Review

Neonatology
formerly Biology of the Neonate

Neonatology 2009;95:368–372
DOI: 10.1159/000209303

Published online: June 4, 2009

Current Trials in the Treatment of Respiratory Failure in Preterm Infants

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Key Words
Ventilation · Surfactant · Continuous positive airway pressure · Inhaled nitric oxide · Chronic lung disease

Abstract
The end of the 20th century brought significant improvements in the outcome of extremely low-birth-weight infants related to the increased use of antenatal corticosteroids and the introduction of postnatal surfactant to prevent or treat respiratory distress syndrome. As we complete the first decade of the 21st century, less progress in improving clinical outcome in this population has been accomplished. Newer modes of ventilation and the use of inhaled nitric oxide have made few demonstrable improvements in outcome. Surprisingly, the greatest hope for improvement may come from the refinement of currently available care including less invasive respiratory support and the combining of various known therapies (such as continuous positive airway pressure and surfactant).
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Introduction

The end of the 20th century brought significant improvements in the outcome of extremely-low-birth-weight infants [1]. Increased use of antenatal corticosteroids for promoting lung maturity and the introduction of postnatal surfactant to prevent or treat respiratory distress syndrome (RDS) has been credited with much of this progress. As we complete the first decade of the 21st century, it is hard to identify what specific further improvements have been made in the treatment of respiratory failure in preterm infants. The following article will review clinical trials in a variety of areas that have addressed respiratory care in very preterm infants.

High-Frequency Ventilation

High-frequency ventilation (HFV) appeared to hold great promise for neonatal care in the 21st century. High-frequency ventilators apply continuous distending pressure and deliver small tidal volumes superimposed on an extremely rapid rate. In animal models, this approach to ventilation has demonstrated less lung damage. Three basic types of HFV are currently utilized: high-frequency oscillatory ventilation (HFOV), high-frequency flow interrupters (HFFI) and high-frequency jet ventilation (HFJV). All have been tested in the preterm population.

The use of HFV has become widespread. More than 20% of all very-low-birth-weight infants are placed on HFV at some point during their course in neonatal intensive care [2]. Despite the widespread introduction of HFV, there seems to be little appreciation of the clinical impact of this relatively new therapy. Henderson-Smart et al. [3] have reviewed randomized controlled trials comparing the elective use of HFOV with conventional ventilation in preterm infants who are mechanically ventilated for pulmonary dysfunction. This systematic review includes studies that randomized preterm infants with respiratory dysfunction to either elective HFOV (or HFFI) or to conventional ventilation soon after mechanical ventilation

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1661–7800/09/0954–0368$26.00/0

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was started. In their search of the literature, the authors found 15 randomized controlled trials that met the criteria for inclusion. The size of studies varied considerably ranging from 40 to 673 infants. Most of the studies focused on very-low-birth-weight infants; however, 3 studies included infants weighing as much as 2,000 g. The age at randomization varied from less than 1–12 h of age.

In the analysis of all included trials, surprisingly few improvements in clinical outcome were noted. No individual trial reported a decrease in pulmonary air leak. In fact, the meta-analysis reports a slight increase in the risk of pulmonary air leak [10 trials; typical relative risk (TRR) 1.19, 95% confidence interval (CI) 1.05–1.34]. Nine trials reported rates of neonatal mortality. None of the individual trials demonstrated any difference in mortality and the overall analysis demonstrated no difference in the risk of death at 28 days (TRR 1.09, 95% CI 0.88–1.35). Six trials reported rates of oxygen dependency at 28–30 days in surviving infants. No individual trial reported a decrease in the risk of oxygen dependency at 28–30 days and the meta-analysis of these 6 trials demonstrated no difference in the risk of oxygen dependency at 28 days (TRR 0.98, 95% CI 0.88–1.10).

The status of infants at 36–37 weeks' postmenstrual age is not significantly altered by elective HFOV. Thirteen trials reported rates of death by 36–37 weeks' postmenstrual age or at the time of discharge. None of the individual trial demonstrated a difference in mortality. The meta-analysis demonstrated no difference in mortality at 36–37 weeks' postnatal age or discharge (TRR 0.98, 95% CI 0.83–1.14). Of the 13 studies that reported rates of chronic lung disease at 36–37 weeks' postmenstrual age or discharge in surviving infants, 4 demonstrated a decrease in risk. The meta-analysis suggested a small decrease in the risk of chronic lung disease at 36–37 weeks' postmenstrual age or discharge in surviving infants (TRR 0.89, 95% CI 0.81–0.99). The combined outcome of death or chronic lung disease at 36–37 weeks' postmenstrual age or discharge is marginally affected by elective HFOV (TRR 0.93, 95% CI 0.86–1.00). However, an increased risk in intraventricular hemorrhage (IVH) and white matter damage has been reported in individual trials of HFOV, though the meta-analysis does not suggest a significant increase in the risk of IVH (TRR 1.05, 95% CI 0.96–1.15). Two trials of elective HFOV reported an increase in the risk of severe IVH and there was a trend towards an increase in severe IVH (grades III and IV) noted in the meta-analysis (TRR 1.11, 95% CI 0.95–1.30). Only 6 trials have addressed long-term developmental status. One trial reported worse developmental outcome; the other studies did not report any significant differences. The methods and timing of developmental testing were too heterogeneous to allow for meta-analysis.

Based on the results of the systematic overview, Henderson-Smart et al. [3] concluded that there is no clear evidence that elective HFOV offers important advantages when used as an initial ventilation strategy in preterm infants with acute pulmonary dysfunction. In particular, they noted that there is no evidence for a reduction of death rate, although there may be a small reduction in chronic lung disease. Adverse effects on short-term neurological outcome have been observed in some studies, but the effects are not significant overall. It is disappointing to note the limited improvement reported with HFOV. Further analyses, such as individual patient data meta-analysis, are underway to try to ascertain whether or not there are specific ventilators, ventilation strategies, or subgroups of patients that benefit from this therapy. Until that is known, there is little reason to have great hope in HFOV as the breakthrough therapy of the 21st century.

Noninvasive Ventilation Strategies

At the opposite end of the spectrum, strategies involving less invasive ventilation have become increasingly utilized. Although first introduced in the 1970s, continuous positive airway pressure (CPAP) did not gain wide acceptance in neonatal intensive care units until the late 1980s. Renewed interest in CPAP began after a survey of centers that were all recipients of National Institutes of Health SCORE Grants for neonatal lung disease [4]. This survey showed a great deal of variation in the incidence of bronchopulmonary dysplasia (BPD, defined as oxygen use at 28 days of age) among these centers. The center with the lowest rate of BPD, Columbia Babies Hospital in New York, had the most unique approach to stabilization of the sick newborn infant. Their policy included stabilization on CPAP using short nasal prongs. Since then there have been many reports in the literature regarding the association between introduction of nasal CPAP and the improvement of pulmonary outcome [5]. However, limited data are available from large randomized controlled trials [6]. The recent landmark trial in this area is the COIN (Cpap Or INtubation) Trial, from the Australasian Trial Network [7]. This trial assessed whether nasal CPAP applied in spontaneously breathing preterm infants shortly after birth compared to intubation and ventilation would reduce the rate of death or BPD. Morley et al. [7] randomly assigned 610 infants who were born at 25–

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28 weeks' gestation to CPAP or intubation and ventilation at 5 min of age. At 36 weeks' postmenstrual age, 33.9% of 307 infants who were assigned to receive CPAP had died or had BPD as compared with 38.9% of 303 infants who were assigned to receive intubation (odds ratio 0.80, 95% CI 0.58–1.12). There was little difference in overall mortality. There was a slight increase in death in the least mature infants (25–26 weeks' gestation) in the CPAP group. In addition, there was a concerning overall increase in pneumothorax (3 vs. 9.1%, $p = 0.001$). It is not clear what lessons to draw from the COIN trial. Although the trial demonstrated that early stabilization of these infants is feasible, the results regarding pneumothorax and mortality (in the most immature infants) are of concern.

Another innovative approach to non-invasive ventilation is the addition of intermittent mandatory ventilation to non-invasively applied continuous distending pressure. Nasal intermittent positive pressure ventilation (NIPPV) has been used in the newborn since the 1980s. In a survey of tertiary care centers in Canada, Ryan et al. [8] reported that over 50% of centers used NIPPV. As the use of NIPPV increased, reports of complications surfaced. Garland et al. [9] reported an association between the use of NIPPV and increased risk of gastrointestinal perforation. Since then the use of NIPPV has decreased. However, a close examination of the older evidence and newer studies suggest that NIPPV may still hold some promise as a less invasive means of respiratory support from the preterm infant.

In a meta-analysis of trials using NIPPV to prevent complications after extubation in preterm infants, Davis et al. [10] noted a decrease in the risk of respiratory failure in infants who were extubated to NIPPV (TRR 0.21, 95% CI 0.10–0.45). This is a clinically significant reduction in respiratory failure; only 3 infants (95% CI 2–5 infants) needed to be treated with NIPPV to prevent one extubation failure. No complications of therapy were reported in the trials. Recently, several studies have evaluated stabilization of preterm infants on NIPPV. Kugelman et al. [11] evaluated the use of NIPPV compared to nasal CPAP in preterm infants of less than 35 weeks' gestation with RDS. In this randomized controlled trial, Kugelman enrolled 41 infants to nasal CPAP and 43 to NIPPV. Infants assigned to receive NIPPV needed less assisted ventilation (25 vs. 49%, $p < 0.05$) and had a decreased incidence of BPD (2 vs. 17%, $p < 0.05$) compared to those treated with nasal CPAP. This was particularly true for infants weighing <1,500 g (5 vs. 33%, $p < 0.05$). Bhandari et al. [12] evaluated the use of synchronized NIPPV compared with conventional ventilation. Infants with birth weights 600–1,250 g were randomized to receive either synchronized NIPPV or conventional ventilation. 21 infants were managed on conventional ventilation and 20 on synchronized NIPPV. Fewer infants managed on synchronized NIPPV had BPD or died (20 vs. 52%, $p = 0.03$). Moretti et al. [13] compared flow synchronized NIPPV to nasal CPAP. Consecutive infants with birth weights ≤1,250 g who required endotracheal intubation within 48 h of birth were randomized at the time of extubation. Most of these infants (30/32 or 94%) were successfully extubated to flow synchronized NIPPV but only 61% (19/31) to conventional nasal CPAP. Larger trials that evaluate the use of NIPPV as a modality for initial stabilization or in surfactant-treated infants at the time of extubation are required to fully understand the effects of this therapy.

Pulmonary Surfactant

The development of surfactant treatment at the end of the 20th century was one of the great advances in respiratory care [14]. Refinements in surfactant therapy will contribute to ongoing improvement in the 21st century. New surfactant preparations composed of synthetic phospholipids and essential hydrophobic surfactant protein analogs have been developed [15]. These surfactant protein analogs have been produced by peptide synthesis and recombinant technology to provide a new class of synthetic surfactant that may be a suitable alternative to animal-derived surfactants. Preliminary clinical studies have shown that treatment with these novel surfactant preparations can ameliorate RDS and improve clinical outcomes. Clinicians will need to further understand the difference in clinical impact between these newer products and the well-tested animal-derived products.

In addition, the use of surfactant for other indications and the timing of treatment need to be further studied. In larger infants the approach of treating spontaneously breathing infants with evolving RDS with surfactant and then extubating to nasal CPAP has become incorporated in practice. The meta-analysis of Stevens et al. [16] evaluated this approach to treatment compared to maintaining infants on nasal CPAP. In these trials there was a significant reduction in the long-term need for mechanical ventilation (6 trials; TRR 0.67, 95% CI 0.57–0.79) and a decrease in the risk of air leak and pulmonary interstitial emphysema (6 trials; TRR 0.52, 95% CI 0.28–0.96) in infants receiving this approach to treatment. Obviously surfactant utilization increased in this population. In the 4 studies that reported rates of BPD, there was a trend to-

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wards less oxygen requirement at 28 days of life (TRR 0.51, 95% CI 0.26–0.99). Recently, Rojas et al. [17] completed a study of early surfactant therapy with immediate extubation compared to continued support with nasal CPAP in very preterm infants treated soon after birth. Eight centers in Columbia participated in this randomized controlled trial. Infants born between 27 and 31 weeks' gestation with evidence of respiratory distress were randomly assigned to intubation, surfactant treatment, extubation and restabilization on nasal CPAP or to nasal CPAP alone within the first hour of life. 279 infants were enrolled (141 to the treatment group and 138 to the control group). The need for mechanical ventilation was lower in the treatment group compared to the control group (26 vs. 39%). Air leaks were seen less frequently in the treatment group (2 vs. 9%). Fewer infants in the treatment group had an oxygen requirement at 36 weeks' postmenstrual age (49 vs. 59%). These studies open the door for the potential use of early surfactant treatment and extubation to other noninvasive forms of ventilation, such as NIPPV.

Inhaled Nitric Oxide

Inhaled nitric oxide (iNO) is an attractive therapeutic agent to consider for use in the preterm newborn. Elevated pulmonary vascular resistance and pulmonary artery pressure can be demonstrated in premature animals with respiratory distress due to lung immaturity and iNO can improve oxygenation in these animal models. In addition to this effect on vascular muscle tone, NO plays a role in early lung development.

The potential use of iNO could involve several populations of critically ill preterm infants. Potential indications include early administration of iNO to ventilated preterm infants to prevent hypoxemic respiratory failure and the need for increased ventilator support, administration of iNO to preterm infants with hypoxemic respiratory failure in the initial phases of RDS and, lastly, administration of iNO to preterm infants with evolving chronic lung disease. Barrington and Finer [18] review all three of these populations in their systematic overview. In total, 11 published randomized controlled trials of iNO are included in this review. Seven of the included trials address the use of iNO in preterm infants eligible within the first 3 days of life based on hypoxemic respiratory failure. In these studies there is a trend towards a reduction in BPD in infants receiving iNO (TRR 0.89, 95% CI 0.76–1.05). However, no statistically significant reduction in death was noted (TRR 1.05, 95% CI 0.91–1.22). Overall, a trend towards decreased death or BPD at 36 weeks' postmenstrual age was noted (TRR 0.95, 95% CI 0.88–1.02). The incidence of IVH was similar in the 3 studies that reported this outcome (TRR 1.00, 95% CI 0.73–1.37). However, there was a disconcerting increase in the risk of severe IVH in infants who received iNO (TRR 1.27, 95% CI 0.99–1.62). Few of these studies assessed the infants' neurodevelopmental status at 18–24 months, so the long-term impact of this finding is uncertain.

Infants who received iNO after 3 days of age based on their increased risk for BPD have also been studied. Two studies address this issue and the study of Ballard et al. [19] is significantly larger and dominates the review. In this study there was a borderline reduction in the risk of BPD at 36 weeks' postmenstrual age in surviving infants who received iNO (RR 0.88, 95% CI 0.76–1.02). Mortality prior to discharge was not improved. There was a trend toward improvement in death or BPD at 36 weeks' postmenstrual age (RR 0.89, 95% CI 0.78–1.02). No follow-up data are available from the large trial of Ballard et al. [19], so it is unclear whether the impact of this therapy in the long term is meaningful.

Of interest, trials that evaluated the routine use of iNO in intubated preterm infants have some of the most promising results, although there was no effect on the risk of BPD at 36 weeks' postmenstrual age (TRR 0.96, 95% CI 0.85–1.08). However, there was a slight decrease in the risk of death or BPD at 36 weeks' postmenstrual age in infants who received iNO (TRR 0.91, 95% CI 0.84–0.99). Both studies report rates of severe IVH and periventricular leukomalacia. There was a significant decrease in the risk of these serious intracranial lesions (TRR 0.70, 95% CI 0.53–0.91). To date, only one of the studies has presented developmental follow-up on enrolled infants [20]. In this study there was a trend towards a decrease in neurodevelopmental disability in the infants who received iNO (RR 0.53, 95% CI 0.33–0.87). Follow-up of infants in these trials will be important to understand whether or not this therapy has long-term benefits.

The recent European study of Mercier et al. [21] is not included in the meta-analysis but does not add further support for the use of iNO in preterm infants. Mercier et al. enrolled preterm infants with gestational ages of 24+0 to 28+6 weeks who had respiratory distress requiring either surfactant or CPAP >4 cmH_2O with FiO_2 >0.30 to maintain an oxygen saturation >85%. Infants were excluded if they required FiO_2 >0.50. Infants were randomly assigned to 'low-dose' iNO (5 ppm) or placebo within 24 h after birth for 7 days and up to 21 days if they still required respiratory support. 800 infants were randomized

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at 36 centers in 9 European countries. The median gestational age was 26.6 weeks and median birth weight was 835 g. 90% were intubated at study entry and 10% were on CPAP. The median duration of study therapy was 20.7 days. There was no difference reported in the primary outcome measure of survival without BPD (iNO treatment 65.3% vs. control 65.5%, p = 0.73). The rate of serious adverse events was comparable between treatment groups. Long-term follow-up of this study population is ongoing.

To date there is little to support the contention that iNO will lead to improved survival in any of the populations studied. Importantly follow-up data from a variety of studies are still awaited and will determine whether iNO will prove to be useful in these very preterm infants.

Conclusions

Overall, there have been fewer improvements in the respiratory care of the extremely-low-birth-weight infants in the first decade of the 21st century than the end of the 20th century. Despite the widespread testing of innovative therapies such as HFV or iNO, little clinical improvement can be demonstrated. Perhaps the best chance for improvement lies in less invasive approaches to respiratory support, such as NIPPV, or in the refinement of our approach to support with already proven therapies, such as surfactant administration.

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