Optimal Conventional Mechanical Ventilation in Full-Term Newborns

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Ved henvisning til publikasjonen, bruk fullstendig referanse:

Solberg, M. T., Solevåg, A. L., & Clarke, S. (2018). Optimal Conventional Mechanical Ventilation in Full-Term Newborns: A Systematic Review. *Advances in neonatal care : official journal of the National Association of Neonatal Nurses*. doi: 10.1097/anc.0000000000000525

Mechanical ventilation in full term newborns

Abstract

Background: Most studies examining the best mechanical ventilation strategies in newborn infants have been performed in premature infants with respiratory distress syndrome.

Purpose: To identify and synthesize the evidence regarding optimal mechanical ventilation strategies in full term newborns.

Method: Systematic review carried out according to the methods described in the PRISMA statement.

Search Strategy: Searches in Medline, Embase, CINAHL and The Cochrane Library in March 2017, with an updated search and hand searches of reference lists of relevant articles in August 2017.

Study selection: Studies were included if they were published between 1996 and 2017, involved newborns with gestational age 37-42 weeks, were randomized controlled trials, intervention - or crossover studies, and addressed outcomes affecting oxygenation and/or ventilation, and/or short-term outcomes including duration of mechanical ventilation.

Due to the large heterogeneity between the studies, it was not possible to synthesise the results in meta-analyses. The results are presented according to thematic analysis.

Results: No individual study reported research exclusively in newborns 37-42 weeks of gestation. Eight studies fulfilled the inclusion criteria, but the population in all these studies included both premature and term newborns. Evidence about mechanical ventilation tailored exclusively to full term newborns is scarce

Implication for Practice: Synchronized intermittent mandatory ventilation with a 6 ml/kg tidal volume, and a positive end-expiratory pressure of 8 cm H_2O may be advantageous in full term newborns.

Implication for research: There is an urgent need for high quality studies, preferably RCTs, in full term newborns requiring mechanical ventilation to optimize oxygenation, ventilation, and short-term outcomes, potentially stratified according to the underlying pathology.

Key words: Full term newborns; Mechanical ventilation; Oxygenation; Ventilation; Short term outcome; Systematic review

Abbreviations

Assist-Control Ventilation (AC)
Carbon dioxide (CO_2)
Fraction of inspired oxygen (FiO_2)
Gestational age (GA)
Inspiratory time (TI)
Intermittent Mandatory Ventilation (IMV)
Mandatory minute ventilation (MMV)
Mean airway pressure (MAP)
Meconium aspiration syndrome (MAS)
Peak inspiratory pressure (PIP)
Positive end-expiratory pressure (PEEP)
Pressure-limited ventilation (PLV)
Pressure Support Ventilation (PSV)
Respiratory distress syndrome (RDS)
Respiratory rate (RR)
Synchronized Intermittent Mandatory Ventilation (SIMV)
Tidal volume (VT)
Work of breathing (WOB)

Introduction

Mechanical ventilation was introduced for use in newborns in the 1960s [1, 2], and proved to be lifesaving and cost-effective in full term newborn infants [3]. However, more recently, mechanical ventilation has been recognized as a highly challenging component of respiratory care of the newborn [4]. The goal of mechanical ventilation treatment in newborns is to secure oxygenation and ventilation without injuring the lungs [5]. Mechanical ventilation in newborns should improve gas exchange through lung recruitment and adequate minute ventilation, and minimize work of breathing (WOB) [4,6]. Mechanical ventilation strategies in the neonate can vary extensively, depending on the underlying diseases [4], and depending on individual neonatal provider [7, 8]. Term newborns, i.e. with gestational ages ≥37+0 weeks at birth [4, 9] may need mechanical ventilation if they have pulmonary diseases or syndromes such as transient tachypnea of the newborn or meconium aspiration syndrome (MAS) [10]. Term newborns with non-pulmonary conditions such as sepsis, congenital heart disease, persistent pulmonary hypertension, depression of the respiratory drive due to medications or neurological disease, and surgery may also require mechanical ventilation [11].

Few studies have examined how mechanical ventilation can best be achieved in full term neonates [12], and many of the guiding principles for modern treatment are based on the by far more abundant studies performed in prematurely born newborns with respiratory distress syndrome (RDS) [13]. In contrast to full term newborns, premature infants more often require mechanical ventilation because of lung immaturity with a lack of endogenous surfactant causing RDS, insufficient respiratory drive and apnea of prematurity [12]. We cannot, therefore, use studies carried out on premature infants to inform how to best carry out mechanical ventilation treatment in full term newborns. One review concluded that mechanical ventilation in term newborn infants usually includes time cycled, pressure limited ventilation with rates of 30 to 40 inflations per minute [12]. However, that review has a high risk of bias due to not having a methods section, and not including a quality assessment of the included articles. Consequently, the evidence regarding optimal mechanical ventilation strategies in full term newborns remains unclear.

The primary purpose of this systematic review was to identify and synthesize the evidence regarding optimal mechanical ventilation strategies in full term newborns. The following research question was developed: What does the evidence tell us about how to optimize oxygenation, ventilation, and short-term outcomes in full term newborns receiving conventional mechanical ventilation treatment?

As part of defining the inclusion criteria for the systematic review, we have reviewed the different terms used to describe newborn mechanical ventilation. An overview and classification is provided in Table 1.

Terminology - Conventional mechanical ventilation

Minute ventilation is the product of the rate of artificial breaths and tidal volume [6]. The breath is initiated either by the ventilator or triggered by the newborn [13]. A mandatory breath occurs independently of the infant, while a patient-triggered breath is delivered in response to the newborn generating an inspiratory flow that exceeds a set flow or volume, i.e. the trigger level [14, 15]. The mode of ventilation is defined by how the ventilator interacts with the patient's spontaneous breathing efforts [4]. More specifically, the mode refers to how the ventilator adjusts the pressure, volume and flow within a breath, along with a description of how the individual breaths are sequenced [16].

When choosing a strategy of mechanical ventilation, clinicians need to consider the infant's pathophysiologic condition and risk for lung injury [6, 17]. Even though there is no consensus regarding preferred modes [17], patient-triggered or synchronized modes are currently considered standard treatment in high-income countries [14, 17]. Synchronized Intermittent Mandatory Ventilation (SIMV) and Assist-Control Ventilation (AC) are most commonly used [14]. However, there is a lack of consistency in mode terminology used by different manufacturers. Sometimes the manufacturers use the same name to describe different modes, while sometimes different names are used to describe the same mode [2]. With regard to modern microprocessor ventilators that are capable of delivering and combining various volume and pressure ventilation modes [4], we classified the different modes based on how the ventilator initiates the breaths, either by mandatory initiation, or by assisting the infant's spontaneous breathing efforts in Table 1.

Table 1 approximately here

Oxygenation

Oxygenation is a well-known term, but seldom defined in the literature. We have therefore used the following definition for the purposes of this review: Oxygenation includes oxygen transport in the blood and oxygen delivery to the tissue, and is characterized by the availability of oxygen to meet tissue metabolic demands [27]. Oxygenation is dependent upon inspired gas, lung tissue properties, the alveolar gas equation, concentration of hemoglobin with its oxygen content, and blood flow [7]. One way the mechanical ventilator controls oxygenation is by titrating the fraction of inspired oxygen (FiO_2) [9]. A high FiO_2 may cause hyperoxia, which exposes newborns to tissue injury through the formation of free radicals, and may prolong ventilator treatment [28, 29]. The ventilator also controls the oxygenation by regulation of the mean airway pressure (MAP), commonly 6-14 cm H_2O, depending on the medical condition [9]. The MAP in turn is dependent on the positive end-expiratory pressure (PEEP), peak inspiratory pressure (PIP), and inspiratory time (TI) [5, 9, 30]. Oxygenation in neonates can be improved by using a lung recruitment strategy using high levels of PEEP [19], but little research exists regarding optimal PEEP [11]. Even though PEEP between 4–6 cm H_2O is commonly used, higher PEEP values might be lung protective [11]. Based on physiological considerations, ventilation of sick lungs using inadequate PEEP, results in repeated alveolar collapse and expansion with each inflation [31]. An established approach to severe MAS is therefore to keep PEEP at higher levels (6-8 cm H_2O and increase as needed) to achieve an acceptable end-expiratory lung volume [17].

Ventilation

Ventilation, which can be defined as carbon dioxide (CO_2) excretion [5], is determined by minute ventilation and must be adapted to the full term newborns' needs and take into account the underlying pathophysiology [32]. Optimal ventilation balances between hyperventilation causing hypocarbia, and hypoventilation causing hypercarbia. Appropriate ventilation is commonly defined as maintaining a $PaCO_2$ of approximately 5.3 kPa (40 mm Hg) [5, 33], while hypocarbia is defined as $PaCO_2 < 4.7$ kPa (35 mm Hg) [9], and extreme hypocarbia as $PaCO_2 <$ 4 kPa (30 mm Hg) [34].

Method

The systematic review was carried out using the guidelines detailed in the PRISMA statement [35]. The protocol was registered in PROSPERO under a different working title [36].

Search strategy

We conducted a systematic search of Medline, Embase, CINAHL and the Cochrane Library in March 2017. An additional final search was carried out in PubMed (Search terms: mechanical ventilation, clinical queries: therapy, narrow, and review, narrow; limited to newborns) for the most recently added articles in August 2017. See Appendix 1 for the full search strategy in Medline. The search strategy was broad, combining keywords and subject headings for "artificial respiration" and "mechanical ventilation", and limiting with clinical queries filters for reviews, therapy, and crossover studies. We also limited to neonatal/newborn. There was no language limit applied at this stage. The reference lists of potentially relevant articles were screened, and we also searched the names of key authors to see if we could identify additional studies.

Study selection

After retrieval of the articles, the titles and abstracts were screened by one author for relevance (MTS). After screening, 86 articles remained (see PRISMA flow chart, Figure 1). Two authors (MTS and ALS) read the studies independently of each other and selected them for inclusion based on the inclusion/exclusion criteria described below. Disagreements were solved by discussion and consensus. Seventeen articles remained at this stage and were assessed for quality and risk of bias and summarized using a data extraction form based on PRISMA /ERC [35].

Figure 1 approximately here

Data extraction

Criteria for inclusion and data extraction were agreed upon before the literature search. Inclusion criteria were: (1) Published between 1996 and 2017 (current), (2) Newborns with gestational age (GA) 37-42 weeks, (3), Intervention studies, randomized controlled trials (RCT) or crossover studies (4), Outcome measures that affect oxygenation and/or ventilation, and/or short-term outcomes including duration of mechanical ventilation. We wanted to investigate conventional mechanical ventilation and thus excluded high frequency oscillatory- and neutrally adjusted ventilator assist ventilation.

Summary data for each study included: Design, aim, population, type of ventilator, intervention, outcome, key findings, and risk of bias (Table 2). The quality of each study and risk of bias were evaluated by two authors (MTS, ALS) independently using the JADAD quality assessment scale for randomized controlled trials [37], crossover study checklist [38] and a tool for assessing risk of bias in non-randomized studies of interventions, ROBINS-1 [39].

Results

No individual study reported research exclusively in newborns 37-42 weeks of gestation. At the stage in the selection process with 86 remaining articles (see PRISMA flow chart), we had three Cochrane systematic reviews [40-42] that were potentially relevant. However, on closer inspection of the individual included studies, they were found to only include premature newborns and thus disregarded. A further six studies were excluded as they investigated neurally adjusted ventilatory assist [43], did not include newborns beyond 36 weeks' gestation [23, 44], physiological study [45] intervention included bag-mask ventilation [46], and did not involve patients [47], respectively. See PRISMA flow chart for an overview of the reason for excluding the remaining articles.

Eight studies fulfilled the inclusion criteria regarding publication date, design and outcomes, but the population in all these studies included both premature and term newborns. We screened the reference lists of the remaining 8 articles, but there were no further studies identified which fulfilled the inclusion criteria for our review. Only one of the included studies stratified the results by GA [48]. Although our primary aim was to include studies assessing parameters of oxygenation and ventilation, our search identified studies that involved short-term outcomes including time to extubation and pneumothorax [48, 49]. We included those studies because they compared different modes of ventilation and stratified according to GA and/or underlying pathology. Table 2 presents characteristics of the included studies.

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Description of the included studies

Three articles used a prospective crossover design [20, 25, 51] and one was a prospective descriptive study [53]. Three studies were RCTs [48-50], and one was a non-randomised intervention study [52]. Most of the included studies excluded newborns with severe pulmonary disease [20, 52], congenital malformations [20, 50, 52], including congenital diaphragmatic hernia [51], severe perinatal asphyxia [51, 52], MAS or pneumothorax [50]. They also excluded sedated newborns [20].

Quality assessment and synthesis of findings

The studies were assessed using the crossover study checklist [20, 25, 51, 53] the JADAD scale [48-50], and the ROBINS-1 tool [52]. No study had a low risk of bias, the majority of studies had some shortcomings, and there were only 3 RCT studies included. It was not possible to pool the studies for a statistical meta-analysis due to heterogeneity between studies, so a thematic analysis was carried out. We present the results under the themes Oxygenation, Ventilation and Short-term outcomes.

Factors associated with oxygenation

Only two articles presented results of relevance to oxygenation [50, 52]. Bernstein et al. [50] found that infants ventilated with SIMV and intermittent mandatory ventilation (IMV) had similar FiO_2, MAP and oxygenation index after 3 hours of ventilation, regardless of GA group. De Waal et al. [52] found that a brief increase in PEEP improved dynamic lung function without changes in systemic blood flow.

Factors associated with ventilation

Abubakar et al. [20] found that compared to SIMV the mode PSV + volume guarantee was best suited to deliver a stable VT, as all the newborns' breathing efforts were supported. However, the blood gas results were not affected by the choice of mode. Two articles presented results regarding minute ventilation [25, 53]. Guthrie et al. [25] found that SIMV and mandatory minute ventilation (MMV) generated similar minute volumes and end-tidal CO_2 values, whereas Mathur and Bathia [53] found that targeting minute ventilation was useful to optimize the ventilator settings, and a minute volume of 160 ml/kg/min was well tolerated. The remaining two articles found that a VT of 6 ml/kg was associated with a lower WOB compared with a lower VT [49, 51].

Short-term outcomes

The duration of mechanical ventilation was significantly shorter in SIMV compared to IMV in the study by Bernstein et al. [50], with no difference in the duration of nasal positive airway pressure after extubation. Chen et al. [48] found no significant differences in time to extubation comparing SIMV and IMV. Volume-targeted ventilation compared to PLV mode resulted in a similar time to successful extubation, but PLV caused more episodes with hypocarbia [49]. MMV may reduce long term complications due to lower MAP requirement compared to the mode SIMV [25].

Discussion

In this systematic review, we identified only a small number of studies that partially fulfilled our inclusion criteria. Most of the eight included studies were of medium quality with a risk of bias due to a lack of methodological descriptions regarding e.g. randomization and blinding.

We found two studies concluding that a VT of 6 ml/kg was associated with a lower WOB [49, 51], however these results were not stratified by GA. A small study conducted by Chowdhury et al. [12] demonstrated that a higher, rather than a lower VT was beneficial: Setting a higher volume guarantee (5 or 6 ml/kg) decreases the WOB in near-term or term infants, as a lower volume guarantee or using no volume guarantee caused the newborn to breathe spontaneously at higher VT to achieve an equivalent MV. Nevertheless, caution should be taken at high volume guarantees as hypocarbia may result [51]. In full term newborns, the relationship between lung physiology and mechanical ventilation treatment may not be easily understood, as a study previously demonstrated that a VT > 8 ml/kg in 310 measurements was found to have only a weak negative correlation to $PaCO_2$ [54].

This review found a study that recommended to use volume guarantee when treating newborns whose lung compliance changes rapidly over time, for example after surfactant replacement therapy in RDS [20]. RDS in the newborn occurs particularly in premature newborns under 36 weeks of gestation [4]. Even though RDS can also be seen in late preterm infants and term infants of diabetic mothers [9], and term MAS can cause requirements for exogenous surfactant[17], this argument of optimizing MV treatment is not always applicable to full term newborns. The benefit of the results presented in Abubakar and Keszler [20] therefore remains unclear for term newborns in general.

Bernstein et al. [50] showed some positive effects of SIMV compared to IMV mode in newborns >2000g. In the smaller infants, the duration of mechanical ventilation was significantly shorter with SIMV. On the contrary, Chen et al. [48] found no significant differences in duration of mechanical ventilation when comparing these modes. We do not know the reasons for these conflicting results, but Chen et al. stratified the results by GA, whereas Bernstein et al. did not. The study by Chen et al. was assessed to have a medium to high risk of bias, while the study of Bernstein et al. was judged to be of a higher quality.

The studies in this review describe mechanical aspects of ventilator treatment. Mechanical ventilation is complex to manage because it involves several types of modes, techniques and strategies [55, 56]. In recent years, more focus has been given to care bundles that include measures to improve general well-being and nutritional status to increase the success of (pulmonary) recovery and extubation. Most studies of newborns receiving mechanical ventilation, including some of the studies in this review, include newborns at very different stages of lung maturation, leaving the question of age appropriateness of supporting measures widely unanswered [57].

In conclusion, this systematic review has identified a gap in the current evidence base regarding how to identify the best strategy for mechanical ventilation in full term newborns receiving mechanical ventilation. We identified no high quality RCT or crossover studies investigating how to optimize oxygenation and ventilation in mechanically ventilated full term newborns only. There is an urgent need for high quality studies, preferably RCTs, in full term newborns requiring mechanical ventilation, and potentially stratified according to the underlying pathology. Based on the current evidence, the SIMV mode with a 6 ml/kg VT, and a PEEP of 8 cm H_2O may be advantageous in full term newborns.

Declarations of interest: None

Summary of recommendations for practice and research:

What we know:

- Newborn mechanical ventilation treatment is largely based on evidence targeting premature infants
- Evidence about how to optimize oxygenation and ventilation in full term newborns receiving mechanical ventilation is lacking

What needs to be studied:

- There is an urgent need for high quality studies, preferably RCTs, in full term newborns requiring mechanical ventilation to optimize oxygenation, ventilation, and short-term outcomes, potentially stratified according to the underlying pathology

What we can do today:

- Use the mode SIMV and give 6 ml/kg per artificial breath
- Ensuring a positive end-expiratory pressure of 8 cm H_2O may be advantageous in full term newborns

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Figure Legends

Figure 1 Study Selection.

PRISMA 2009 Flow Diagram for the study "Optimal conventional mechanical ventilation in full term newborns"