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Review article

Neonatal ventilation strategies and long-term respiratory outcomes

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ABSTRACT

Long-term respiratory morbidity is common, particularly in those born very prematurely and who have developed bronchopulmonary dysplasia (BPD), but it does occur in those without BPD and in infants born at term. A variety of neonatal strategies have been developed, all with short-term advantages, but meta-analyses of randomized controlled trials (RCTs) have demonstrated that only volume-targeted ventilation and prophylactic high-frequency oscillatory ventilation (HFOV) may reduce BPD. Few RCTs have incorporated long-term follow-up, but one has demonstrated that prophylactic HFOV improves respiratory and functional outcomes at school age, despite not reducing BPD. Results from other neonatal interventions have demonstrated that any impact on BPD may not translate into changes in long-term outcomes. All future neonatal ventilation RCTs should have long-term outcomes rather than BPD as their primary outcome if they are to impact on clinical practice.

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1. Introduction

Chronic respiratory morbidity is a common outcome of very premature birth, particularly in those who had developed bronchopulmonary dysplasia (BPD), chronic oxygen dependency beyond 28 days after birth. BPD was initially described in infants who had severe lung disease, so-called old BPD. Affected infants usually required high inspired oxygen concentrations and intermittent positive pressure ventilation with high peak inflating pressures. It can, however, occur in very prematurely born infants who had minimal or even no initial respiratory distress, so-called new BPD. The latter has been suggested to be a maldevelopment sequence resulting from interruption/interference of the normal development signalling for terminal maturation [1]. Unfortunately, infants with BPD suffer chronic respiratory morbidity. They may require supplementary oxygen for many months,

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although few remain oxygen dependent beyond two years of age [2]. Hospital readmission is common, particularly for respiratory problems [3]. Troublesome respiratory symptoms requiring treatment can occur in childhood [4] and persist into adulthood [5]. Children and adults who had BPD have lung function abnormalities. In the first two years, they may have high airways resistance, gas trapping and ventilation inhomogeneity. Lung growth and remodelling results in a progressive improvement in lung function, but airflow limitation persists [6], such that airway obstruction and impaired gas transfer is seen in adults who had BPD [7].

BPD has a multifactorial aetiology, which includes volutrauma and oxygen toxicity. As a consequence, there has been much research in developing and optimizing new mechanical ventilation and noninvasive respiratory support techniques with the hope of reducing the occurrence of BPD and chronic respiratory morbidity. The aim of this review is, by examining the literature, to determine how successful the newer ventilator strategies have been in decreasing BPD and, more importantly, if their introduction has influenced long-term respiratory outcomes. It should also be noted that infants born at term and who required mechanical ventilation can also suffer chronic adverse effects [8]. Unfortunately, as this review will also highlight there have been few studies investigating respiratory support techniques in that population.

2. Noninvasive respiratory support

2.1. CPAP

An early meta-analysis of RCTs of prophylactic trials demonstrated no advantage in outcomes of prophylactic nCPAP [9]. Subsequently, there have been RCTs of differing design with differing results. The COIN trial [10] (early CPAP versus intubation and ventilation) demonstrated a significantly lower risk of death from need for supplementary oxygen at 28 days, but there was no significant difference in the need for supplementary oxygen at 36 weeks PMA and the CPAP group had a significantly higher incidence of pneumothorax. The SUPPORT trial (intubation and early surfactant versus early CPAP) [11] reported no differences in death or BPD and the CURPAP trial (prophylactic surfactant followed by CPAP versus early CPAP) reported no significant differences in the primary outcome of need for mechanical ventilation within five days. The Breathing Outcomes Study [12], a secondary study to SUPPORT, compared respiratory morbidities at six-month intervals from hospital discharge to 18–22 months corrected age (CA); infants randomized to CPAP had significantly fewer episodes of wheezing without a cold, respiratory illnesses diagnosed by a doctor, and physician or emergency room visits for breathing problems. Further studies are required to determine the optimal technique for delivering nCPAP. It has been suggested that weaning from CPAP by reduction in time rather than pressure might increase the likelihood of BPD [13]. The Cochrane review of three trials [14] highlighted that one trial in which nCPAP was just stopped had shown a significant decrease in the duration of oxygen therapy and a decreased length of stay. Trials are required to determine whether simply stopping nCPAP versus a reduction in pressure might influence long-term outcomes.

2.1.1. Nasal intermittent positive pressure ventilation

Non-randomized or short-term studies have demonstrated advantages of nasal intermittent positive-pressure ventilation (NIPPV) compared to nCPAP. A RCT [15] in which 1009 ELBW infants were enrolled, however, demonstrated no significant differences in death or survival with BPD between NIPPV and CPAP.

2.1.2. Heated, humidified, high-flow nasal cannula

Heated, humidified and high-flow nasal cannula (HHFNC) technique has become popular, as highlighted by 63% of units in Australia and New Zealand being reported to be using HHFNC in 2010 [16]. In addition, a survey of 57 level 2 or 3 neonatal units in the UK reported in 2013 that HHFNC was used in 77% of units [17]. In a multicentre trial of 303 infants less than 32 weeks of gestational age, however, infants randomized to HHFNC compared to those randomized to nCPAP did not differ significantly with regard to the primary outcome—treatment failure within seven days. There were no significant differences in the rates of death before discharge, need for oxygen supplementation at 36 weeks PMA, pneumothorax, PDA requiring treatment, NEC, retinopathy of prematurity (ROP) or IVH [18]. In another randomized trial of 432 infants of 28 to 42 weeks of gestational age, no significant difference was seen in early (<72 hours) extubation failure between infants on HHFNC (10.8%) compared to nCPAP (8.2%) [19]. Infants remained on HHFNC longer than on nCPAP (median, 4 versus 2 days, $p = 0.01$). There were no significant differences with regard to days on supplemental oxygen (median, 10 versus 8 days) or the incidence of BPD (20% versus 16%). There is insufficient evidence to support the routine use of HHFNC for premature infants and further research is required [20].

2.2. Pressure-limited ventilation

Pressure-limited ventilation (PLV) remains a popular mode of ventilation [21,22]. During intermittent positive pressure ventilation (IMV) or intermittent positive pressure ventilation (IPPV), ventilator inflations are delivered at a predefined rate regardless of the infant's spontaneous respiratory efforts. This can lead to asynchrony, active expiration and air leaks [23]. Asynchrony and air leaks can be reduced by the administration of neuromuscular blocking agents [24], but then higher peak pressures are required and infants can become oedematous. An alternative approach to abolish asynchrony is to use fast ventilator rates (60–120/min high-frequency positive pressure ventilation, HFPPV), which more closely reflects the infant's spontaneous respiratory rate; meta-analysis of the results of RCTs [25] show that HFPPV compared to slower rate PLV significantly reduces air leaks (RR, 0.69; 95% CI, 0.51–0.93), but only in prematurely born infants [9,11].

2.3. Permissive hypercapnia

Permissive hypercapnia, defined as partial pressure of blood carbon dioxide (pCO_2) of more than 7 kPa, may be routinely practiced in neonatal intensive care units in Europe [26]. In a cross-sectional survey of 173 units, hypercapnia was present in 31% of blood gases. Yet, systematic review of two randomized trials that enrolled 269 infants did not demonstrate any overall benefit of hypercarbia, with no significant reductions in death, BPD at 36 weeks PMA, IVH or PVL [27]. Indeed, one trial [28] was terminated prematurely as there were trends towards a higher mortality and incidence of neurodevelopmental impairment in the "minimal" ventilation arm in which the pCO_2 target was 55 to 65 mmHg compared to 35 and 45 mmHg and the combined outcome of mental impairment or death was significantly greater in the minimal ventilation arm.

2.4. Patient-triggered ventilation (PTV)

2.4.1. Assist control and synchronised intermittent ventilation

PTV was reintroduced into neonatal intensive care in the 1980s, initially as assist-control (AC, inflations are triggered by every spontaneous breath that exceeds the critical trigger threshold) and synchronised intermittent mandatory ventilation (SIMV, only the preset number of inflations are triggered regardless of the infant's spontaneous respiratory rate). It was hoped that these ventilation modes would be more likely to promote synchrony between the infant and ventilator inflations and hence reduce air leaks and bronchopulmonary dysplasia (BPD). Although improvements in oxygenation and reductions in asynchrony were demonstrated in physiological studies, meta-analysis of RCTs comparing AC/SIMV to PLV [25] demonstrated no significant differences in the rates of BPD, severe ICH, air leaks or mortality. The duration of

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