Prophylactic nasal intermittent positive pressure ventilation (NIPPV) versus prophylactic nasal continuous positive airway pressure (NCPAP) for preterm infants

Introduction

Bronchopulmonary dysplasia (BPD), also known as chronic lung disease (CLD), is the most common serious morbidity associated with premature birth, particularly among those infants who have respiratory distress syndrome (RDS) and receive mechanical ventilation after birth. BPD is characterized by lung inflammation and scarring, which are thought to be the effects of excessive (or inadequate) ventilator pressure or volume. Mechanisms of injury that have been explored are barotrauma (lung trauma due to the use of excessive pressure during ventilation), volutrauma (trauma due to the use of excessive ventilation volumes), and atelectotrauma (trauma due to the collapse of alveoli after the use of inadequate ventilation volumes), among others [1]. Various strategies have been developed to avoid the use of mechanical ventilation which would, presumably, limit lung damage and reduce the incidence of BPD. Indeed, nasal continuous positive airway pressure (NCPAP) has been used for decades to treat RDS, and it is a less invasive form of respiratory support that maintains functional residual capacity, improves ventilation-perfusion mismatch, and minimizes damage to the neonatal lungs. Recently, nasal intermittent positive pressure ventilation (NIPPV), which provides mechanical “sigh” breaths in addition to NCPAP, has been used to treat RDS as well. While it is becoming widely accepted that these gentler forms of ventilation may spare premature infants’ lungs and improve clinical outcomes, it is still unclear whether NCPAP or NIPPV offers a greater reduction in important morbidities of prematurity, most notably BPD. We intend to search the current literature for all randomized, controlled trials and to combine these results for a meta-analysis for the Neonatal Cochrane Collaboration comparing mortality and BPD, among other important morbidities, in neonates randomized to one of these two methods of respiratory support.

Hypothesis

We hypothesize that there will be sufficient literature available to support either NIPPV or NCPAP as a superior method of ventilation for treatment of preterm infants with respiratory distress syndrome (RDS).

Specific Aims

1. Identify randomized, controlled trials of NIPPV vs. NCPAP for RDS. We will use the guidelines set forth in “Prophylactic nasal intermittent positive pressure ventilation (NIPPV) versus prophylactic nasal continuous positive airway pressure (NCPAP) for preterm infants (Protocol)” [2] to search electronic databases (e.g. Pubmed, CINAHL, etc.).
2. Use the Cochrane Collaboration guidelines to assess each paper for its systematic bias and methodological quality and either include or exclude each paper for a Cochrane meta-analysis.

3. Use Reference Manager software, available through the Cochrane Collaboration, to perform a meta-analyses of the randomized, controlled trials. Results will be published as a Cochrane Review meta-analysis in the Cochrane Library.

Background

Bronchopulmonary dysplasia (BPD), also known as chronic lung disease (CLD), is a significant risk in preterm infants with respiratory distress syndrome (RDS) treated with mechanical ventilation. Once defined broadly as the need for oxygen supplementation in neonates, BPD is most commonly defined as the need for supplemental oxygen at 36 weeks postmenstrual age, a later time point in the neonatal period of the infant [3]. BPD is characterized by extensive lung inflammation and scarring, although with the advent of new therapies such as surfactant administration, symptoms are usually now limited to decreased alveolar septation and arrested lung development [4]. Regardless of the exact definition, BPD is widely characterized by abnormal lung function and chest films, and these effects are thought to be caused by the volume or pressures used in mechanical ventilation of preterm infants. Dreyfus and Saumon postulated that volutrauma, a major mechanism behind BPD, can be caused when the lungs are inflated to volumes greater than the total lung capacity of the infant [5]. Hernandez et al supported this argument for the role of volutrauma by showing that when lung expansion is limited by casting of the chest, even high ventilation pressures can be administered without significant lung injury [6]. Other studies have shown that too-low volumes of air can also be harmful to lungs through the continuous collapse and re-opening of the alveoli; this mechanism of injury is known as atelectotrauma. To avoid atelectotrauma, it is now believed that adequate positive end expiratory pressure (PEEP) is beneficial during ventilation. Prophylactic nasal ventilation in the form of nasal continuous positive airway pressure (NCPAP) or nasal intermittent positive pressure ventilation (NIPPV) offer the benefits of PEEP while avoiding the risks associated with endotracheal tube insertion and mechanical ventilation.

Nasal continuous airway pressure involves the constant flow of pressured oxygen through nasal prongs into the airway of the premature infant. The benefits of nasal continuous positive airway pressure (NCPAP) ventilation have been explored clinically with mixed results. Whereas successful NCPAP helps support lung expansion and prevent alveolar collapse [7], NCPAP failures are common and result in endotracheal intubation and mechanical ventilation [8]. Nasal intermittent positive pressure ventilation (NIPPV), on the other hand, delivers intermittent breaths of higher pressure into the nasal prongs and neonatal airway. This NIPPV can be either synchronized to the neonate’s breathing pattern (SNIPPPV) or unsynchronized. It is important to note that the administration of NIPPV is not without risk; NIPPV has also been associated with increased risk of gastrointestinal perforations [9].

To date, there have been no meta-analyses comparing prophylactic NIPPV versus NCPAP in preterm infants. There have been a small number of randomized clinical trials comparing the two methods of ventilation, but the results of these trials have yet to be systematically evaluated for bias
and methodology and combined into a clear discussion of which method provides the better option for clinicians treating preterm infants. A study by Aghai et al showed that SNIPPV decreases the work of breathing in premature infants with respiratory distress syndrome compared with NCPAP [10]. Furthermore, a study by Lin et al showed that patients treated with NIPPV had a greater reduction in apnea of prematurity than infants treated with NCPAP alone [11]. Kugelman et al have shown clinically that NIPPV was associated with a decreased incidence of bronchopulmonary dysplasia and a decreased requirement for endotracheal ventilation as compared with NCPAP [12]. Similarly, Bisceglia et al showed that NIPPV is associated with more carbon dioxide tension, less apnea, and a shorter duration of respiratory support as compared to NCPAP [13].

While these studies look promising, it will be important to consolidate this information into a systematic and unbiased review. The Cochrane Collaboration provides a means by which to conduct such a review using extensive searching methodologies and checkpoints to protect against bias. Any abstracts and plain language summaries of findings are publically available on the Cochrane database (http://www.cochrane.org/reviews/) and are meant to be used by physicians to facilitate clinical decision-making.

Research Design and Methods

1. Use the limits set forth in “Prophylactic nasal intermittent positive pressure ventilation (NIPPV) versus prophylactic nasal continuous positive airway pressure (NCPAP) for preterm infants (Protocol)” [2] to search Pubmed for current literature comparing NIPPV and NCPAP.
   a. The following search terms will be used: Newborn, birth-1 month AND (randomized controlled trial OR clinical trial) AND (NIPPV OR nasal positive pressure OR NCPAP OR nasal distending pressure).
   b. Pubmed, CINAHL, and the Cochrane Central Register of Controlled trials (CENTRAL) and the Neonatal Review Group Registry of Trials will be searched.
   c. Reference lists from each identified article will be used to locate other relevant articles.
   d. Abstracts of the Pediatric Academic Societies’ and European Society for Pediatric Research annual meetings from 1990-2004 will be searched using nasal intermittent positive pressure ventilation (NIPPV) or nasal continuous positive airway pressure (NCPAP) as search terms.

2. We will assess each paper for its systematic bias and methodological quality.
   a. Systematic bias will be evaluated using the standards set forth by the Cochrane Neonatal Review Group; selection bias (blinding of randomization), performance bias (blinding of intervention), attrition bias (complete follow-up) and detection bias (blinding of outcome assessment) will be assessed. Authors will be contacted if needed.
   b. Methodological quality will be evaluated using the Cochrane Neonatal Review Group approach: Each paper will receive a grade of Grade A (adequate concealment), Grade B (unclear) or Grade C (inadequate concealment).

3. Results will be published as a Cochrane Review meta-analysis in the Cochrane Library.
a. Primary outcomes assessed will include mortality at 28 days and rate of chronic lung
disease (measured by the need for oxygen therapy at 36 weeks postmenstrual age).
b. Other outcomes taken into consideration will include mortality before hospital
discharge, mechanical ventilation (need for an endotracheal tube), duration of
mechanical ventilation, use of surfactant, pneumothorax, duration of oxygen
dependence, intraventricular hemorrhage, intestinal perforation, necrotizing
enterocolitis, duration of hospital stay, retinopathy of prematurity, patent ductus
arteriosus, sepsis, and nasal septal injury.
c. Significant heterogeneity between the methods will be checked using statistical
methods outlined by the aforementioned protocol [2].
d. Number needed to treat and number needed to harm will be calculated and reported.
e. The data will be further analyzed for the causative effects of gestational age, birth
weight, and synchronized versus unsynchronized NIPPV.
f. Data will be compiled using the standard method of the Cochrane Neonatal Group.
Bibliography