acute exacerbations of COPD [15].

Methods

This was a retrospective cohort survey of in-patient admissions to a dedicated NIV unit based on a respiratory ward between 1st August 2004 and 31st December 2009 with AHRF unrelated to COPD. Ward based NIV in our institution is administered by specialist trained physiotherapists following a standard protocol with supervision by

respiratory physicians with a specialist interest in NIV. Where relevant, NIV settings from previous admissions were used to guide treatment. However, in general the initial inspiratory positive airway pressure was 12 cm H_2O with incremental increases in pressures, according to patient tolerability and response, to a median of 20 cm H_2O (maximum of 26 cm H_2O) as described previously [16]. The expiratory positive airway pressure was set to a median of 5 cm H_2O. Patients also received standard medical therapy and controlled oxygen to achieve target oxygen saturations of 88 to 92%. Patients managed on the critical care unit were excluded from the survey unless they were also subsequently managed in the NIV unit of the respiratory ward.

This was a retrospective case note audit and patient treatment followed standard trust protocols. In accordance with UK national guidelines, [17] ethical approval and individual patient consent were therefore not required for this audit which was registered with Heart of England NHS Foundation Trust (HEFT Audit Tracker #335).

Inclusion and exclusion criteria

All patients included in this survey had a pre-NIV $CO_2 > 6.0$ kPa and pH<7.35, and a diagnosis of AHRF unrelated to COPD formulated by an experienced consultant respiratory physician at the time of admission. For the purposes of the current survey, we included patients with obesity related respiratory failure, thoracic cage disease, neuromuscular disease and interstitial lung disease. A respiratory physician also retrospectively reviewed clinical records, spirometric tests and imaging to exclude patients with a previous or subsequent clinical diagnosis of COPD, asthma or a pre-bronchodilator $FEV_1/FVC < 0.7$ (where available). To reduce selection bias, patients were included in the survey irrespective of any decisions regarding limitations in escalation of care (including cardiopulmonary resuscitation, invasive ventilation, inotropic support or renal replacement therapy).

Analysis

The primary outcome for this survey was survival to discharge, and secondary outcomes were survival to 30, 90 and 365 days post initiation of NIV. In addition to survival, the survey recorded diagnosis, age, sex, spirometry (where available), and pre and post NIV arterial O_2, CO_2 and pH.

Statistical analyses were performed using IBM SPSS Statistics Version 21.0.0.0 for Windows (New York, NY, USA). Normality was tested for using the Kolmogorov-Smirnov test and statistical significance was taken as p<0.05. Data were non-parametric and are therefore presented as median (interquartile range). Multivariate analysis was performed using binary logistic regression (backward stepwise Wald) and Mann-Whitney tests were used to compare values between 2 groups. Chi squared analysis was used to determine differences between the observed and expected numbers within groups.

Results

There were132 patient episodes (from 105 unique patients) which met criteria for inclusion in the survey. The patient episodes included 45 men (34%) and 87 women (66%). The arterial blood gases were performed immediately before commencing NIV and data were available for all 132 patient episodes as per standard practice. Spirometry was performed when in the clinically stable state at least 6 weeks after any admission and data were available for 74 patient episodes (56.06%).

The patient episodes were categorised into 4 groups based on the underlying diagnosis: obesity related respiratory failure (n=60,

45.45%), thoracic cage disease (n=33; 25.00%), neuromuscular disease (n=31; 23.48%) and interstitial lung disease (n=8; 6.06%). The majority of patients were managed on a specialist NIV unit of a dedicated respiratory ward (123 episodes; 93.20%), however 9 episodes (6.80%) included episodes of care on both the respiratory ward and critical care.

In 105 patient episodes (79.55%), the patient survived to hospital discharge with a median length of stay of 14 days (IQR 9.00 – 23.00). In univariate analysis, there were no statistically significant differences in pH between those who survived compared to those who did not. Also, survival to hospital discharge did not vary significantly (p=0.565) by diagnostic category: obesity related (n=51; 85.00%), neuromuscular (n=23; 74.19%), thoracic cage disease (n=25; 75.76%) or interstitial lung disease (n=6; 75%).

Multivariate analysis was performed for survival to each time point and demonstrated that age and sex were independent predictors of survival, although both were not relevant at each time point. There were no sex differences between the diagnostic groups (p=0.111), and pre-NIV pH and age did not differ between sexes (p=0.100 and p=0.376 respectively). Also, while diagnosis was related to survival to 365 days post NIV in univariate analysis, it was not important at any other time point.

In univariate analysis, FEV_1 did not influence survival to discharge (p=0.347), 30 days (p=0.438) or 90 days (p=0.258), however it was significantly higher (p=0.006) in patients who survived to 365 days with a median of 1.12 (0.78 – 1.38) compared to those who did not (median 0.80; 0.50 – 0.95). However, since FEV_1 was only associated with survival at one time point and available for 74 patient episodes, it was not included in the multivariate analysis.

Discussion

This survey reports the outcomes for the use of NIV in patients with AHRF unrelated to COPD (with a pre-NIV pH<7.35 and CO2>6.0) who were predominantly managed in a dedicated unit on a specialist respiratory ward rather than critical care. The survey showed a survival to hospital discharge rate of 79.55% which is greater than the reported survival of 75% for patients with COPD related AHRF who required NIV in a UK nationwide audit [15]. The in-hospital mortality rate reported in the current study and the national COPD audit is greater than that quoted in the initial clinical trials of NIV on general medical wards in patients with COPD [2]. However, the national COPD NIV audit concluded that this excess mortality related to the inclusion of patients who were unlikely to survive due to the severity of their illness and co-morbidities [15]. Similarly, in our institution, NIV is offered to most patients who present with AHRF with few exclusion criteria, unless clearly futile or against patient wishes. In the absence of effective predictors of mortality, we feel that this is a pragmatic approach for an intervention which is generally well tolerated and relatively easy to withdraw if appropriate. Furthermore, it is important to recognise that many patients would undergo similar treatment again despite high levels of functional disability [18] and in general patients accept a 'high burden' of intervention if necessary to save their life [19].

Patients who required critical care (for example for immediate intubation or with 2 or more organ failure without limitations of care) were only included in the current survey if they were subsequently managed on the NIV unit of the respiratory ward. Nevertheless, the survey included patients with a broad spectrum of underlying disease processes. Unfortunately limitation of care decisions were not recorded in the current survey and therefore the impact of these on mortality

cannot be determined. Additionally, data was not recorded on the patients who declined NIV or in whom it was clearly futile which may have also influenced the outcomes of the current survey.

The in-hospital mortality rate of 15% for patients with obesity related respiratory failure was lower than other diagnostic groups, although this difference did not achieve statistical significance. Mortality rates have previously been reported to be lower in patients with obesity related respiratory failure managed with NIV compared to those with COPD [13] in a survey which only included patients managed in a critical care environment for which patient selection was not clearly reported. In contrast, the current survey includes patients with a wide spectrum of co-morbidities who were predominantly managed in a ward based environment. The contribution of selection bias to the outcomes of the critical care based survey is also suggested by their relatively high 12 month survival rate, which exceed that of previous studies [20] as well as the current survey. Nevertheless, the good outcomes both in critical care and the current survey indicate that patients with obesity related AHRF should be considered for NIV, potentially in specialist NIV units rather than critical care.

Even within the 12-month follow-up period of this survey, survival beyond discharge decreased rapidly across all diagnostic groups, and only 60.61% of patients survived to 365 days post-initiation of NIV. This prognostic information is useful, and although replication in a larger prospective study is required, it emphasises the importance of appropriate medical care for patients admitted with AHRF following discharge to identify appropriate interventions to prolong survival or palliate symptoms, particularly for those with thoracic cage disease or ILD.

Predictors of survival

Age and sex were both important independent predictors of survival in this non-COPD cohort requiring acute NIV for AHRF, however diagnostic category (predominant cause of respiratory failure), pH and pre-NIV O_2 were not. The association between age and survival to discharge would be expected since age is not a limitation to treatment in our institution and in general being older is associated with a worse prognosis. However, the association between sex and survival is more surprising, particularly since there appeared to be no link between sex and pH, age or diagnostic code. However, the R^2 value for the logistic regression was relatively low (0.206 for survival to discharge) which indicates that other factors not recorded in the current survey are also likely to be important predictors of survival and this may therefore represent confounding rather than a true association. Future audits and studies should therefore include other potential prognostic markers such as FEV_1, pulse, blood pressure and co-morbidities, in addition to recording any decisions to limit treatment options such as invasive ventilation.

Since pH was not associated with survival, the current survey suggests that pH should not be used to determine prognosis nor be an exclusion factor for the use of NIV in patients with AHRF unrelated to COPD in a specialist NIV unit. Conversely, a UK national audit of the use of NIV in patients with COPD reported pH to be a significant determinant of mortality,[15] and therefore the mechanisms leading to AHRF in patients with and without COPD, and their subsequent treatment responses, are likely to differ.

FEV_1 is also an established predictor of all-cause mortality [21] and cardiovascular morbidity, [22] and therefore it is not only a severity marker for respiratory disease but also a surrogate marker of overall health, and may therefore be an important predictor of survival in

patients with AHRF. In the current survey, FEV_1 predicted survival to 365 days but not other time points, although it was only available for 56.06% of patient episodes. It may be possible in future prospective studies to collect more spirometric data, however stable state measures would still only be available for patients who died during the admission if they had previously undergone respiratory assessment.

Ideally these data require confirmation in an RCT, however given the clear efficacy of NIV, it may be difficult to justify a placebo arm in any future trial for AHRF unrelated to COPD. It will nevertheless be important to continue to audit the use of NIV in patients with and without COPD, ideally at a national or international level.

Conclusions

In patients with AHRF unrelated to COPD (with obesity related respiratory failure, thoracic cage disease, neuromuscular disease or interstitial lung disease) and a pH<7.35, the use of NIV is associated with a survival to hospital discharge rate which is greater than that reported for patients with acute exacerbations of COPD. NIV is widely used, even in patients in whom invasive ventilation would likely prove futile, and therefore in a more selected population the mortality would be anticipated to be lower, although this may not be consistent with patient wishes. Further studies are required to establish the major prognostic factors for patients presenting with AHRF without COPD, however at present, arbitrary pH thresholds should not be used to exclude patients from treatment, nor to determine place of care (critical care versus NIV unit). Despite the absence of controlled trials these data and those of the critical care study [13] indicate that NIV is an effective treatment that should be considered for all patients presenting with AHRF unrelated to COPD with a CO2>6.0 and pH<7.35.

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