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Neurally adjusted ventilatory assist compared to other forms of triggered ventilation for neonatal respiratory support (Review)

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Neurally adjusted ventilatory assist compared to other forms of triggered ventilation for neonatal respiratory support.
Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD012251.
DOI: 10.1002/14651858.CD012251.pub2.

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TABLE OF CONTENTS

[Intervention Review]

Neurally adjusted ventilatory assist compared to other forms of triggered ventilation for neonatal respiratory support

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Editorial group: Cochrane Neonatal Group.
Publication status and date: New, published in Issue 10, 2017.

Citation: Rossor TE, Hunt KA, Shetty S, Greenough A. Neurally adjusted ventilatory assist compared to other forms of triggered ventilation for neonatal respiratory support. *Cochrane Database of Systematic Reviews* 2017, Issue 10. Art. No.: CD012251. DOI: 10.1002/14651858.CD012251.pub2.

ABSTRACT

Background

Effective synchronisation of infant respiratory effort with mechanical ventilation may allow adequate gas exchange to occur at lower peak airway pressures, potentially reducing barotrauma and volutrauma and development of air leaks and bronchopulmonary dysplasia. During neurally adjusted ventilatory assist ventilation (NAVA), respiratory support is initiated upon detection of an electrical signal from the diaphragm muscle, and pressure is provided in proportion to and synchronous with electrical activity of the diaphragm (EADi). Compared to other modes of triggered ventilation, this may provide advantages in improving synchrony.

Objectives

Primary

• To determine whether NAVA, when used as a primary or rescue mode of ventilation, results in reduced rates of bronchopulmonary dysplasia (BPD) or death among term and preterm newborn infants compared to other forms of triggered ventilation

• To assess the safety of NAVA by determining whether it leads to greater risk of intraventricular haemorrhage (IVH), periventricular leukomalacia, or air leaks when compared to other forms of triggered ventilation

Secondary

• To determine whether benefits of NAVA differ by gestational age (term or preterm)

• To determine whether outcomes of cross-over trials performed during the first two weeks of life include peak pressure requirements, episodes of hypocarbia or hypercarbia, oxygenation index, and the work of breathing

Search methods

We performed searches of the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cohrane Library; MEDLINE via Ovid SP (January 1966 to March 2017); Embase via Ovid SP (January 1980 to March 2017); the Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO host (1982 to March 2017); and the Web of Science (1985 to 2017). We searched abstracts from annual meetings of the Pediatric Academic Societies (PAS) (2000 to 2016); meetings of the European Society of Pediatric Research (published in *Pediatric Research)*; and meetings of the Perinatal Society of Australia and New Zealand (PSANZ) (2005 to 2016). We also searched clinical trials databases to March 2017.

Selection criteria

We included randomised and quasi-randomised clinical trials including cross-over trials comparing NAVA with other modes of triggered ventilation (assist control ventilation (ACV),synchronous intermittent mandatory ventilation plus pressure support (SIMV ± PS), pressure support ventilation (PSV), or proportional assist ventilation (PAV)) used in neonates.

Data collection and analysis

Primary outcomes of interest from randomised controlled trials were all-cause mortality, bronchopulmonary dysplasia (BPD; defined as oxygen requirement at 28 days), and a combined outcome of all-cause mortality or BPD. Secondary outcomes were duration of mechanical ventilation, incidence of air leak, incidence of IVH or periventricular leukomalacia, and survival with an oxygen requirement at 36 weeks' postmenstrual age.

Outcomes of interest from cross-over trials were maximum fraction of inspired oxygen, mean peak inspiratory pressure, episodes of hypocarbia, and episodes of hypercarbia measured across the time period of each arm of the cross-over. We planned to assess work of breathing; oxygenation index, and thoraco-abdominal asynchrony at the end of the time period of each arm of the cross-over study.

Main results

We included one randomised controlled study comparing NAVA versus patient-triggered time-cycled pressure-limited ventilation. This study found no significant difference in duration of mechanical ventilation, nor in rates of BPD, pneumothorax, or IVH.

Authors' conclusions

Risks and benefits of NAVA compared to other forms of ventilation for neonates are uncertain. Well-designed trials are required to evaluate this new form of triggered ventilation.

PLAIN LANGUAGE SUMMARY

Neurally adjusted ventilatory assist for neonatal respiratory support

Review question: Is neurally adjusted ventilatory assist ventilation (NAVA) a more effective method of supporting the breathing of prematurely born infants than conventional ventilation methods?

Background: Neurally adjusted ventilatory assist involves using the electrical signal from the baby's main breathing muscles to inform the ventilator as to when the baby is trying to breathe, such that the ventilatory may support the baby's own efforts. Synchronising the efforts of the infant with the activity of the ventilator may reduce required pressures required, along with damage to the lungs. Using the baby's own breathing control mechanisms may also reduce fluctuations in carbon dioxide levels in the blood and variations in blood flow to the brain.

Study characteristics: During literature searches completed until March 2017, we found one randomised controlled study that met the inclusion criteria for this review.

Key results: We found one eligible study that was conducted to evaluate the use of NAVA in providing neonatal respiratory support. This study reported no significant differences in outcomes of interest between NAVA and patient-triggered time-cycled pressure-limited ventilation. Well-designed studies are needed to further evaluate the role of this potentially exciting technique in providing breathing support for the neonatal population.

BACKGROUND

Despite improved survival rates among preterm infants, the incidence of ventilator-related complications remains high. In particular, the incidence of bronchopulmonary dysplasia (BPD) has been unchanged over the past two decades (Costeloe 2012).

Bronchopulmonary dysplasia has been defined in various ways. The National Institute of Child Health and Human Development (NICHD), the National Heart, Lung and Blood Institute (NHLBI), and the Office of Rare Disease Research Workshop have defined BPD as oxygen dependency at 28 days of life (Jobe 2001), and have further subdivided infants at 36 weeks' postmenstrual age (PMA) as to whether they have mild BPD (no longer oxygen dependent), moderate BPD (with oxygen requirement < 30%), or severe BPD (with oxygen requirement > 30%; or requirement for continuous positive airway pressure (CPAP) or mechanical ventilation). Oxygen dependency at 36 weeks' PMA is also widely used as a definition of BPD.

Bronchopulmonary dysplasia has a multi-factorial origin that includes oxygen toxicity and volutrauma. Pneumothorax is another important ventilator-related complication, as it often precedes intracerebral haemorrhage in prematurely born infants. Pneumothoraces occur in infants whose respiratory efforts are asynchronous with mechanical inflations as they actively expire (Greenough 1984a). In contrast, infants whose respiratory efforts are synchronous with mechanical ventilation have improved oxygenation and do not develop pneumothoraces. Synchrony can be achieved with fast rates (≥ 60 breaths per minute (bpm)) or patient-triggered ventilation (Greenough 1986). A Cochrane Review compared methods of improving synchronisation using fast rates (60 to 120 bpm), high-frequency positive-pressure ventilation (HFPPV), or patient-triggered ventilation (assist control ventilation (ACV) or synchronous intermittent mandatory ventilation (SIMV)) versus conventional mechanical ventilation (CMV) (Greenough 2008). Meta-analysis demonstrated that HFPPV when compared to CMV was associated with reduced risk of air leak, and that patient-triggered ventilation when compared to CMV was associated with a shorter duration of ventilation, but that no significant reduction in BPD occurred when either mode was used to improve synchrony.

During ACV and SIMV, ventilation is triggered by pressure or flow sensors, which determine when inflation is initiated. In the neonatal population with small tidal volumes, high respiratory rates, and often significant leak from uncuffed endotracheal tubes, sensitive triggering can be challenging, and hence some of the benefits of triggered ventilation may not materialise. During neurally adjusted ventilatory assist (NAVA), the electrical activity of the diaphragm, detected via electrodes on a modified nasogastric tube, enables both the start and the end of an inflation to be synchronised with the infant's respiratory effort. Indeed, by using NAVA, respiratory support can be tailored throughout to match the infant's respiratory cycle. Thus, it is likely that NAVA may provide superior support compared to other forms of triggered ventilation.

In this review, we will evaluate whether evidence shows short-term and long-term benefits of NAVA over other methods of triggered ventilation in the neonatal population.

Description of the condition

Most neonates breathe during mechanical ventilation. Asynchrony occurs when the ventilator delivers mechanical support out of phase with the respiratory efforts of the infant. In a study of 34 infants undergoing mechanical ventilation, eight infants who went on to develop pneumothoraces were found to actively exhale against a ventilator inflation (Greenough 1983). In a randomised controlled trial (RCT), investigators randomised preterm ventilated infants with asynchrony to paralysis with pancuronium or to no paralysis. Pneumothoraces developed in all 11 unparalysed infants, but in none of those randomised to paralysis (Greenough 1984b). Asynchrony may predispose to other morbidity. Perlman found an association between fluctuations in cerebral blood flow and subsequent development of intraventricular haemorrhage (IVH). Fluctuations in cerebral blood flow and both the incidence and the severity of IVH were reduced with muscle paralysis (Perlman 1985). Synchronisation of respiratory effort with ventilator inflation reduces asynchrony and is associated with improved oxygenation and carbon dioxide elimination (Donn 2003). Synchronisation of inspiratory efforts with positive-pressure inflations should therefore result in adequate ventilation using lower inflation pressures and should reduce the risk of lung injury by volutrauma or hyperoxia.

Description of the intervention

Several modes of triggered ventilation have been used in the neonatal population and will be considered in this systematic review. Both ACV and SIMV deliver breaths triggered by the infant's respiratory effort, with the former supporting all breaths that are greater than the critical trigger level, and the latter supporting only the number of breaths set by the practitioner (breaths above that preset number are not supported by positive-pressure inflations). During ACV and SIMV, inflations can be pressure limited or volume targeted. During volume-targeted ventilation, a prespecified volume is delivered to the infant regardless of changes in lung function. In both modes, timing of the onset of inflation is determined by the infant's inspiratory efforts but inflation is terminated when the set inflation time is reached. Patient-triggered ventilation has usually relied on flow or pressure changes to trigger inspiration. The infant must initiate a sufficient change in pressure or flow to trigger ventilator support, and this may result in delay in delivery of an inflation (trigger delay), increasing the infant's work of breathing. In contrast, during pressure support ventilation (PSV),

both the beginning and the end of inflation are determined by the infant's inspiratory efforts, reducing the likelihood of asynchrony (Dimitriou 1998). During proportional assist ventilation (PAV), applied pressure is servo controlled throughout each spontaneous breath and is increased in proportion to the tidal volume and flow generated by the infant. Frequency, timing, and magnitude of lung inflation are controlled by the infant.

Similarly, NAVA provides respiratory support throughout the infant's respiratory cycle, but the electrical activity of the diaphragm is used to 'control' respiratory support. This technique has been successfully used in very low birth weight infants weighing as little as 640 grams (Beck 2009). Diaphragmatic activity is determined by assessing the electrical activity of the diaphragm (EAdi) using a series of electrodes mounted on a modified nasogastric feeding tube.

How the intervention might work

Changes in electrical activity in the diaphragm at the beginning of inspiration precede changes in pressure and flow, hence NAVA may have a shorter trigger delay than other modes of triggered ventilation. During NAVA, termination of inflation is also controlled by the EAdi signal, hence asynchrony is less likely to occur. Reduction in asynchrony may result in a lower incidence of pneumothoraces and intracerebral haemorrhage. Improved synchronisation could improve oxygenation and carbon dioxide clearance. Furthermore, respiratory support through the infant's respiratory cycle is likely to be more effective as demonstrated during PAV, with a reduction in the oxygenation index (Bhat 2015), and during NAVA, effective ventilation could be achieved at lower pressures or volumes.

Why it is important to do this review

Patient-triggered ventilation should reduce respiratory morbidity among neonates by improving synchronisation, but results of RCTs to date have yielded limited positive results. NAVA is a more sophisticated form of PTV that has been developed recently for neonates. To our knowledge, no systematic reviews have evaluated the use of this modality in the neonatal population; hence, it is important to assess the benefits of NAVA versus other triggered modes.

OBJECTIVES

Primary

- To determine whether NAVA, when used as a primary or rescue mode of ventilation, results in reduced rates of bronchopulmonary dysplasia (BPD) or death among term and preterm newborn infants compared to other forms of triggered ventilation
- To assess the safety of NAVA by determining whether it leads to greater risk of intraventricular haemorrhage, periventricular leukomalacia, or air leaks when compared to other forms of triggered ventilation

Secondary

- To determine whether benefits of NAVA differ by gestational age (term or preterm)
- To determine whether outcomes of cross-over trials performed during the first two weeks of life include peak pressure requirements, episodes of hypocarbia or hypercarbia, oxygenation index, and the work of breathing

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised and quasi-randomised, but not cluster-randomised, controlled studies. For RCTs evaluating NAVA as the primary mode of ventilation, randomisation must have occurred within 24 hours of birth. If randomisation occurred after 24 hours but within 28 days, the study may be included to evaluate NAVA as a rescue mode of ventilation.

We also considered cross-over studies, if they occurred within 28 days of birth with a minimum study period of one hour on each intervention. We included studies even if they did not report all outcomes of interest.

Types of participants

Infants born at term and preterm infants requiring mechanical ventilation and studied at a postmenstrual age of less than 44 weeks.

Types of interventions

- NAVA - delivered via an endotracheal tube with diaphragmatic electromyography (EMG) used as the trigger device versus other triggered modes
    - Synchronised intermittent mandatory ventilation (SIMV) (either pressure limited or volume targeted)

- Assist control ventilation (ACV) (either pressure limited or volume targeted)
- SIMV or ACV with pressure support
- PAV

- NAVA compared to "control" interventions as
  - Primary mode of ventilation (randomised within 24 hours of birth)
  - Rescue mode (randomised after 24 hours, following any other mode of ventilation)

We considered studies in which ventilation was delivered by a trigger mode; any differences in outcome attributable to trigger mode were considered as part of the subgroup analysis.

Types of outcome measures

Primary outcomes

- All-cause mortality
- Bronchopulmonary dysplasia defined as an oxygen requirement at 36 weeks' postmenstrual age for infants of less than 32 weeks' gestational age, and defined as an oxygen requirement at 28 days' postmenstrual age for infants of more than 32 weeks' gestational age (Jobe 2001)
- All-cause mortality or bronchopulmonary dysplasia as previously defined

Secondary outcomes

- Duration of mechanical ventilation (days)
- Incidence of air leak: pneumothorax or pulmonary interstitial emphysema (PIE) (study author defined)
- Incidence of intracerebral haemorrhage or periventricular leukomalacia
- Survival with an oxygen requirement at 36 weeks' postmenstrual age

Outcomes of cross-over trials assessed during each of the study periods:

- Maximum fraction of inspired oxygen (FiO_2)
- Mean peak inspiratory pressures (cm H_2O)
- Episodes of hypocarbia (pCO_2 < 35 mmHg) defined as any episode during the study period
- Episodes of hypercarbia ($PaCO_2$ > 60 mmHg) defined as any episode during the study period

At the end of each period on each comparator ventilation mode:

- Work of breathing (transdiaphragmatic pressure time product/cm H_2O.seconds/minute)
- Oxygenation index ((FiO_2 × mean airway pressure)/PaO_2)
- Thoraco-abdominal asynchrony using respiratory inductance bands (phase angle/degrees)

pCO_2: partial pressure of carbon dioxide
$PaCO_2$: partial pressure of carbon dioxide in arterial blood
PaO_2: partial pressure of oxygen in arterial blood

Search methods for identification of studies

We used the standard search strategy of the Cochrane Neonatal Group.

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 2) in the Cochrane Library; MEDLINE via Ovid SP (January 1966 to 26 March 2017); Embase via Ovid SP (January 1980 to 26 March 2017); the Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO host (1982 to 26 March 2017); and Web of Science (1985 to 26 March 2017). In addition, we searched abstracts from annual meetings of the Pediatric Academic Societies (PAS) (2000 to 2016); meetings of the European Society of Pediatric Research published in *Pediatric Research*; and meetings of the Perinatal Society of Australia and New Zealand (PSANZ) (2005 to 2016). We used the Cochrane highly sensitive search strategy for identifying RCTs, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used the following medical subject headings (MeSH): infant, newborn AND Interactive Ventilatory Support AND the text word "neurally adjusted" or "NAVA". We performed a second search using the following MeSH headings: infant, newborn AND text word "neurally adjusted" OR "NAVA". We combined results of the two searches and applied no restrictions on date, language, or publications.

Searching other resources

In addition, we searched the following registries.

- http://www.controlled-trials.com.
- http://clinicaltrials.gov.
- http://www.anzctr.org.au.
- http://www.who.int/ictrp/en/.

We checked the reference lists of all identified studies for further relevant studies and searched conference abstracts for relevant unpublished studies.

Data collection and analysis

Selection of studies

Two review authors (TR, KH) undertook the study selection process, independently identified studies, and assessed whether inclusion criteria were fulfilled. We resolved disagreements by consultation with another review author (AG).

We have listed details of all excluded studies along with reasons for exclusion in the Characteristics of excluded studies table.

Data extraction and management

Two review authors (TR, KH) independently extracted data using a standardised form and resolved discrepancies by discussion and when necessary by consultation with another review author (AG).

Assessment of risk of bias in included studies

Two review authors (TR, KH) independently assessed risk of bias using the Cochrane domain-based tool for assessing risk of bias. We scored selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. We rated overall risk of bias for each study as 'high', 'low', or 'unclear' according to guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by consensus or when necessary by discussion with another review author (AG).

We assessed the following risk of bias domains.

- Sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Any other bias.

One review author (TR) entered data into Review Manager software, and a second review author (KH) verified the data (RevMan 2014). See Appendix 1 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

We planned to extract categorical data for each intervention group and to calculate the risk ratio (RR) and the risk difference (RD). If the RD was statistically significant, we would calculate the number needed to treat for an additional beneficial (NNTB) or harmful outcome (NNTH). We intended to report each continuous outcome as a weighted mean difference (WMD) with a 95% confidence interval (CI)

Analysis of cross-over trials depended on the risk of carry-over or period effects. Were these not considered a problem, we planned to calculate an effect estimate using the generic inverse variance method provided in RevMan (Higgins 2011). If data were insufficient to include a paired analysis within a meta-analysis, we would treat data as two parallel arms, acknowledging the loss of statistical power.

Unit of analysis issues

When data available from cross-over trials were insufficient to incorporate paired data in a meta-analysis, we would consider the measurements from each arm separately as if they were derived from a parallel-group trial. As this can result in a unit of analysis error, we would have included the results if they were demonstrably similar to the results of a paired analysis (Higgins 2011).

Dealing with missing data

When we noted apparently missing data, we would have contacted trial authors when possible. When data were missing from one period of a cross-over trial, we planned to exclude data from both periods from analysis.

Assessment of heterogeneity

We would have quantified heterogeneity using the I^2 statistic, calculated as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Thresholds for interpreting I^2 would include the following.

- 0% to 25%: no heterogeneity.
- 25% to 49%: low heterogeneity.
- 50% to 74%: moderate heterogeneity.
- $\geq$ 75%: high heterogeneity.

Were I^2 to equal or exceed 75%, we would have conducted a sensitivity analysis to explain the source of heterogeneity.

Assessment of reporting biases

Had we identified at least 10 trials for inclusion in a meta-analysis, we would have created a funnel plot to assess publication bias.

Data synthesis

Were sufficient eligible studies available, we would have performed meta-analysis in RevMan using a fixed-effect model when we identified two or more RCTs with comparable populations and treatment interventions. We would consider RCTs to be comparable if investigators used NAVA as the primary mode of ventilation or in a discreet analysis as rescue mode.

We would have presented our results with 95% CIs. When investigators used different scales to measure the same continuous data between trials, we would have calculated standardised mean differences (SMDs). For continuous data, we would have extracted means and standard deviations and would have performed analysis using weighted mean differences (WMDs). When investigators measured outcomes using differing scales, we would have used SMDs.

We would have assessed WMDs, RRs, and RDs and would have analysed outcomes of comparable trials using 95% CIs to estimate treatment effect. If appropriate, we would have compared results

using forest plots, with the RR as the point estimate for dichotomous outcomes, and WMD as the point estimate for continuous outcomes.

Quality of evidence

We planned to use the GRADE approach, as outlined in the *GRADE Handbook* (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes.

- All-cause mortality.
- Bronchopulmonary dysplasia defined as an oxygen requirement at 36 weeks' postmenstrual age for infants of less than 32 weeks' gestational age, and at 28 days' postmenstrual age for more mature infants.
- All-cause mortality or BPD as previously defined.

Review authors planned to independently assess the quality of evidence for each of the outcomes above. We planned to consider evidence from RCTs as high quality but to downgrade evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of evidence, precision of estimates, and presence of publication bias. We planned to use the GRADEproGDT Guideline Development Tool to create a 'Summary of findings' table to report the quality of evidence (GRADEpro GDT).
The GRADE approach results in an assessment of the quality of a body of evidence according to one of four grades.

- High: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- Very low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

We would have performed subgroup analysis as follows.

- Gestational age category: term (≥ 37 weeks' gestational age) or preterm (< 37 weeks' gestational age).
- Type of triggered ventilation: ACV, SIMV or ACV, SIMV + PSV, PAV.

Sensitivity analysis

If we identified sufficient studies, we would have performed a sensitivity analysis to evaluate the robustness of results and to investigate any source of heterogeneity. We may have performed sensitivity analysis by separating studies according to risk of bias in each of the previously specified domains. We may have used a sensitivity analysis particularly in evaluating data from cross-over studies to determine the effect of including data from both study periods.

RESULTS

Description of studies

Results of the search

We recovered 191 records using the search technique. With removal of duplicates, this corresponded to 177 studies. Following primary screening, we reviewed 17 full-text articles and excluded 16 studies. We have listed reasons for exclusion in the Characteristics of excluded studies table and have discussed these reasons below. We included one RCT that evaluated use of NAVA as a rescue mode of ventilation (see Characteristics of included studies).

Included studies

The study selection process initially yielded no eligible studies. Kallio 2016 was excluded as randomisation was performed in some cases after 24 hours of age. Following discussion, the eligibility criteria were revisited and the study was subsequently included as it fulfilled the criteria for inclusion as a rescue therapy rather than as an evaluation of NAVA as a primary mode of ventilation.
We identified only one RCT (Kallio 2016) that was eligible for inclusion. This well-designed RCT randomised 60 prematurely born infants to NAVA or pressure-controlled triggered ventilation. Randomisation did not occur within 24 hours in many cases; therefore, we included the study as an evaluation of NAVA as a mode of rescue ventilation. Investigators reported no significant differences between modes of ventilation with regards to duration of mechanical ventilation and rates of BPD, pneumothorax, or IVH. They reported lower peak inspiratory pressures in the NAVA group than in groups given control methods of ventilation (see Characteristics of included studies).

Excluded studies

We detected 16 studies that we found to be not eligible for inclusion in the review (see Characteristics of excluded studies).
We excluded five studies as they were retrospective reviews or case control studies (Guichoux 2011; Lee 2017; Maroszynska 2013; Piastra 2014; Rahmani 2015). One was an observational study in which four infants with congenital diaphragmatic hernia were ventilated with NAVA (Guichoux 2011). We excluded this study in the absence of a comparison arm. Another excluded trial was a retrospective review of medical records (Lee 2017). We also excluded a review of eight prematurely born infants ventilated with

NAVA with no control arm (Maroszynska 2013). We excluded a case control study that compared 10 infants ventilated with NAVA versus 20 infants ventilated with PSV (Piastra 2014). In addition, we excluded a retrospective notes review of seven preterm infants (Rahmani 2015).

We excluded nine cross-over studies. Seven of these were not randomised (Beck 2009; Colombo 2011; Grassino 2011; Grassino 2011a; Bordessoule 2012; Stein 2013; Longhini 2015). The two randomised cross-over trials studied infants after 28 days of age in some cases (Lee 2012; Shetty 2017).

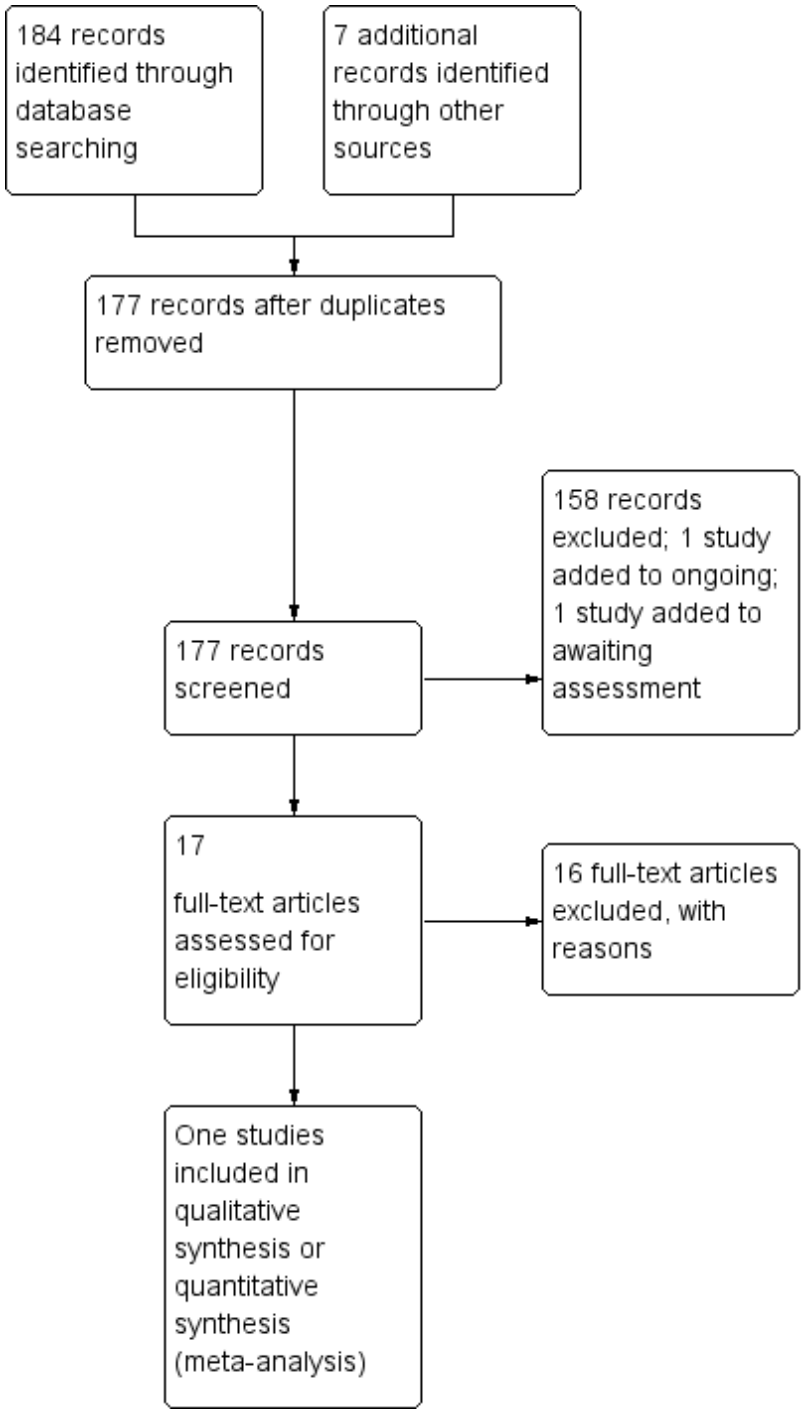
In one excluded study, investigators included seven infants initially given conventional triggered ventilation, then transferred onto NAVA (Beck 2009). They reported improved patient-ventilator interaction. We excluded this study as study authors reported no randomisation of the order in which modes were delivered, and one of the seven infants was over two weeks of age at the time of the study. We excluded a non-randomised cross-over trial that included eight preterm infants with acute respiratory distress in a comparison with pressure-regulated volume-controlled ventilation (Colombo 2011). Researchers reported that NAVA was associated with fewer high-volume breaths (> 8 mL/kg) but noted no significant differences on blood gas analysis. We excluded this study because infants were studied in a non-randomised sequence. In another trial, investigators studied eight preterm infants who were given SIMV, then NAVA, and showed lower peak inspiratory pressure (PIP) on NAVA (Grassino 2011). As study authors provided no randomisation of sequence, we excluded this study. These same investigators later studied 10 preterm infants given SIMV, then NAVA, and reported lower PIP on NAVA (Grassino 2011a). We excluded this study in view of non-randomisation of the sequence in which infants were studied. It is probable that this study shared participants and data with the 2011 study (Grassino 2011).

Bordessoule studied 10 infants given both NAVA and conventional triggered ventilation (Bordessoule 2012). We excluded this study because all infants were outside the neonatal period and trialists did not randomise the order of ventilation mode. We identified a non-randomised cross-over study including five premature infants in which investigators reported lower PIP, respiratory rate, and end-tidal CO_2 during the NAVA period (Stein 2013). We excluded this study as the sequence of the study was non-randomised and infants were studied after two weeks of age in many cases. Another non-randomised cross-over study included 14 prematurely born infants who received PRVC ventilation first, then NAVA (Longhini 2015). Investigators reported less asynchrony on NAVA. However, as the sequence of ventilation modes was not randomised, we excluded this study.

We identified a well-designed randomised cross-over study that compared NAVA versus SIMV with pressure support (Lee 2012). Study authors found lower PIP with NAVA. However, as measurements were performed after 28 days of age in many cases, this study did not fulfil the inclusion criteria of this review. Another well-designed randomised cross-over study of nine prematurely born infants compared NAVA versus ACV (Shetty 2017). However, as some infants were studied after 28 days, this study did not meet the inclusion criteria for this review.

We found one ongoing study that is eligible and added it to the list of 'ongoing studies'. We added another study to the list of 'studies awaiting classification', as it is reported as complete but has yielded no publication (Figure 1).

Figure 1. Study flow diagram.



Risk of bias in included studies

We included one randomised controlled study (Kallio 2016). We discuss risk of bias below.

Allocation

Investigators used a computer-generated randomisation code in sealed opaque envelopes, which were allocated after written consent had been obtained. We deemed this study to have low risk.

Blinding

Researchers undertook no blinding. Therefore, we considered these domains to introduce high risk.

Incomplete outcome data

Study authors reported outcome data for all participants. Therefore, we considered the study to be at low risk for this domain.

Selective reporting

Investigators reported all outcomes that were specified in the registered protocol. We considered this to introduce low risk.

Other potential sources of bias

We identified no other potential sources of bias.

Effects of interventions

We identified one study that was eligible for inclusion in this systematic review (Kallio 2016). Study authors reported no significant differences in duration of mechanical ventilation, nor in rate of BPD, pneumothorax, or IVH, between NAVA and patient-triggered time-cycled pressure-limited ventilation. They reported lower peak inspiratory pressures in the NAVA arm..

DISCUSSION

Synchronisation of infant respiratory effort with mechanical ventilation has been the objective of numerous ventilation strategies. Triggered ventilation, conventionally driven by flow or pressure sensors, has been shown to improve tidal volume and oxygenation; however, impact on long-term outcomes such as bronchopulmonary dysplasia (BPD) remains unclear. Neurally adjusted ventilatory assist ventilation (NAVA) allows the infant to initiate support of inspiration and termination of inspiration, potentially allowing efficient ventilation at lower pressures. Furthermore, using the respiratory drive of the infant to control ventilation may help avoid hypocarbia and hypercarbia.

Use of NAVA for infants requiring mechanical ventilation is in its infancy. We found two randomised cross-over trials (Lee 2012; Shetty 2017) including a total of 35 infants that compared NAVA versus other modes of triggered ventilation in this population; however some included infants were beyond four weeks of age, leading to exclusion of these studies from this review. Cross-over trials allow assessment of short-term physiological parameters but not of long-term outcomes related to mode of ventilation. Although no safety issues have been highlighted in the course of these small studies, we cannot assess safety outcomes derived using this trial design.

We identified one randomised controlled trial that compared NAVA versus conventional triggered ventilation in the neonatal population (Kallio 2016). This study reported lower peak inspiratory pressure (PIP) in the NAVA group than in the control group. As many infants were randomised beyond 24 hours of age, this study was eligible for inclusion in this review as investigators examined a rescue mode of ventilation. This study demonstrated no significant differences between the two modes of ventilation in the outcomes relevant to this review: duration of mechanical ventilation, mortality, BPD, intraventricular haemorrhage (IVH), and pneumothorax. Investigators reported lower peak inspiratory pressures delivered by NAVA compared with assist control ventilation (ACV).

Well-designed randomised controlled trials comparing NAVA versus other modes of triggered ventilation in the neonatal population are required to evaluate the safety and potential benefits of this novel mode of ventilation.

Summary of main results

Only one study was eligible for inclusion (Kallio 2016). Investigators demonstrated no significant difference in rates of BPD, pneumothorax, or IVH between infants ventilated with NAVA and those given pressure-limited triggered ventilation. Resuls show no significant difference in the duration of mechanical ventilation.

Overall completeness and applicability of evidence

We found insufficient data to justify comment on the safety or long-term outcomes of NAVA compared to other methods of triggered ventilation.

Quality of the evidence

We included one good quality randomised controlled study with potential for bias as it was unblinded (Kallio 2016). Randomisation occurred after 24 hours in some cases; therefore researchers could not evaluate use of NAVA as the primary mode of ventilation.

Potential biases in the review process

We carried out this review with one deviation from the published protocol: We considered cross-over studies as eligible if investigators studied infants within 28 days from birth rather than 14 days, as specified in the protocol. This did not affect review outcomes. Two review authors carried out searches independently and showed good agreement.

Agreements and disagreements with other studies or reviews

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AUTHORS' CONCLUSIONS

Implications for practice

The risks and benefits of neurally adjusted ventilatory assist ventilation (NAVA) compared to other forms of ventilation for neonates remain uncertain. The one randomised controlled study that was eligible for inclusion in this review reported no significant difference in the outcomes of interest. Well-designed trials evaluating this new form of triggered ventilation are required.

Implications for research

Several case series and non-randomised cross-over studies have suggested a physiological benefit associated with NAVA compared to other forms of triggered ventilation in the neonatal population. Additional well-constructed randomised controlled trials are required to explore the important outcomes of death, bronchopulmonary dysplasia, and intraventricular haemorrhages when NAVA is used as a primary mode of ventilation, or as a clearly defined rescue therapy.

ACKNOWLEDGEMENTS

We would like to acknowledge the assistance of Cochrane Neonatal in reviewing this protocol, and Deirdre Gibbons in providing secretarial support.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Kallio 2016

Methods	Randomised controlled study
Participants	Prematurely born infants born at between 28 and 37 weeks' gestation who required invasive ventilation for at least 4 hours owing to respiratory distress syndrome. We excluded neonates with a known defect of the diaphragm and those who were unable to receive a nasogastric or orogastric tube owing to congenital anomalies, along with patients with severe perinatal asphyxia (pH < 7.0 or signs of hypoxic-ischaemic encephalopathy) or known chromosomal abnormalities
Interventions	Neurally adjusted ventilatory assist ventilation (NAVA) vs patient-triggered time-cycled pressure-controlled ventilation, both delivered using Servo-i (Maquet Nordic, Solna, Sweden)
Outcomes	Mortality, peak inspiratory pressure, duration of ventilation, bronchopulmonary dysplasia (BPD) at 36 weeks' postmenstrual age, pneumothoraces, intraventricular haemorrhage (IVH)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised random number generator used, with sealed opaque envelopes
Allocation concealment (selection bias)	Low risk	As above, allocated after written consent obtained
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding possible
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding possible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some infants did not receive NAVA for the entire study for technical reasons
Selective reporting (reporting bias)	Low risk	All outcomes specified in the registered protocol were reported

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Beck 2009	Seven infants; not randomised
Bordessoule 2012	Not randomised; postneonatal infants
Chen 2013	Unable to obtain translation; therefore unable to ascertain whether this study fulfilled inclusion criteria
Clement 2011	Not neonatal; not randomised
Colombo 2011	Non-randomised cross-over study
Grassino 2011	Non-randomised cross-over study
Grassino 2011a	Non-randomised cross-over study
Guichoux 2011	Case series
Lee 2012	Some infants enrolled after 28 days
Lee 2017	Retrospective case review
Longhini 2015	Non-randomised trial
Maroszynska 2013	Case series
Piastra 2014	Case control; non-randomised trial
Rahmani 2015	Retrospective study
Shetty 2017	Some infants enrolled after 28 days
Stein 2013	Non-randomised cross-over study

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT01156467

Methods	Neurally Adjusted Ventilatory Assist (NAVA) in Ventilatory Care of Premature Infants Randomised controlled trial
Participants	All children of postconceptional age from 28 + 0 to 36 + 6 weeks needing mechanical ventilation for at least 60 minutes

NCT01156467 (*Continued*)

Interventions	Control: Infants randomised to this arm will receive a regular nasogastric tube and routine ventilatory care. Ventilation with i-Servo or Stephanie NAVA Infants randomised to this arm will receive an Edi-catheter as an oro-/nasogastric tube; the Edi-signal will be monitored and when possible NAVA ventilation used Device: neurally adjusted ventilatory assist, i-Servo, Maquet Nordic (Solna, Sweden)
Outcomes	Duration of mechanical ventilation, complications associated with mechanical ventilation
Notes	ClinicalTrials.gov Identifier: NCT01156467 Contact person: Merja Ålander University Hospital of Oulu, Oulu, Pohjois-Pohjanmaa, Finland 90100

Characteristics of ongoing studies *[ordered by study ID]*

Greenough 2016

Trial name or title	Neurally Adjusted Ventilatory Assist vs Proportional Assist Ventilation
Methods	Randomised cross-over study
Participants	Born at less than 32 weeks' gestation and ventilated after 1 week of life
Interventions	Ventilation with neurally adjusted ventilatory assist (NAVA) or proportional assist ventilation (PAV)
Outcomes	Oxygenation index (OI)
Starting date	November 2016
Contact information	Anne Greenough, MD, FRCPCH, King's College London
Notes	ClinicalTrials.gov Identifier: NCT02967549

DATA AND ANALYSES

This review has no analyses.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: AG.

Co-ordinating the review: AG.

Writing the protocol: AG, TR.

Commenting on and reviewing the protocol: SS.

Writing the review: AG, TR, KH.

Serving as guarantor for the review (one review author): AG.

DECLARATIONS OF INTEREST

AG has held grants from various ventilator manufacturers and has received honoraria for giving lectures and advising various ventilator manufacturers.

SS: none known.

TR: none known.

SOURCES OF SUPPORT

Internal sources

- National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have increased the eligibility period for cross-over studies, including those performed up to 28 days after birth.

While not a deviation from protocol, a study excluded during the initial searches by TR and KH was subsequently included following discussion and reinterpretation of the inclusion criteria. While not fulfilling the eligibility criteria for inclusion as a study evaluating NAVA as a primary mode of ventilation as randomisation occurred in some cases after 24 hours of age, Kallio 2016 was included as a study evaluating NAVA as a rescue mode of ventilation.

We have added methods and plans for 'Summary of findings' tables and GRADE recommendations, which were not included in the original protocol.