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EDITORIAL

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Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: a new gold standard?

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Non-invasive ventilation (NIV) has been shown to be an effective treatment for ventilatory failure resulting from acute exacerbations of chronic obstructive pulmonary disease in a number of randomised controlled trials (RCTs) and in a recent meta-analysis [1]. It has been used in a variety of countries and settings, with different ventilator modes and interfaces and in differing degrees of severity.

In the studies in which NIV was applied in the ICU [2, 3, 4, 5] the most striking finding was a reduction in the need for endotracheal intubation (ETI) and mechanical ventilation (MV), which in the largest study translated into improved survival, reduced complication rates and length of both intensive care unit (ICU) and hospital stay [2]. These studies showed that NIV is feasible in acute exacerbations of COPD, and that the prevention of ETI is advantageous. Because paralysis and sedation are not needed with NIV, ventilation outside the ICU is an option; given the considerable pressure on ICU beds in most countries, the high costs and the fact that for some patients admission to ICU is a distressing experience [6], this is an attractive option. NIV can be instituted at an earlier stage in the natural history of the condition before mechanical ventilation would normally be considered necessary. There have been a number of prospective randomised controlled studies of NIV outside the ICU either on general wards or in accident and emergency departments [7, 8, 9, 10, 11, 12, 13]. NIV was instituted at a higher pH than that reported in the ICU studies and most failed to show any significant advantage to NIV when analysed on an intention to treat basis, but in one study [7] when those unable to tolerate NIV were excluded a significant survival benefit was seen (9/30 vs. 1/26, p=0.014). These studies were all relatively small and may have lacked sufficient statistical power to show a difference in the need for intubation and mortality given that most patients with a mild exacerbation of COPD (defined by the degree of acidosis) would not be expected to need ETI and MV anyway [14]. In a large (n=236) multicentre RCT of NIV in acute exacerbations of COPD on general respiratory wards in 13 centres [12] 'treatment failure', a surrogate for the need for intubation, defined by a priori criteria, was reduced from 27% to 15% by NIV (p<0.05). In-hospital mortality was also reduced from 20% to 10% (P<0.05). Sub-group analysis suggested that the outcome in patients with pH lower than 7.30 after initial treatment was inferior to that in the studies performed in the ICU. NIV was applied by the usual ward staff, most of whom had had little or no previous experience of NIV, using a bilevel device in spontaneous mode, according to a simple protocol. This study suggests that with adequate staff training NIV can be applied with benefit outside the ICU and that the early (pH <7.35 on admission to the ward) introduction of NIV on a general ward results in a better outcome than providing no ventilatory support for acidotic patients outside the ICU. The results in the more severely affected patients (pH<7.30 after initial management) were not as good as those seen in the ICU studies suggesting that this simple approach is not appropriate in these patients, and that they are best managed in a higher dependency setting with a more sophisticated ventilator individually adjusted to their requirements.

None of these studies involved the use of a placebo arm because of concern that this was impractical and might make the patients worse; it is therefore possible that the results may have been influenced by bias. However, a recent study [15] of patients with acute cardiogenic pulmonary oedema or an acute exacerbation of

COPD presenting to the emergency department found that placebo NIV had no effect upon physiological measures, such as arterial blood gas tensions and respiratory rate, and in all cases rescue therapy with active NIV or intubation was required. In seven of the ten patients the institution of active NIV resulted in a prompt improvement. By contrast there was a rapid improvement in physiological variables in all patients in the group treated with active NIV from the outset and none required intubation.

A number of studies have suggested that NIV is less likely to be successful in more severely affected patients [2, 16, 17], and all the studies reported to date have excluded patients who required immediate ETI and MV. The study of Wood et al. [9] suggested that failure to move to ETI in a timely fashion may have explained a trend towards a worse survival in the NIV group. The concern has been voiced therefore that, particularly in the more severely ill, NIV may be harmful by delaying the institution of the "gold" standard therapy, namely ETI and MV.

Conti et al. [18] report in this journal a prospective RCT of NIV vs. immediate ETI and MV in patients with an exacerbation of COPD. Not surprisingly their patients were sicker than those reported in previous studies, as evidenced by the mean pH of 7.2, compared with 7.27 in the study of Brochard et al. [2] and 7.32 in the study of Plant et al. [12]. In these sicker patients they showed that NIV was no worse than ETI and MV. In those who could be managed successfully with NIV there was an advantage both in the short term but also in the year after hospital discharge. This confirms the findings of two previous studies comparing NIV patients with historical controls who had been invasively ventilated [19, 20]. Imperfect matching is one possible explanation in these studies [21], but patients who are intubated and mechanically ventilated may lose a considerable amount of muscle bulk rendering them susceptible to further episodes of ventilatory failure [22, 23, 24, 25]. Longer term follow-up from the study of Plant et al. [17] failed to show any statistically significant benefit from NIV compared with conventional therapy, although, importantly, the study showed a median survival in both groups of over 1 year, indicating that the patients salvaged by NIV were not just those who had a very poor prognosis. It may be significant that few patients in either group were intubated and ventilated and this is an important difference when compared with the studies mentioned above. The intubation rate of 52% in the NIV group in the study by Conti et al. [18] was higher than in other RCTs, which is not surprising given that these were a sicker group of patients. It does, however, reinforce the view that NIV is best instituted early [26].

In common with other studies some patients were still excluded, in particular those intubated prior to transfer to the ICU or those with respiratory arrest or pauses, psychomotor agitation requiring sedation, heart rate below 60 or systolic blood pressure below 80 mmHg. NIV remains a complimentary technique to invasive ventilation but for patients intubated, either from the outset or after a failed trial of NIV, non-invasive ventilation may have a role in weaning [27, 28] or in the management of respiratory failure following extubation [29]. Further studies are needed but NIV is likely to be useful in selected patients.

There are no absolute contraindications to NIV, although a number have been suggested [16, 30]. These include coma or confusion, inability to protect the airway, severe acidosis at presentation, significant co-morbidity, vomiting, obstructed bowel, haemodynamic instability (two studies have shown only small changes in cardiac output when NIV is initiated [31, 32], but haemodynamic collapse comparable to that often seen when patients are intubated is very rare), radiological evidence of consolidation, and orofacial abnormalities which interfere with the mask/face interface. In part, these "contraindications" have been determined by the fact that they were exclusion criteria for the controlled trials. It is therefore more correct to state that NIV is not proven in these circumstances rather than that it is contraindicated. In a recent epidemiological study of 42 ICUs over a 3-week period NIV was never used in coma [33]. Although mask positive pressure ventilation is far away the most widely used non-invasive modality, negative pressure ventilation using an iron lung still has its advocates [34], and this technique has been used successfully in comatose patients [35]. Its use, however, is confined to a few specialised units. Whether NIV should be attempted in a particular patient must depend on individual circumstances. For instance, if invasive ventilation is not considered appropriate, but NIV would be acceptable, there is nothing to be lost by a trial of NIV, and there are no contraindications in this situation. NIV may not be appropriate in well-documented end-stage disease or when several co-morbidities are present. That the patient can continue to have a say is one potential advantage in this situation.

When NIV can be successfully applied there are clear advantages, particularly a reduction in infectious complications [36, 33, 37, 38] and length of ICU and hospital stay [2], with an attendant reduction in costs [39]. There is no convincing evidence to date that a failed trial of NIV is harmful. However, there is always the danger that, as confidence grows, NIV may be continued for too long in an individual patient to the point of cardiorespiratory arrest. Further data are needed as to when NIV should be abandoned in favour of invasive ventilation. When embarking upon a trial of NIV there should be a clear plan of what will be done should the patient fail and how failure will be recognised.

The study of Conti et al. [18] is a further, perhaps the final, piece in the jigsaw of when NIV is indicated in pa-

tients with an acute exacerbation of COPD. It now seems reasonable to suggest a trial of NIV in the vast majority of patients acidotic because of an acute exacerbation of COPD. Early intervention is more likely to be successful [12, 17], but even when patients present later in the natural history of their exacerbation there is still a role for NIV. Being first is often a significant factor when defining a gold standard. Perhaps the time has now come, on the basis of the published evidence, to define NIV as the gold standard mode of ventilatory support for exacerbations of COPD, with ETI and MV regarded as second-line rescue therapy when it fails; as with second-line chemotherapy for cancer this often comes at greater expense and with more risk to the patient.

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