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Neurally adjusted ventilatory assist for neonatal respiratory support (Protocol)

Rossor TE, Shetty S, Greenough A

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Neurally adjusted ventilatory assist for neonatal respiratory support.

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Neurally adjusted ventilatory assist for neonatal respiratory support

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine whether NAVA compared to other forms of triggered ventilation results in reduced rates of BPD or death in newborn infants, either used as a primary or rescue mode of ventilation. To assess the safety of NAVA by determining if there is a greater risk of episodes of hypocarbia or hypercarbia, intraventricular haemorrhage, periventricular leukomalacia, or air leaks compared to other forms of triggered ventilation.

Secondary objectives will be to determine whether any benefits differ by gestational age (term or preterm). In crossover trials, outcomes include peak pressure requirements, oxygenation index and the work of breathing.

BACKGROUND

Despite improvements in survival rates of preterm infants, there remains a high incidence of ventilator-related complications. In particular, the incidence of bronchopulmonary dysplasia (BPD) has been unchanged over the last two decades (Costeloe 2012).

Various definitions have been used to define BPD. The National Institute of Child Health and Human Development (NICHD), National Heart, Lung and Blood Institute (NHLBI) and Office of Rare Disease Research workshop defined BPD as oxygen dependency at 28 days of life (Jobe 2001). Infants are then further subdivided at 36 weeks postmenstrual age (PMA) as to whether they have mild BPD (no longer oxygen dependent), moderate BPD (an oxygen requirement less than 30%) or severe BPD (an oxygen

requirement of greater than 30%; or a requirement for continuous positive airways pressure (CPAP) or mechanical ventilation). Oxygen dependency at 36 weeks' postmenstrual age (PMA) is also widely used as a definition of BPD.

BPD has a multifactorial aetiology including 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 by the use of fast rates

(≥ 60 breaths per minute (bpm)) (Greenough 1986); or patient-triggered ventilation. 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 (either assist control ventilation (ACV) or synchronous intermittent mandatory ventilation (SIMV)) with conventional mechanical ventilation (CMV) (Greenough 2008). The meta-analysis demonstrated that HFPPV compared to CMV was associated with a reduction in risk of air leak and patient-triggered ventilation was associated with a shorter duration of ventilation compared to CMV, but there was no significant reduction in bronchopulmonary dysplasia using either mode to improve synchrony.

During ACV and SIMV, triggering is via either pressure or flow sensors which determine the initiation of inflation. 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 end of an inflation to be synchronised with the infant's respiratory effort. Indeed, using NAVA, respiratory support can be tailored throughout to 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 there is evidence for short- and long-term benefits of NAVA over other methods of triggered ventilation in the neonatal population.

Description of the condition

The majority of 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 preterm ventilated infants with asynchrony were randomised to paralysis with pancuronium, or 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 1985 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 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 pres-

ures and reduce the risk of lung injury by either 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. ACV and SIMV both 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 pre-specified volume is delivered to the infant regardless of changes in their lung function. In both modes, the 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 a delay in delivering an inflation (trigger delay) increasing the infant's work of breathing. In contrast, during pressure support ventilation (PSV), both the beginning and end of inflation are determined by the infant's inspiratory efforts, reducing the likelihood of asynchrony (Dimitriou 1998). During proportional assist ventilation (PAV) the applied pressure is servo controlled throughout each spontaneous breath. The applied pressure increases in proportion to the tidal volume and flow generated by the infant. The 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 electric 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 effective ventilation could be achieved at lower pressures or volumes. In addition reduction in asynchrony may result in a lower incidence of pneumothoraces and intracerebral haemorrhage. 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). NAVA may, therefore, have a shorter trigger delay than other modes of triggered ventilation.

During NAVA, termination of inflation is also controlled by the EAdi signal and hence asynchrony is less likely to occur. Improved synchronisation could improve oxygenation and carbon dioxide clearance.

Why it is important to do this review

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

OBJECTIVES

To determine whether NAVA compared to other forms of triggered ventilation results in reduced rates of BPD or death in newborn infants, either used as a primary or rescue mode of ventilation. To assess the safety of NAVA by determining if there is a greater risk of episodes of hypoxia or hyperoxia, intraventricular haemorrhage, periventricular leukomalacia, or air leaks compared to other forms of triggered ventilation.

Secondary objectives will be to determine whether any benefits differ by gestational age (term or preterm). In crossover trials, outcomes include peak pressure requirements, oxygenation index and the work of breathing.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised and quasi-randomised (but not cluster-randomised) controlled studies. For randomised controlled studies evaluating NAVA as the primary mode of ventilation, randomisation must occur within 24 hours of birth.

Cross-over studies will also be considered, if they have occurred in the first two weeks after birth and there is a minimum study period of one hour on each intervention. Studies will be included even if all outcomes of interest are not reported.

Types of participants

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

Types of interventions

NAVA - delivered via an endotracheal tube using diaphragmatic electromyography (EMG) as the trigger device versus other triggered modes:

- 1) Synchronous intermittent mandatory ventilation (SIMV) (either pressure limited or volume targeted)
- 2) Assist control ventilation (ACV) (either pressure limited or volume targeted)
- 3) SIMV or ACV with pressure support or
- 4) PAV

NAVA will be compared to the 'control' interventions as:

- 1) primary mode of ventilation (randomised within 24 hours of birth)
- 2) rescue mode (randomised after 24 hours, following any other mode of ventilation)

We will include studies in which ventilation is delivered by a trigger mode; any differences in outcome attributable to trigger mode will be considered as part of the sub-group analysis.

Types of outcome measures

Primary outcomes

- All-cause mortality
- Bronchopulmonary dysplasia as defined as an oxygen requirement at 36 weeks' postmenstrual age for infants of less than 32 weeks' gestational age and at 28 days for more mature infants.
- 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) (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 FiO_2 (fraction of inspired oxygen)
- Mean peak inspiratory pressures (cmH_2O)

- Episodes of hypocarbia ($p\text{CO}_2 < 35$ mmHg) defined as any episode during the study period

- Episodes of hypercarbia ($\text{PaCO}_2 > 60$ mmHg) defined as any episode during the study period

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

- Work of breathing (transdiaphragmatic pressure time product/ $\text{cmH}_2\text{O}\cdot\text{seconds/minute}$)

- Oxygenation index ($(\text{FiO}_2 \times \text{mean airway pressure})/\text{PaO}_2$)

- Thoraco-abdominal asynchrony using respiratory inductance bands (phase angle/degrees)

Search methods for identification of studies

The standard search strategy of the Cochrane Neonatal Group will be used.

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*); MEDLINE via Ovid SP (January 1966 to date); EMBASE via Ovid SP (January 1980 to date); CINAHL via EBSCO Host (1982 to date); and Web of Science (1985 to date). In addition, we will search abstracts of the Pediatric Academic Societies Annual Meetings (PAS) (2000 to current); the Meetings of the European Society of Pediatric Research published in Pediatric Research; and the Meetings of the Perinatal Society of Australia and New Zealand (PSANZ) (2005 to current). We will use the Cochrane Highly Sensitive Search Strategy for identifying randomised controlled trials as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will use the MeSH heading: infant, newborn AND Interactive Ventilatory Support AND the text word “neurally adjusted” or “NAVA”. A second search will be performed using the MeSH heading: infant, newborn AND text word “neurally adjusted” OR “NAVA”. The results of the two searches will be combined. There will be no restriction on date, language or publications to our searches.

Searching other resources

In addition we will search the following registries:

- <http://www.controlled-trials.com>
- <http://clinicaltrials.gov>
- <http://www.anzctr.org.au/>

We will check the reference lists of all identified studies for further relevant studies. We will search conference abstracts for relevant unpublished studies.

Data collection and analysis

Selection of studies

Three review authors (AG, TR, SS) will undertake the study selection process. Two authors (TR, SS) will independently identify the studies and assess whether inclusion criteria are fulfilled. Where there is disagreement, this will be resolved by consultation with AG.

The details of all excluded studies will be listed with reason for exclusion in the table ‘Characteristics of excluded studies’.

Data extraction and management

Two review authors (TR, SS) will independently perform data extraction using a standardised form. Where there is discrepancy between the two authors this will be resolved by discussion and, when necessary, consultation with AG.

Assessment of risk of bias in included studies

Risk of bias will be independently assessed by two reviewers (TR, SS) using the Cochrane’s domain-based tool for assessing risk of bias. Selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias will be scored. An overall risk of bias for each study will be ‘high risk of bias’, ‘low risk of bias’ or ‘unclear risk of bias’. This will be made according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements will be resolved by consensus or, when necessary, discussion with AG.

The following risk of bias domains will be assessed:

1) Selection bias:

a) random sequence generation;

- Low risk: adequate (any truly random process e.g. random number table; computer random number generator)
- High risk: inadequate (any non-random process e.g. odd or even date of birth; hospital or clinic record number; allocation by availability of intervention)
- Unclear risk: no or unclear information provided

b) allocation concealment;

- Low risk: adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes)
- High risk: inadequate (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth; case record number)
- Unclear risk: no or unclear information provided

2) Performance bias:

a) blinding of participants and personnel;

- Low risk: adequate (blinding ensured and unlikely to have been broken; no or incomplete blinding but unlikely to have influenced outcome)

- High risk: inadequate (blinding attempted but likely that it could have been broken and influenced outcome; no or incomplete blinding that is likely to have influenced outcome)
- Unclear risk: no or unclear information provided

3) Detection bias:

a) blinding of outcome assessment;

- Low risk: adequate (blinding of outcome assessment ensured and unlikely to have been broken; no or incomplete blinding but unlikely to have influenced outcome)
- High risk: inadequate (blinding of outcome assessment attempted but likely that it could have been broken and influenced outcome; no or incomplete blinding that is likely to have influenced outcome)
- Unclear risk: no or unclear information provided

4) Attrition bias:

a) incomplete outcome data;

- Low risk: adequate (no missing outcome data; reasons for missing data unlikely to be related to true outcome; missing outcome data balanced across groups; missing data insufficient to have a clinically relevant impact on effect estimate or size; missing data imputed using appropriate methods)
- High risk: inadequate (reason for missing outcome data likely to be related to true outcome; missing data sufficient to have a clinically relevant impact on effect estimate or size; 'as-treated' analysis done with substantial departure from randomised allocation)
- Unclear risk: no or unclear information provided

5) Reporting bias:

a) selective reporting;

- Low risk: adequate (the study protocol is available and all of the study's pre-specified primary and secondary outcomes that are of interest to the review are reported in the pre-specified way; the protocol is not available but it is clear the published reports include all expected outcomes)
- High risk: inadequate (not all pre-specified outcomes reported; one or more primary outcomes is reported using measurements, analysis, methods or subsets that were not pre-specified; one or more primary outcomes were not pre-specified; one or more outcomes of interest are incompletely reported so that they cannot be entered in meta-analysis; the study fails to report a key outcome that would have been expected to be reported)
- Unclear risk: no or unclear information provided

6) other sources of bias.

- Low risk: the study appears free of other sources of bias
- High risk: at least one important risk of bias (related to study design; study has been claimed to be fraudulent)
- Unclear risk: no or unclear information provided

Data entry into the Review Manager software ([Review Manager \(RevMan\)](#)) will be undertaken by one author (TR) and verified by a second author (SS).

Quality of evidence

We will assess the quality of evidence for the main comparison at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach ([Guyatt 2011a](#)). This methodological approach considers evidence from randomised controlled trials as high quality that may be downgraded based on consideration of any of five areas: design (risk of bias); consistency across studies; directness of the evidence; precision of estimates; and presence of publication bias ([Guyatt 2011a](#)). The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades: "1) High: We are very confident that the true effect lies close to that of the estimate of the effect; 2) 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; 3) Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; 4) 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" ([Schünemann 2013](#)).

The review authors will independently assess the quality of the evidence found for outcomes identified as critical or important for clinical decision making. The critical outcome measures to be included in the summary of findings are: all-cause mortality or BPD as previously defined.

In cases where we consider the risk of bias arising from inadequate concealment of allocation, inadequately randomised assignment, incomplete follow-up or inadequately blinded outcome assessment reduces our confidence in the effect estimates, we will downgrade the quality of evidence accordingly ([Guyatt 2011b](#)). Consistency will be evaluated by similarity of point estimates, extent of overlap of confidence intervals (CIs) and statistical criteria including measurement of heterogeneity (I^2). The quality of evidence will be downgraded when inconsistency across results of studies was present, large and unexplained (i.e. some studies suggest important benefit and others no effect or harm without a clinical explanation) ([Guyatt 2011d](#)). Precision will be assessed taking into account the 95% CI around the pooled estimation ([Guyatt 2011c](#)). When trials were conducted in populations other than the target population, we will downgrade the quality of evidence because of indirectness ([Guyatt 2011e](#)).

We will enter data (i.e. pooled estimates of the effects and corresponding 95% CI) and explicit judgements for each of the aspects assessed above into the Guideline Development Tool ([GRADEpro 2008](#)), the software used to create 'Summary of findings' (SoF) tables. We will explain all judgements involving the assessment of the study characteristics described above in footnotes or comments in the SoF table.

Measures of treatment effect

We will extract categorical data for each intervention group and calculate the risk ratio (RR) and risk difference (RD). If the risk difference is statistically significant, we will calculate the number needed to treat for an additional beneficial outcome or for an additional harmful outcome.

Analysis of cross-over trials will depend on the risk of carry-over or period effects. When these are not considered a problem then an effect estimate will be calculated using the generic inverse variance method in RevMan (Higgins 2011). Where there are insufficient data to include a paired analysis in a meta-analysis, data will be treated as two parallel arms, acknowledging the loss of statistical power.

Unit of analysis issues

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

Dealing with missing data

We will contact the authors when we detect that data appear to be missing. If data are missing from one period of a cross-over trial, we will exclude data from both periods from analysis.

Assessment of heterogeneity

Heterogeneity will be quantified with the I^2 statistic calculated as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The thresholds for interpreting I^2 will be:

- 0% to 25%: no heterogeneity
- 25% to 49%: low heterogeneity
- 40% to 74%: moderate heterogeneity
- $\geq 75\%$: high heterogeneity

Where I^2 exceeds 75% we will conduct a sensitivity analysis to explain the source of heterogeneity.

Assessment of reporting biases

If there are at least 10 trials included in a meta-analysis a funnel plot will be performed to assess publication bias.

Data synthesis

Meta-analysis will be performed using RevMan and a fixed-effect model if there are two or more RCTs with comparable populations and treatment interventions. The RCTs will be considered comparable if NAVA is used as the primary mode of ventilation or in a discrete analysis as rescue mode.

We will present our results with 95% CIs. Where different scales are used to measure the same continuous data between trials the standardised mean differences (SMDs) will be calculated. For continuous data the mean and standard deviation will be extracted and analysis performed using the weighted mean differences (WMD). Where the outcomes are measured using differing scales the standardised mean difference will be used.

We will assess WMDs, RRs and RDs. The outcomes of comparable trials will be analysed with 95% CIs to estimate treatment effect. We will compare results using forest plots, with the RR as the point estimate for dichotomous outcomes and WMD as the point estimate for continuous outcomes.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be performed according to:

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

Sensitivity analysis

If there are sufficient studies we will perform a sensitivity analysis to evaluate the robustness of the results, and investigate any source of heterogeneity. Sensitivity analysis may be performed by separating studies according to risk of bias in each of the previously specified domains. A sensitivity analysis may be used particularly in evaluating data from cross-over studies, determining the effect of including both study periods.

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REFERENCES

Additional references

Beck 2009

Beck J, Reilly M, Grasselli G, Mirabella L, Slutsky A S, Dunn M S, et al. Patient-ventilator interaction during neurally adjusted ventilatory assist in low birth weight infants. *Pediatric Research* 2009;**65**(6):663–8.

Bhat 2015

Bhat P, Patel DS, Hannam S, Rafferty GF, Peacock JL, Milner AD, et al. Crossover study of proportional assist versus assist control ventilation. *Archives of Disease in Childhood: Fetal and Neonatal Edition* 2015;**100**(1):F35–8.

Costeloe 2012

Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *BMJ* 2012;**345**:e7976.

Dimitriou 1998

Dimitriou G, Greenough A, Laubscher B, Yamaguchi N. Comparison of airway pressure-triggered and airflow-triggered ventilation in very immature infants. *Acta Paediatrica* 1998;**87**(12):1256–60.

Donn 2003

Donn SM, Sinha SK. Can mechanical ventilation strategies reduce chronic lung disease?. *Seminars in Neonatology* 2003;**8**(6):441–8.

GRADEpro 2008 [Computer program]

Brozek J, Oxman A, Schünemann H. GRADEpro [Version 3.2 for Windows]. The GRADE Working Group, 2008.

Greenough 1983

Greenough A, Morley C, Davis J. Interaction of spontaneous respiration with artificial ventilation in preterm babies. *The Journal of Pediatrics* 1983;**103**(5):769–73.

Greenough 1984a

Greenough A, Morley CJ. Pneumothorax in infants who fight ventilators. *Lancet* 1984;**1**(8378):689.

Greenough 1984b

Greenough A, Wood S, Morley C J, Davis JA. Pancuronium prevents pneumothoraces in ventilated premature babies who actively expire against positive pressure inflation. *Lancet* 1984;**1**(8367):1–3.

Greenough 1986

Greenough A, Morley CJ, Pool J. Fighting the ventilator--are fast rates an effective alternative to paralysis?. *Early Human Development* 1986;**13**(2):189–94.

Greenough 2008

Greenough A, Dimitriou G, Prendergast M, Milner AD. Synchronized mechanical ventilation for respiratory support in newborn infants. *Cochrane Database of Systematic Reviews* 2008, Issue 1. [DOI: 10.1002/14651858.CD000456.pub3]

Guyatt 2011a

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383–94. [PUBMED: 21195583]

Guyatt 2011b

Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *Journal of Clinical Epidemiology* 2011;**64**(4):407–15. [PUBMED: 21247734]

Guyatt 2011c

Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines: 6. Rating the quality of evidence--imprecision. *Journal of Clinical Epidemiology* 2011;**64**(12):1283–93. [PUBMED: 21839614]

Guyatt 2011d

Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. *Journal of Clinical Epidemiology* 2011;**64**(12):1294–302. [PUBMED: 21803546]

Guyatt 2011e

Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *Journal of Clinical Epidemiology* 2011;**64**(12):1303–10. [PUBMED: 21802903]

Higgins 2011

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Jobe 2001

Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *American Journal of Respiratory and Critical Care Medicine* 2001;**163**(7):1723–9.

Perlman 1985

Perlman JM, Goodman S, Kreusser KL, Volpe JJ. Reduction in intraventricular hemorrhage by elimination of fluctuating cerebral blood-flow velocity in preterm infants with respiratory distress syndrome. *The New England Journal of Medicine* 1985;**312**(21):1353–7.

Review Manager (RevMan) [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schünemann 2013

Schünemann H, Brozek J, Guyatt G, Oxman A, editors. GWG. GRADE handbook for grading quality of evidence and strength of recommendations. Available from www.guidelinedevelopment.org/handbook updated October 2013.

* Indicates the major publication for the study

CONTRIBUTIONS OF AUTHORS

Conceiving the review: AG

Co-ordinating the review: AG

Writing the protocol: AG, TR

Commenting on and reviewing the protocol: SS

Guarantor for the review (one author): AG

DECLARATIONS OF INTEREST

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

SS: none known

TR: none known

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