Volume-targeted versus pressure-limited ventilation in the neonate (Review)

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TABLE OF CONTENTS

[Intervention Review]

Volume-targeted versus pressure-limited ventilation in the neonate

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ABSTRACT

Background

Damage caused by lung overdistension (volutrauma) has been implicated in the development bronchopulmonary dysplasia (BPD). Modern neonatal ventilation modes can target a set tidal volume as an alternative to traditional pressure-limited ventilation using a fixed inflation pressure. Volume targeting aims to produce a more stable tidal volume in order to reduce lung damage and stabilise pCO_2

Objectives

To determine whether volume-targeted ventilation (VTV) compared with pressure-limited ventilation (PLV) leads to reduced rates of death and BPD in newborn infants. Secondary objectives were to determine whether use of VTV affected outcomes including air leak, cranial ultrasound findings and neurodevelopment.

Search strategy

The search strategy comprised searches of the Cochrane Central Register of Controlled Trials, MEDLINE PubMed 1966 to January 2010, and hand searches of reference lists of relevant articles and conference proceedings.

Selection criteria

All randomised and quasi-randomised trials comparing the use of volume-targeted versus pressure-limited ventilation in infants of less than 28 days corrected age.

Data collection and analysis

Two review authors assessed the methodological quality of eligible trials and extracted data independently. When appropriate, meta-analysis was conducted to provide a pooled estimate of effect. For categorical data the relative risk (RR) and risk difference (RD) were calculated with 95% confidence intervals. Number needed to treat was calculated when RD was statistically significant. Continuous data were analysed using weighted mean difference.

Main results

Twelve randomised trials met our inclusion criteria; nine parallel trials (629 infants) and three crossover trials (64 infants).

The use of VTV modes resulted in a reduction in the combined outcome of death or bronchopulmonary dysplasia [typical RR 0.73 (95% CI 0.57 to 0.93), NNT8 (95% CI 5 to 33)]. VTV modes also resulted in reductions in pneumothorax [typical RR 0.46 (95% CI 0.25 to 0.84), NNT 17 (95% CI 10 to 100)], days of ventilation [MD -2.36 (95% CI -3.9 to -0.8)], hypocarbia [typical RR 0.56 (95%CI 0.33 to 0.96), NNT 4 (95% CI 2 to 25)] and the combined outcome of periventricular leukomalacia or grade 3-4 intraventricular haemorrhage [typical RR 0.48 (95% CI 0.28 to 0.84), NNT 11 (95% CI 7 to 50)].

Authors' conclusions

Infants ventilated using VTV modes had reduced death and chronic lung disease compared with infants ventilated using PLV modes. Further studies are needed to identify whether VTV modes improve neurodevelopmental outcomes and to compare and refine VTV strategies.

PLAIN LANGUAGE SUMMARY

A comparison of volume targeted ventilation modes with traditional pressure limited ventilation modes for newborn babies

Preterm babies may need help to breathe. The risk of lung problems increases with increasing immaturity. For some babies, the assistance of a ventilator (breathing machine) can be life saving, however ventilators may also injure the baby's immature lungs. New 'volume targeted' modes of ventilation have been developed which aim to reduce lung injury by controlling the amount of air entering the lungs with each breath. This review has compared the outcome of infants ventilated with volume targeted modes, with infants ventilated using traditional 'pressure limited' modes.

Babies ventilated using volume targeted modes of ventilation were more likely to survive free of lung damage. They needed ventilator assistance for a shorter duration and were less likely to develop pneumothorax (a condition when air escapes from the lung into the chest). They had more stable carbon dioxide levels in the blood, and had fewer brain ultrasound abnormalities. There was no evidence that volume targeted modes were more likely to harm the baby than traditional modes. More research is needed to understand whether volume targeted modes also lead to improvements in the development of movement and intellect. More research is also needed comparing different volume targeting techniques.

BACKGROUND

Description of the condition

Mechanical ventilation remains an essential tool in the care of critically sick and very preterm infants, despite improvements in perinatal care, including increased use of antenatal steroids and non-invasive ventilation. The Vermont-Oxford network reported for the year 2008 that median 64% (IQR 54 to 75%) of VLBW-infants (< 1500 g) received mechanical ventilation during their stay in the neonatal intensive care unit (VON 2008). The main indications for mechanical ventilation in preterm infants are respiratory distress syndrome, lung immaturity and poor respiratory drive. Although the respiratory difficulties resolve in most of these infants, median 26% (IQR 13% to 31%) infants < 1500 g, and 65% (50 to 85%) of infants 500 to 750 g develop bronchopulmonary dysplasia (BPD) with oxygen dependency at 36 weeks' corrected age. The resulting burden includes increased duration of respiratory support and hospital stay, the need for home oxygen, impaired neurodevelopmental outcome, more readmissions to hospital and increased mortality.

Bronchopulmonary dysplasia (Northway 1967) is defined as the requirement for supplemental oxygen at either 28 days postnatal age (NIH 1979) or at 36 weeks corrected age (Shennan 1988). It is characterized by the histopathological findings of impaired alveolarization, altered pulmonary microvasculature and pulmonary fibrosis. The development of BPD has been linked to lung immaturity, intrauterine growth restriction (Bardin 1997; Gortner 1999), infection (Hannaford 1999), oxidant stress (Warner 1998), in-utero inflammation (Watterberg 1996) and mechanical ventila-

tion (Coalson 1999; Clark 2000). Ventilation strategies have been identified as potentially modifiable cause of bronchopulmonary dysplasia, and research has been devoted to developing ventilation strategies which avoid the overdistension, atelectasis and shear stresses that are thought to lead to lung injury and consequently BPD. The fact that lung injury has been demonstrated following six large inflations immediately after birth (Bjorklund 1997), highlights the potential importance of early use of protective ventilation strategies in the neonate.

Description of the intervention

Volume-targeted ventilation (VTV) strategies have been developed, which aim to deliver a consistent tidal volume (VT). Volume oriented modes have been in use in paediatric and adult practice for many years. However, the technological limitations of older ventilators precluded their use in the preterm neonate because they were unable to accurately deliver the small VT required when ventilating small preterm infants. Modern microprocessor-controlled neonatal ventilators with flow sensors permit accurate measurement and delivery of a set VT. Earlier designs included a flow sensor built into the ventilator, however with this design, VT measurements are affected by the compliance of the ventilator circuit. Newer designs include sensors that can be placed at the Wye piece between the ventilator circuit and the endotracheal tube. With appropriate software the ventilators measure and control ventilator parameters to target the delivered VT, and reduce VT variability delivery compared with PLV modes (Abubakar 2001).

When using a ventilator in a VTV mode, the clinician sets a target VT. Different VTV-modes measure either inspired VT, expired VT or both to control VT delivery. Expired VT is less affected by endotracheal tube (ETT) leaks, and measuring both inspired and expired VT enables ETT leak to be quantified. There are many different forms of VTV. Depending on the ventilator design and the mode selected the ventilator adjusts one or more of the peak inspiratory pressure (PIP), inflation time and inspiratory flow. Some ventilators offer more than one VTV mode. A summary of the main neonatal ventilators and VTV modes is shown in Table 1.

Table 1. Characteristics of Volume Targeting Modes of Ventilation

Manufacturer and model	Tidal volume measurement	VTV Mode (Manufacturer terminology)	Volume targeting technique	Adjustment for leak	Adjustment for circuit compliance?
Bearcub	At ventilator Optionally at ETT	Volume Limit	Volume limited mode, adjusts inflation time in response to inspired VT. Terminates inflation when target VT delivered.	None. Clinician can increase target VT	None. Clinician can increase target VT.
Drager Babylog 8000plus	At ETT	Volume Guarantee (VG)	Adjusts PIP in response to expired VT. Pressure limited mode, with PIP controlled by value of previous expired VT. Different algorithms are used for triggered and non-triggered inflations. Mode also limits VT: Terminates inflation if inspired tidal volume	Automatic. Claimed accurate for leaks up to 40-60%	Not applicable

Table 1. Characteristics of Volume Targeting Modes of Ventilation (*Continued*)

			> 130% of target expired tidal volume.		
Leoni Plus	At ETT	Volume Guarantee (VG)	Adjusts PIP in response to expired VT. Pressure limited mode, with PIP controlled by value of previous expired VT.	Automatic. Claimed, accurate for leaks up to 50%.	Not applicable
		Volume limit	Volume limited mode. Terminates inflation when target VT delivered.	None	
Maquet Servo 300	At ventilator	Pressure-regulated volume control (PRVC)	Adjusts PIP in response to inspired VT. Pressure-limited mode. Adjusts PIP (up to 5 cm H_2O below max limit) to achieve targetVT. PIP controlled by previous expired VT.	No	None. Clinician can increase target VT.
		Volume controlled (VC)	Flow cycled with pressure increasing during inflation. Inflation controlled by inspired VT.		
Maquet Servo-i	At ventilator Optionally at ETT	Pressure-regulated volume control (PRVC)	Adjusts PIP in response to previous VT. Pressure-limited mode. Adjusts PIP (up to 5 cm H_2O below max limit) to achieve target VT. PIP controlled by previous expired VT.	Yes	Not applicable

Table 1. Characteristics of Volume Targeting Modes of Ventilation (*Continued*)

SLE 5000	At ETT	Targeted tidal volume (TTV, old software)	Volume limited mode. Ti controlled by inspired VT.	No	Not applicable
		Targeted tidal volume (TTV ^{plus} , software version 4.3 or later)	Hybrid mode. Inspiratory time controlled by inspired VT, but PIP controlled by previous inspired VT. Ti may vary, but is maintained within 75% to 100% of the set Ti.	Clinician can set manual leak compensation (up to 20 %)	Not applicable
Stehanie Infant ventilator	At ETT	Volume Limitation	Pressure limited mode, with PIP controlled by previous expired VT.	Automatic. Claimed accurate for leaks up to 50%.	Not applicable
		Volume Control (VC)	Target VT can be controlled by either inspired or expired VT. Flow-cycled inflation where flow pattern is manually set. PIP needed to achieve target VT varies up to a set PIP limit.	Automatic if VC based on expired VT. Claimed accurate for leaks up to 50%.	Not applicable
V.I.P. Bird Gold	At both ventilator and ETT	Volume-assured pressure support (VAPS)	Hybrid mode, targeting inspired VT. Inflation commenced as a pressure-support (flow-cycled) inflation. If the target VT is not delivered by end of set inflation time, ventilator transition to flow cycled inflation by prolonging the Ti.	Leak compensation not available with infant sensor. Clinician can increase target VT.	Not applicable

Table 1. Characteristics of Volume Targeting Modes of Ventilation (*Continued*)

		Volume Control (VC)	Ti controlled by inspired VT. Flow-cycled inflation where the flow is either a constant (square waveform) or decelerating until delivery of a preset target VT. Once target VT has been delivered the flow terminates and cycles to exhalation. Mode is controlled by inspired VT.	Leak compensation not available with infant sensor. Clinician can increase target VT.	Not applicable
Viasys Avea	At ETT	Pressure-regulated volume control (PRVC)	Hybrid mode targeting inspired VT. Inflation commenced as time-cycled pressure-limited. Extends Ti and changes to flow cycled inflation if low inspired VT. Algorithm of Avea claimed to avoid excess Ti.	'On/off' Clinician can increase target VT.	Not applicable. A manually setting adjusts ventilator to circuit characteristics.

How the intervention might work

Traditionally, neonatologists treating infants with severe respiratory conditions have employed continuous flow, time-cycled, pressure-limited ventilation (PLV). In this mode, the assistance provided by the ventilator is controlled in two ways. The magnitude of each inflation is determined by the change in airway pressure, i.e. the difference between PIP and the baseline or positive end-expiratory pressure (PEEP). The VT for any breath depends on both this pressure difference, which drives gas movement, and the lung compliance. Although VT is indirectly determined by the clinician when the PIP and PEEP are set, VT may not be consistent when compliance changes. For example, following administration of artificial surfactant, improved compliance may result in the delivery of increased VT if the PIP is not reduced.

In the past, there was concern about lung damage caused by high-pressures ("barotrauma"), however, several studies have indicated that lung collapse and overdistension (or atelectasis and "volutrauma") are the major instigators of inflammation in the preterm lung (Dreyfuss 1993; Dreyfuss 1998). This is supported by animal studies comparing high PIP in an animal model where a cast was used to reduce chest wall compliance and hence VT (Hernandez 1989). Histological examination demonstrated a significant reduction in lung inflammation in the animals protected from high VT. Further support comes from a randomised controlled trial comparing high VT (12 ml/kg) with low VT (6 ml/kg) strategies in adults with acute lung injury, which was stopped prematurely when interim analysis revealed a significant reduction in both mortality and duration of ventilation in the latter group (ARDS Network 2000). Lung compliance changes rapidly and substantially during the evolution and treatment of hyaline membrane disease (Hentschel 2002; Wheeler 2009). Ventilation strategies that adapt to these changes may enhance stability and reduce lung

injury.

There is a paucity of information regarding the optimal VT for preterm infants. An observational study of VT values in infants < 800 g ventilated using VTV during the first three weeks of life, reported obtaining acceptable blood gases using target VT of 5 to 6 ml/kg with the Drager Babylog 8000plus (Keszler 2009). Other studies have suggested a VT ≤ 4 ml/kg may increase lung inflammation and work of breathing (Lista 2006; Patel 2009). When selecting target VT for devices which measure VT at the ventilator (rather than at the Wye piece), allowance must be made for the additional compressible gas volume and compliance of the ventilator circuit (Cannon 2000; Al-Majed 2004).

Why it is important to do this review

The uptake of VTV varies between countries and continents. Recent surveys have shown that 5 to 63 % of neonatal units in Europe, Australia and New Zealand routinely use VTV modes and perceptions vary as to whether the use of VTV modes leads to improved outcomes (Sharma 2007; Klingenberg 2010). It is important to understand how outcomes of infants ventilated using VTV modes compare with those of infants ventilated using PLV modes.

OBJECTIVES

This review investigated outcomes of participants of randomised studies comparing volume-targeted ventilation (VTV) with pressure-limited ventilation (PLV). Infants were eligible if corrected gestational age was less than term plus 28 days. The primary objectives were to determine:

- whether the use of VTV strategies compared with PLV reduced rates of death and bronchopulmonary dysplasia;

- in addition these strategies were compared to determine any differences in the incidences of complications of prematurity and adverse neurological outcomes.

Subgroup analyses

Three subgroup analyses were planned based on:

1. mode of volume-targeted ventilation;

2. age at recruitment into study;

3. maturity / birth weight of the infants.

1. In view of the differences between the modes of volume-targeted ventilation, it was originally intended that subgroups would be defined according to:

i) Volume-controlled (VC) ventilation

ii) Volume guarantee (VG) ventilation

2. Subgroups were defined according to postnatal age at time of recruitment into studies:

i) early recruitment, i.e. commencement of ventilation strategy at birth or within the first four hours of life;

ii) late recruitment, i.e. beyond four hours of age. This subgroup included trials in which VTV was tested as a rescue strategy.

3. In view of the increased risk of BPD in the smallest, most immature infants, subgroups were defined according to:

i) birth weight, with a cut-off of 1000 grams;

ii) gestational age, with a cut-off of 30 weeks' gestation.

Modifications of these subgroup analyses for this update (post hoc after considering the technical changes in ventilator design)

Subgroup analysis based on VTV mode was not performed. Since the original protocol was written (McCallion 2002), the range of available VTV modes has changed, and the suggested subgroup classification is not appropriate (Table 1). We have analysed all VTV modes together without attempting to subdivide them into different modes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised studies were eligible for inclusion in this review.

Types of participants

All intubated infants of less than 28 days corrected age who were being mechanically ventilated with intermittent positive pressure ventilation at the time of study entry. Infants of all gestational ages and both paralysed and non-paralysed infants were eligible.

Types of interventions

Volume-targeted versus time-cycled, pressure-limited modes of mechanical ventilation. The review only included studies comparing VTV modes of ventilation with PLV modes.

Types of outcome measures

The two **primary outcomes** were death, and death or requirement for supplemental oxygen at defined time points (as below).

- Mortality defined in two ways:

i) death before discharge from the primary hospital;
ii) death before two years corrected age.

- Death or supplemental oxygen requirement assessed at two time points:

i) supplemental oxygen requirement at 28 days or death prior to 28 days;
ii) supplemental oxygen requirement at 36 weeks corrected gestational age or death prior to 36 weeks.

The **secondary objectives** of this review were to compare volume-targeted modes of ventilation with time-cycled, pressure-limited ventilation with respect to:

a) failure of mode of ventilation (clinical decision to change to different mode of ventilation)
b) addition of neuromuscular paralysis where previously not paralysed
c) ventilation data

- days of intermittent positive pressure ventilation (IPPV)
- days of continuous positive airway pressure (CPAP)
- total duration of respiratory support in days (IPPV and CPAP)

d) effectiveness of gas exchange as shown on arterial or capillary blood gas sampling

- any pH < 7.25
- any episode of hypocarbia (pCO_2 < 35 mm Hg/4.7 kPa)
- any episode of respiratory acidosis (pH<7.25 with pCO2 > 60 mm Hg/8 kPa)

e) inspired oxygen concentrations (FiO_2)
f) patent ductus arteriosus (PDA)
g) incidence of air leak

- overall incidence air leak
- incidence pneumothoraces
- incidence pulmonary interstitial emphysema (PIE)

h) growth

- days to regain birth weight (BW)
- grams weight gain per week until discharge

i) intracranial pathology

- all cranial ultrasound abnormalities (intraventricular haemorrhage and periventricular leukomalacia)
- intraventricular haemorrhage (IVH)
- cystic periventricular leukomalacia (PVL)

j) adverse neurosensory sequelae at two years

- cerebral palsy
- blindness
- deafness
- moderate to severe developmental delay as assessed on performance in formal neurodevelopmental testing (Bayley score, WIPPSI etc.)

k) Surviving infants with bronchopulmonary dysplasia

- supplemental oxygen requirement at 28 days after birth
- supplemental oxygen requirement at 36 weeks corrected gestational age

Modifications of these outcome measures (post hoc after viewing the available data):

1. Duration of intermittent positive (endotracheal) ventilation (IPPV): This outcome measure was calculated in survivors only.
2. Failure of ventilatory mode: This outcome measure was clarified as a change from the assigned mode of ventilation within the study intervention period.
3. Intraventricular haemorrhage (IVH): Outcomes for both total incidence of IVH and incidence of IVH grade 3 - 4 were collected.
4. Cystic PVL: Most studies did not define PVL. Outcomes for studies reporting any PVL were included.
5. Data from studies reporting BPD rates have been included for all patients when data on survivors was unavailable.

Search methods for identification of studies

The search was performed using the standard strategy of the Neonatal Review Group of the Cochrane Collaboration. MEDLINE (1966 to January 2010) was searched using the MeSH terms: infant, newborn and respiration, artificial and the text word: volume. These terms were also used in a search of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2009), CINAHL. No language restrictions were applied. A review (1981 to 2010) of abstracts published by the Society for Pediatric Research and the European Society for Pediatric Research completed the literature search. This was combined with cross-referencing of previous reviews, the use of expert informants and newer additional resources such as clinicaltrials.gov.

Data collection and analysis

The standard methods of the Neonatal Review Group of the Cochrane Collaboration were used. Trial searches, assessments of methodology and extraction of data were performed independently by two review authors (KW and CK) with comparison and resolution of any differences found at each stage. Review authors based quality assessment on 1) blinding of randomisation, 2) blinding of intervention, 3) blinding of outcome measurements 4) completeness of follow-up and 5) other characteristics of study design with potential for bias.

For categorical data (e.g. death or number developing bronchopulmonary dysplasia) the relative risk (RR), risk difference (RD) and

number needed to treat (NNT) with 95% confidence intervals were calculated. Continuous data (e.g. duration of ventilation) were analysed using weighted mean difference (WMD). The fixed effect model was used for all analyses and evaluation of heterogeneity was conducted using the I^2 statistic to determine the suitability of pooling results.

A sensitivity analysis limited to true randomised trials only was planned if quasi-randomised trials were identified during the literature search.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

After performing the search and screening article titles, 25 clinical trials (26 publications) comparing VTV with PLV were identified.

Trials included

Thirteen publications reporting twelve randomised controlled trials met our inclusion criteria and reported outcomes defined in our protocol.

Of these, nine were parallel studies, resulting in 10 publications (Sinha 1997; Piotrowski 1997; Keszler 2004a; Lista 2004; Nafday 2005; D'Angio 2005; Singh 2006+2009 (including a separate publication of follow-up data from the inception cohort), Cheema 2007; Piotrowski 2007). Three trials were within-patient crossover studies (Herrera 2002; Polimeni 2006; Hummler 2006).

Trials identified, but excluded

i. The trials of Abubakar 2001; Abd El-Moneim 2005; Wach 2003 and Lista 2000 were not randomised.

ii. The trials of Dotta 2004; Keszler 2004b; Olsen 2002; Ramirez-Del Valle 2006 and Sinha 2008 were randomised, but did not report any of the outcomes specified in the protocol.

iii. The trial of Cheema 2001 was randomised, however, the PIP setting was the same in both arms, which may have interfered with the ventilator's capacity to deliver the set VT and hence affected the outcomes.

iv. The trial of Salvia 2006 was randomised, but only short term outcomes have been presented in abstract form. Longer term follow up is in progress (information from author), and the final published data are awaited.

v. The trial of Colnaghi 2006 was randomised, but data have only been presented in abstract form and they did not report any outcomes specified in our protocol. Final published data are awaited.

vi. The TARDIS trial of volume targeted ventilation from the point of delivery has been registered with the Australian New Zealand Clinical Trials Registry. Recruitment commenced November 2006. No outcomes have been reported.

Study populations of included trials:

Study sample sizes range from 12 to 212 infants.

Inclusion criteria varied, ranging from studies which included only smaller infants (< 1200 g / < 32 weeks), larger infants ≥ 1200 g, or any infant < 2500 g.

Ten trials recruited infants in the early neonatal period. Two crossover trials enrolled older infants: Hummler 2006 enrolled patients at mean (SD) 33 (13) days of age and Polimeni 2006 enrolled patients at mean (SD) 37 (17) days of age. In all trials, infants were studied at less than 28 days postmenstrual age.

Duration of intervention for the parallel trials ranged from median 95 minutes (Cheema 2007) up to almost the full period of mechanical ventilation. In the crossover trials duration of intervention period ranged from 60 minutes (Herrera 2002) up to four hours (Hummler 2006).

Exclusion criteria were similar across the trials and included the following: lethal congenital anomalies, muscle relaxation, suspected sepsis, severe IVH, asphyxia, pneumothorax and meconium aspiration. Some studies specified lack of arterial access, narcotics, endotracheal tube leaks (> 30%) as additional exclusion criteria.

Antenatal steroids and surfactant were available in all participating units.

Further details of the studies are described in Description of studies.

Interventions:

A range of ventilators delivering VTV were used for the experimental groups, including the VIP Bird and Bird Gold, Siemens Servo 300, Draeger Babylog 8000plus and Stephanie Infant ventilator. Further characteristics of the devices are described in Table 1.

The ventilation settings were not always well described in each trial. Further details are shown in Description of studies.

Hybrid studies

In some trials volume targeting was not the only difference between study groups.

i. Use of triggering: The use of triggering in one arm of the trial but not in the other is a potential source of bias Greenough 2008. In the trial of Piotrowski 1997, the control infants received non-triggered intermittent mandatory ventilation, whereas VTV infants received triggered ventilation (PRVC). Sinha 1997 used an assist-control (AC) mode in both arms, but the volume control (VC) arm used pressure-triggering and the PLV arm used flow-triggering.

ii. Different trigger-modes: Three studies (Nafday 2005; Piotrowski 2007; D'Angio 2005) used a mode where all breaths were triggered in the experimental group (AC mode) and synchronized intermittent mandatory ventilation (SIMV) in the control group. This difference in trigger modes is a potential source of bias (Greenough 2008), however, when the inflation rate in the SIMV mode is high (i.e. - 50 to 60/min) the clinical difference between the two modes becomes less important.

iii. Different ventilators: In two studies (Piotrowski 1997; Piotrowski 2007), babies in different groups were ventilated using

different ventilators. This may also be a source of bias.

In view of these differences, a post hoc subgroup analysis of **strict studies** (both groups *initially* ventilated with similar modes/ventilators with VTV being to the only difference) versus **hybrid studies** (other differences between experimental groups, like mode of triggering, different ventilators etc.) has been performed.

Supplemental information:

Raw data and supplemental information was requested to clarify randomisation procedures, outcomes, permit more detailed analysis of duration of ventilation and facilitate the less than 1000 g subgroup analysis. The reviewer authors are grateful to the authors for making the following information available:

Piotrowski 1997: Birth weight, age of death in non-survivors, duration of ventilation.

Keszler 2004a: Birth weight, age of death in non-survivors, BPD, duration of ventilation, pneumothorax, PIE, PVL, IVH, blood gas data.

Lista 2004: Birth weight, age of death in non-survivors, BPD, duration of ventilation, pneumothorax, PIE, PVL, IVH.

D'Angio 2005: Birth weight, age of death in non-survivors, BPD, duration of ventilation, pneumothorax, PIE, PVL, IVH. Information regarding blinding of assessors.

Singh 2006+2009: Birth weight, age of death in non-survivors, BPD, duration of ventilation, pneumothorax, PIE, PVL, IVH, PDA.

Nafday 2005: Birth weight, failure of assigned mode, pneumothorax, PIE, IVH.

Cheema 2007: Blood gas data and data on randomisation procedure.

Piotrowski 2007: Results and translated into English. Information regarding stratification.

Risk of bias in included studies

Methodological quality was described using the standard method for conducting a systematic review as described in the Cochrane Collaboration Handbook. Additional details of each study appear in the table 'Characteristics of included studies'.

Method of study allocation

The twelve randomised trials (thirteen publications) included a combination of nine parallel trials (ten publications) and three crossover trials.

Randomisation pattern

Block randomisation was used by D'Angio 2005; Nafday 2005; Singh 2006+2009; Sinha 1997; Cheema 2007 (supplemental data) and Piotrowski 2007 (supplemental data).

The pattern of randomisation in the trials of Piotrowski 1997 and Keszler 2004a was not specified.

Some trials used stratification by birth weight (D'Angio 2005; Nafday 2005; Singh 2006+2009; Cheema 2007), gestational age (Lista 2004; Piotrowski 2007) and/or centre (Lista 2004; D'Angio 2005).

Blinding of randomisation

The studies by Sinha 1997; Piotrowski 1997; Herrera 2002; Keszler 2004a; Nafday 2005; D'Angio 2005; Hummler 2006; Singh 2006+2009 and Cheema 2007 (supplemental information) used sealed envelopes for blinding of randomisation.

Blinding of randomisation was not specified by Lista 2004 or Polimeni 2006.

Blinding of intervention

None of the studies included in this review attempted to mask the caregivers to the group assignment.

Blinding of outcome assessors

In the majority of studies, the allocated treatment method of each patient was known to those assessing the trial outcomes.

In Sinha 1997, severity of lung disease was assessed by a radiographer blinded to the treatment assignment.

In Singh 2006+2009, information regarding masking during interpretation of cranial imaging was not reported. A questionnaire was used to determine neurodevelopmental follow-up. The questionnaire administrator was masked to the original intervention group.

D'Angio 2005 reported neurodevelopment outcomes at 6 to 18 months as assessed by a Pediatric Neurologist who was blinded to the treatment assignment (supplemental information).

Completeness of study outcome assessment

Piotrowski 1997 excluded three out of 60 enrolled infants after randomisation, two who did not fulfil enrolment criteria and one for whom the allocated ventilator was unavailable. Outcome assessment was otherwise complete.

In the study by Lista 2004 there was an uneven distribution of patients between the VTV (30 infants) and PLV (23 infants) groups.Post-randomisation, seven infants were withdrawn because placental histology confirmed chorioamnionitis (supplemental data).

D'Angio 2005 randomised 213 infants, but one infant was erroneously enrolled without consent and immediately withdrawn from the study at the request of the parents. Follow-up in the hospital was complete for the other 212 infants. However, data on brain ultrasound beyond the first week of life were not available for all infants, and periventricular leukomalacia was assessed in only 173 infants. Neurodevelopmental follow-up data at 6 to 18 months of age were available in 128 infants (64 from each group). These 128 infants represented 83% of the 154 patients that survived to discharge in one of the two study centres.

Singh 2006+2009 randomised 110 infants, but one infant (randomised to the PLV mode) was excluded post-randomisation following diagnosis of a major congenital anomaly (trisomy 13). Follow-up in the hospital was complete for the other 109 infants. Of the 94 infants who survived to discharge, mortality and follow-up data at median age of 22 months was reported on 47/52 (90%) of infants in the VTV group, and 41/42 (98%) infants in the PLV group.

Hybrid studies

As described above, some study designs have potential to be biased as they include comparisons between different ventilator devices and ventilator modes (triggering) in the VTV and the PLV groups. Post hoc subgroup analysis has been performed.

Weaning strategies

Weaning strategies, where reported, differed between the studies and sometimes between the randomised arms. In some trials (Sinha 1997; Singh 2006+2009) both arms were weaned using a PLV-mode. These too have potential for bias.

Effects of interventions

The nine randomised parallel trials recruited a total of 629 infants, of which two trials including 74 patients (Nafday 2005 and Cheema 2007) had an intervention period ≤ 24 hours. The mean duration of mechanical ventilation reported by studies in the review ranged from 3.5 to 26 days. We believed that the short duration of intervention in the trials of Cheema 2007 and Nafday 2005 meant that these trials had a reduced ability to detect differences in longer term outcomes such as BPD, compared to trials that maintained the two treatment groups for a least 72 hours. We, therefore, only included these two trials in pooled analysis of outcomes that occurred during the intervention period e.g. blood gas analysis.

Seven parallel trials, including 555 patients, had an intervention period of 72 hours or longer (Piotrowski 1997; Sinha 1997; Lista 2004; Keszler 2004a; D'Angio 2005; Singh 2006+2009; Piotrowski 2007). Outcomes reported by these seven trials during and beyond their intervention period have been included in the meta-analysis.

Three crossover trials (Herrera 2002; Hummler 2006; Polimeni 2006) recruited a total of 64 infants. The only pre-specified outcome able to be assessed from these studies was inspired oxygen concentration.

There was no disagreement between assessors regarding inclusion/exclusion of studies, quality assessment or data extraction. Available data were pooled and analysed as listed below.

A planned subgroup analysis based on age at enrolment (planned before/after four hours) was not performed as the only study with exclusively early recruitment of all infants (Cheema 2007) only studied infants until their first blood gas. Age at enrolment varied in the other trials. In the parallel trials, study enrolment mainly occurred within first 24 hours of life. In the crossover trials, Herrera 2002 studied patients at mean (range) 5 (2 to 9) days of age, Polimeni 2006 at mean (SD) 37 (17) days of age and Hummler 2006 at mean (SD) 33 (13) days of age.

Piotrowski 1997 and Singh 2006+2009 reported outcomes for subgroup of infants less than 1000 g. Authors of all parallel trials were approached for additional information to supplement this subgroup analysis except Piotrowski 2007 where we received the translated manuscript in time to include reported outcomes only.

Heterogeneity

There was no evidence of substantial heterogeneity in the pooled analyses, i.e. I^2 values were all ≤ 40% except for the following: Duration of ventilation, any IVH and grade 3-4 IVH. Details are provided below.

Primary Outcomes

- Death in hospital

Data on mortality to hospital discharge were analysed from seven trials: Sinha 1997; Piotrowski 1997; Lista 2004; Keszler 2004a (supplemental data), D'Angio 2005; Singh 2006+2009 and Piotrowski 2007. No individual study demonstrated a difference in mortality between VTV and PLV groups and the pooled analysis also showed no significant difference [typical RR 0.80 (95% CI 0.53, 1.20), typical RD -0.03 (95% CI -0.09, 0.03)] Analysis 1.1. There was no significant difference between studies of different design and no significant difference in mortality for infants less than 1000 g [typical RR 0.71 (95% CI 0.42 to 1.21), typical RD -0.06 (95% CI -0.16 to 0.03)] Analysis 2.1.

- Mortality up to two years

This was not formally reported by any trial, although Singh 2006+2009 reported mortality from discharge to follow-up at median age of 22 months. Overall in that trial, there were seven deaths in the VTV group (12%) versus 11 (21%) in the PLV group [OR 0.5 (95% CI 0.1 to 1.4),
p = 0.13].

- Death or need for supplemental oxygen at 28 days

This outcome included data from Piotrowski 1997 (supplemental data) and Lista 2004 (supplemental data). There was no difference between groups [typical RR 0.91 (95% CI 0.60 to 1.39), typical RD -0.04 (95% CI -0.22 to 0.14)] Analysis 1.2. For infants less than 1000 g, only data from Lista 2004 (supplemental) was available [typical RR 0.83 (95% CI 0.22 to 3.18), RD -0.07 (95% CI -0.57 to 0.44)] Analysis 2.2.

- Death or need for supplemental oxygen at 36 weeks.

This combined outcome included data from five trials: Lista 2004; Keszler 2004a; D'Angio 2005; Singh 2006+2009 and Sinha 1997 (All supplemental data). Although no individual trial reported a difference between groups, pooled meta-analysis revealed a reduction in this combined outcome [typical RR 0.73 (95% CI 0.57 to 0.93), typical RD -0.12 (95% CI -0.21 to -0.03), typical NNT = 8 (95% CI 5 to 33)] Analysis 1.3. For infants less than 1000 g differences in this outcomes are of borderline statistical significance [typical RR 0.79 (0.62 to 1.01) p = 0.06, typical RD -0.13 (95% CI -0.26 to 0.00) p = 0.06] Analysis 2.3.

Secondary Outcomes

- Failure of ventilatory mode

Data were analysed from four trials (Sinha 1997; Nafday 2005 (only data from the 24 h intervention period), D'Angio 2005; Singh 2006+2009) reporting this outcome Analysis 1.4. Cheema 2007 reported that no infants needed to be rescued with high frequency ventilation during the intervention period, but these

data are not included in meta-analysis due to the short intervention period (median 95 minutes and before first blood gas analysis was available to the treating physician).
Overall, there was less failure of primarily assigned ventilatory mode in the VTV group [typical RR 0.64 (95% CI 0.43, 0.94), typical RD -.0.09 (95% CI -0.17, -0.02) typical NNT 11 (5, 100)], Analysis 1.4. Subgroup analysis for infants less than 1000 g could not be performed.

- Addition of new neuromuscular paralysis

Keszler 2004a and Piotrowski 1997 reported this outcome. Overall there was no difference between groups [typical RR 0.32 (95% CI 0.07 to 1.40), typical RD -0.12 (95% CI -0.27 to 0.03)] Analysis 1.5.

- Duration of intermittent positive pressure (endotracheal) ventilation

This outcome were included from six trials with at least 72 hours intervention: Sinha 1997, and supplemental data from Piotrowski 1997; Lista 2004; D'Angio 2005; Singh 2006+2009 and Keszler 2004a. Data were analysed in survivors only, except for the trial by Sinha 1997 where this information was unavailable. However, in this trial (Sinha 1997) only one patient died in each arm, and the results are likely to be similar. Methods of meta-analysis assume normally distributed values, but reported data on duration of IPPV were skewed. Meta-analysis performed on the skewed data (Analysis 1.6) gives a mathematical mean difference of -2.36 (-3.90, -0.83) days reduced duration of ventilation using VTV. There was evidence of heterogeneity with this analysis: I^2 = 29% (strict studies 0%, hybrid studies 53%). D'Angio 2005 (a hybrid trial comparing PRVC with SIMV) was the only trial which reported an increase duration of ventilation in the VTV group. With meta-analysis of the subgroup of strict studies alone, there remained a statistically significant reduction in duration of ventilation (MD -3.18; 95% CI -5.36 to -0.99). For hybrid studies alone the difference was not statistically significant (MD -1.56; 95% CI -3.73 to 0.60).
Geometrically normally distributed data was achieved by log transformation of supplemental raw data from five trials provided by Piotrowski 1997 Lista 2004; D'Angio 2005; Keszler 2004a and Singh 2006+2009 (Analysis 1.7). Using this method, after untransforming the log meta-analysis (MD -0.08; 95% CI -0.16 to 0), the mean difference was equivalent to 0.8 (0.7 to 1.0) days shorter ventilation with the VTV modes. As discussed above, there was evidence of heterogeneity between trials I^2 69% (strict studies 20%, hybrid studies 62%)
For infants less than 1000 g, (Analysis 2.4), meta analysis of skewed data did not show a statistically significant difference [MD -0.82 (95% CI -4.43 to 2.80)]. Using log transformed data, MD corresponded to 1.0 (95% CI 0.8 to 1.3) fewer days ventilation with VTV. Analysis 2.5. For these outcomes the was no evidence of heterogeneity (I^2 = 0%)

- Other ventilation data.

i. There were no data on duration of CPAP.
ii. Inspired oxygen concentration (Analysis 1.8) was reported by one parallel study (Cheema 2007) and the three crossover studies (Herrera 2002; Polimeni 2006; Hummler 2006). The oxygen targeting strategies varied, however, no trials reported a difference between groups. The study by Herrera 2002 used the same individual for multiple comparisons (VTV 3.0 ml/kg and 4.5 ml/kg vs PLV). Meta-analysis was only performed using the measurements from the 4.5 ml/kg group. Polimeni 2006 used different groups of patients for the comparisons of VTV 4.5 ml/kg with PLV, and VTV 6.0 ml/kg with PLV. During meta-analysis, any statistical power gained by using a patient as their own control in a crossover trial is lost. Meta analysis did not show a difference between groups [MD -0.10 (95% CI -1.54 to 1.34)].

- Abnormal blood gas measurements

Cheema 2007 reported the incidence of out of range $paCO_2$ ($paCO_2$ < 5 or $paCO_2$ > 7 kPa) and of hypocarbia ($paCO_2$ < 5 kPa) on the first blood gas of 40 enrolled infants. Comparison of all infants did not show a statistically significant difference, but for a post hoc subgroup analysis of infants 26 to 33 weeks of gestation, a reduction was reported for both outcomes. Supplemental data were analysed to identify the incidence of out of range CO_2 by the criteria in this protocol (hypocarbia CO_2 < 35 mmHg, 4.7 kPa, hypercarbia CO_2 > 60 mmHg, 8 kPa)
Keszler 2004a reported the frequency of blood gases falling outside the target range using the number of blood gases as the denominator. He found a reduced rate of hypocarbia (pCO2 < 35 torr, 35 mmHg) in blood gases from the VTV group versus PLV-group (16/77 vs 29/80, p< 0.05). Supplemental data were analysed using the patient as the denominator (a patient event was defined as any out of range result).
i. **Any pH < 7.25:** For all patients (Analysis 1.9) there was no statistically significant difference [typical RR 1.05 (95% CI 0.23 to 4.70), typical RD 0.01 (95% CI -0.15 to 0.16)]. For Infants less than 1000 g (Analysis 2.6), the was no statistically significant difference between groups [typical RR 1.32 (95% CI 0.27 to 6.53), typical RD 0.05 (95% CI -0.25 to 0.35)]
ii. **Hypocarbia** (any pCO_2 < 35 mmHg/4.7 kPa): For all patients (Analysis 1.10) there was a statistically significant reduction in hypocarbia in the VTV group [typical RR 0.56 (95% CI 0.33 to 0.96), typical RD -0.26 (-0.47 to -0.04) typical NNT 4 (95% CI 2, 25)]. For the subgroup of infants less than 1000 g (Analysis 2.7), there was no statistically significant difference between groups [typical RR 0.41 (95% CI 0.11 to 1.51), typical RD -0.29 (95% CI -0.62 to 0.04)].
iii. **Respiratory acidosis** (pH <, 7.25 and pCO_2 > 60 mmHg/8 kPa): For all patients (Analysis 1.11), there was no statistically significant difference between groups [typical RR1.58 (95% CI 0.28 to 8.78), typical RD 0.04 (95% CI -0.11 to 0.18)]. For the subgroup of Infants less than 1000 g (Analysis 2.8), there was no statistically significant difference between groups [typical RR 1.92 (95% CI 0.32 to 11.61), typical RD 0.11 (95% CI -0.19 to 0.40)].

iv. **Either hypocarbia or respiratory acidosis:** For all patients (Analysis 1.12), there was no statistically significant difference between groups [typical RR 0.69 (95% CI 0.42 to 1.12), typical RD -0.18 (95% CI -0.41 to 0.04)]. For infants less than 1000 g (Analysis 2.9) there was no statistically significant difference between groups [typical RR 0.73 (95% CI 0.26 to 2.03), typical RD -0.13 (95% CI -0.49 to 0.23)].

- Patent ductus arteriosus (PDA)

PDA data was reported in six trials: Piotrowski 1997; Sinha 1997; Lista 2004; D'Angio 2005; Singh 2006+2009 and Piotrowski 2007. The definition of PDA was not consistent, and the reported incidence varied between studies. No statistically significant difference was found in any of the individual trials or the pooled analysis [typical RR 1.03 (95% CI 0.85 to 1.25), typical RD 0.01 (95% CI -0.06, 0.09)] Analysis 1.13. Likewise, there was no statistically significant difference in the outcomes for the subgroup analysis for this outcome for infants less than 1000 g [typical RR 1.09 (95% 0.85 to 1.39), typical RD 0.04 (95% CI -0.08 to 0.16)] Analysis 2.10.

- Air leak

i. Data for overall incidence of **any air leak** (pneumothorax and/or pulmonary interstitial emphysema [PIE]) (Analysis 1.14) were reported by Piotrowski 1997; Keszler 2004a; D'Angio 2005 and Nafday 2005 (supplemental data, only including events during intervention period). Pooled data showed no statistically significant difference between groups [typical RR 0.79 (95% CI 0.44 to 1.73), typical RD -0.02 (95% CI -0.09 to 0.04)]. Subgroup analysis for infants less than 1000 g also showed no statistically significant difference [typical RR 1.11(95% CI 0.55 to 2.23), typical RD 0.01 (95% CI -0.09 to 0.12)] Analysis 2.11.

ii. Data on **pneumothorax** (Analysis 1.15) were reported by Piotrowski 1997; Sinha 1997; Keszler 2004a; Lista 2004; D'Angio 2005; Nafday 2005 (supplemental data, only including events during intervention period), Singh 2006+2009 and Piotrowski 2007. A statistically significant reduction was seen in VTV modes [typical RR 0.46 (95% CI 0.25 to 0.84), typical RD -0.06 (95% CI -0.10 to -0.01) typical NNT=17 (95% CI 10 to 100)]. In the subgroup of infants less than 1000 g (Piotrowski 1997; Lista 2004 (supplemental data), Piotrowski 1997 (supplemental data) no statistically significant difference was found [typical RR 0.63 (95% CI 0.29 to 1.37) typical RD -0.04 (95% CI -0.12 to 0.03)] Analysis 2.12.

iii. Data on **pulmonary interstitial emphysema** (Analysis 1.16) were reported by D'Angio 2005; Keszler 2004a; Lista 2004; Nafday 2005 (supplemental analysis of events occurring during intervention period), Piotrowski 1997 and Piotrowski 2007. There was no significant difference for any study, or for overall pooled data [typical RR 1.21 (95% CI 0.63 to 2.30), typical RD 0.01 (95%CI -0.04 to 0.06)]. For the subgroup analysis of infants less than 1000 g (Analysis 2.13) there was no statistically significant difference [typical RR 1.45 (95% CI 0.58 to 3.67), typical RD 0.03 (95% CI -0.05 to 0.12)].

- Growth

None of the studies assessed growth, time taken to regain birth weight, or weight gain as outcomes.

- Cranial ultrasound abnormality

i. Data on **any IVH** (Analysis 1.17) were reported in five trials: Piotrowski 1997; Keszler 2004a (supplemental data), D'Angio 2005; Singh 2006+2009 and Piotrowski 2007. Sinha 1997 reported only the combined outcome of large IVH and/or PVL and Lista 2004 reported only IVH grade 3-4; the outcomes from these trials are not included in this meta analysis but are included in the relevant meta-analyses below. No individual study or pooled analysis showed a statistically significant difference [typical RR 0.91 (0.71, 1.18), typical RD -0.03 (95% -0.12 to 0.05)]. For subgroup analysis of infants less than 1000 g (Analysis 2.14), there was no statistically significant difference between groups [typical RR 0.79 (95% CI 0.55 to 1.16), typical RD -0.08 (95% CI -0.20, 0.04)]. There was evidence of heterogeneity: I^2 = 50% (strict studies 0%, hybrid studies 68%). A non-significant increase in this outcome was reported by Piotrowski 2007 in the VTV group. However, in this study, patients in the VTV group had increased oxygen requirements at enrolment and increased surfactant use compared with the PLV group. The two groups are unlikely to have been at equal inception risk.

ii. Data on **grade 3/4 IVH** (Analysis 1.18) were reported in six trials: Piotrowski 1997; Lista 2004; Keszler 2004a (supplemental data), D'Angio 2005; Singh 2006+2009 and Piotrowski 2007. No individual study, nor pooled analysis showed a statistically significant difference between groups [typical RR 0.71 (95% 0.45, 1.11), typical RD -0.05 (95% CI -0.10, 0.01)]. There was no statistically significant difference for the subgroup of infants less than 1000 g (Analysis 2.15) [typical RR 0.53 [95% CI 0.27, 1.04], typical RD -0.10 (95% CI -0.20, 0.00)]. As with the outcomes for data on any IVH, there was evidence of heterogeneity in the subgroup of hybrid studies: I^2 7% (strict studies 0%, hybrid studies 53%).

iii. Data on **PVL** (Analysis 1.19) were reported in four trials: Lista 2004; D'Angio 2005; Keszler 2004a (supplemental data) and Singh 2006+2009. No individual study showed a difference between groups. For pooled data, there was no statistically significant difference between groups [RR 0.41 (95% CI 0.15 to 1.16), typical RD -0.04 (95% CI -0.08 to 0.01)]. For pooled subgroup analysis for infants less than 1000 g, there was no statistically significant difference between groups [typical RR 0.43 (95% CI 0.15 to 1.24), typical RD -0.05 (95% CI -0.13 to 0.02)] Analysis 2.16. Outcome data from three trials were not included in this meta analysis; Piotrowski 1997 and Piotrowski 2007 did not report PVL, and Sinha 1997 only reported the combined outcome of large IVH and/or PVL.

iv. Data on any cranial ultrasound abnormality (**any IVH or PVL**) (Analysis 1.20) were analysed using data from three trials: Keszler

2004a (supplemental data), D'Angio 2005 and Singh 2006+2009. Pooled analysis did not show a statistically significant difference between groups [typical RR 0.83 (0.58, 1.18), typical RD -0.05 (95% CI -0.16 to 0.05)]. Analysis of the subgroup of infants less than 1000 g did not identify a statistically significant difference (Analysis 2.17) [typical RR 0.90 (95% CI 0.60,1.35), typical RD -0.04 (95% CI -0.17, 0.09)].

v. Data on the combined outcomes of any **grade 3/4 IVH or PVL** were analysed using data from five trials: Sinha 1997; Keszler 2004a (supplemental data), Lista 2004; D'Angio 2005 and Singh 2006+2009. There was statistically significant reduction in the VTV groups [typical RR 0.48 (95% CI 0.28 to 0.84), typical RD -0.09 (95% CI -0.15 to -0.02), typical NNT = 11 (95% CI 7 to 50)] Analysis 1.21.

In the subgroup of infants less than 1000 g, there was also a statistically significant reduction in the VTV group [typical RR 0.44 (95% CI 0.20 to 0.99), typical RD -0.12 (95% CI -0.24 to -0.01]. NNT= 8 (4 to 100). Analysis 2.18. This effect was statistically significant in the strict studies but not the hybrid studies, and for this analysis for I^2 = 11%.

- Neurodevelopmental outcome

No studies reported this outcome as defined by the protocol criteria. D'Angio 2005 and Singh 2006+2009 both reported neurological follow-up using their own definitions. A post-hoc meta analysis has been performed on these outcomes using the individual study criteria (Analysis 3.4). There was no statistically significant difference between groups [typical RR 0.86 (95% CI 0.47 to 1.59), typical RD -0.02 (95% CI -0.12 to 0.08)]. Singh 2006+2009 also reported the combined outcome of death of severe disability [typical RR 0.54 (95% CI 0.27 to 1.06), RD -0.15 (95% CI -0.31 to 0.01)] Analysis 3.5. This study had unequal post discharge follow-up which could be a potential source of bias. Gross motor delay was reported by D'Angio 2005. The results from this single trial did not demonstrate a statistically significant difference between groups (Analysis 3.6) [typical RR 1.00 (95% CI 0.47 to 2.14), RD 0.00 (95% CI -0.13 to 0.13)].

- Surviving infants with bronchopulmonary dysplasia

i. BPD at 28 days (Analysis 1.22) was reported by Piotrowski 1997, Lista 2004 and Piotrowski 2007. No studies, or pooled analysis, showed a statistically significant difference between study groups [typical RR 1.00 (95% CI 0.61 to 1.61), typical RD 0.00 (95% CI -0.13 to 0.13]. Subgroup analysis for infants less than 1000 g did not show a statistically significant difference [typical RR 0.65 (95% CI 0.24 to 1.78), typical RD -0.13 (95% CI -0.43 to 0.17)] Analysis 2.19.

ii. BPD at 36 weeks (Analysis 1.23) was reported by Sinha 1997; Lista 2004; D'Angio 2005; Keszler 2004a and Singh 2006+2009. No individual study showed a difference between groups. Reduction in BPD was of borderline statistical significance in the VTV group [typical RR 0.73 (95% CI 0.53 to 1.00] p = 0.05, typical RD 0.09 (-0.17 to -0.00) p = 0.05]. Subgroup analysis for infants less than 1000 g did not show a statistically significant difference [typical RR 0.81 (95% CI 0.59 to 1.12), typical RD -0.09 (95% CI -0.22 to 0.05)] Analysis 2.20.

Post hoc analyses were performed on the following related outcomes:

iii. Postnatal glucocorticoids for treating BPD (Analysis 3.1) was reported by D'Angio 2005. This study did not show a statistically significant difference between groups [RR 0.93 (95% CI 0.65 to 1.31), RD -0.03 (95% CI -0.16 to 0.10)].

iv. Home oxygen (Analysis 3.2) was reported by D'Angio 2005 and Singh 2006+2009. Neither study or pooled analysis showed a statistically significant difference between groups [typical RR 0.64 (95% CI 0.30 to 1.36), typical RD -0.04 (95 % CI -0.11 to 0.03)]. Only supplemental data D'Angio 2005 was available for the subgroup of infants less than 1000 g (Analysis 3.3). There was no statistically significant difference between groups [RR 0.75 (95% CI 0.25, 2.23), RD -0.03 (95% CI -0.13 to 0.08)].

Subgroup analyses

Subgroup analysis in infants less than 1000 g, where possible, has been reported above, alongside the primary and secondary outcomes.

Post hoc subgroup analysis was performed for trials with strict and hybrid methodologies. Differences between these outcomes or significant heterogeneity between subgroups have been reported above.

DISCUSSION

There are no major concerns about the methodology used in the twelve trials included in this review. Minor concerns include the following:

Imbalances in patient characteristics and follow up

i.There is imbalance in numbers between the control and volume targeted groups in Lista 2004. Post-randomisation, seven infants were excluded because placental histology identified chorioamnionitis.

ii. There were different proportions of infants < 1000 g in the study by Lista 2004

iii. There were imbalances in the study by Piotrowski 2007 in FiO_2 in the first six hours of life, and surfactant use. In the published report, Piotrowski 2007 adjusted for this difference, but in this review the unadjusted outcomes have been used.

Hybrid studies

The fact that some studies varied in the use of ventilator device, triggering mode and technique between VTV and PLV could have had an impact on outcomes such as duration of ventilation and air leak.

Concealment

Except for the short-term crossover trials, it would be difficult, if not impossible, to blind caregivers to the allocated treatment. This could have affected various outcomes (e.g. clinician awareness of allocation might affect clinical practice impacting on reported outcomes e.g. failure of mode, weaning, and duration of ventilation).

Other issues

In view of the differences in VTV implementations, all modes have been grouped together. The possibility exists that different types of volume-targeted strategies may have different safety and efficacy profiles.

We were unable to perform a planned subgroup analysis of studies based on time of initiation of the allocated ventilator strategy.

We are grateful to the authors who provided us with supplementary data permitting more extensive subgroup analysis of infants less than 1000 g than was possible in the previous review. However, the relatively low numbers of infants less than 1000 g (247) in this subgroup may limit the power the meta-analysis to identify differences between interventions.

Findings

Meta-analysis of VTV modes identified a statistically significant reduction in the combined outcome of death and bronchopulmonary dysplasia [typical RR 0.73 (95% CI 0.57 to 0.93), typical RD -0.12 (95% CI -0.21 to -0.03), NNT 8 (95% CI 5 to 33)]. VTV modes also resulted in statistically significant reductions in pneumothorax (typical RR 0.46 (95% CI 0.25 to 0.84), typical RD -0.06 (95% CI -0.10 to -0.01), NNT = 17 (95% CI 10 to 100), duration of ventilation, (MD -2.36; 95% CI -3.90 to -0.83), hypocarbia [typical RR 0.56 (95% CI 0.33 to 0.96), typical RD -0.26 (-0.47 to -0.04), NNT = 4 (95% CI 2 to 25)] and the combined post hoc outcome of PVL or Grade 3-4 IVH [typical RR 0.48 (95% CI 0.28 to 0.84), typical RD -0.09 (95% CI -0.15 to -0.02), NNT = 11 (95% CI 7 to 50)].

Two studies, reported long-term neurodevelopmental outcome using blinded assessors, but were not powered to identify differences. Pooled analysis for neurodevelopmental impairment did not identify a significant reduction [typical RR 0.86 (95% CI 0.47 to 1.59), typical RD -0.02 (95% CI -0.12 to 0.07). Singh 2006+2009 reported the combined outcome of death or severe disability, which was not statistically significant (typical RR 0.54 (95% CI 0.27 to 1.06], RD -0.15 (95% CI -0.31 to 0.01)].

Further comments

It is plausible that VTV modes, by controlling tidal volume, may contribute to a reduction in BPD and death. Additionally, by improving the stability of blood gas parameters and reducing hypocarbia, these modes may have the theoretical advantage of stabilising cerebral perfusion and contribute to a reduction in neonatal brain injury. Studies to date have not been powered to assess longer term neurodevelopmental outcomes. We found no evidence of harm associated with the use of VTV modes.

The studies included in the systematic review were conducted by researchers with expertise in these modes. Detailed education is likely to be important for units considering adopting VTV modes.

VTV modes have been implemented as a strategy to avoid lung injury due to over or under inflation, however the target VT set for the whole lung is based on the infant's weight. Regional distribution of VT may vary depending on lung disease. In non-homogenous lung disease, using a VTV mode does not eliminate the regional risk of lung injury from local volutrauma or shear stress. Strategies to manage these local variation in lung mechanics may be important.

AUTHORS' CONCLUSIONS

Implications for practice

Since the previous review, more studies evaluating short and longer term outcomes of volume-targeted ventilation have been published. In this systematic review we find increasing evidence of improvements in important outcomes favouring a volume-targeted ventilation strategy. Infants ventilated using VTV modes have reduced death and chronic lung disease

This review did not identify an increase in any adverse outcomes associated with the use of VTV compared with PLV. Increasing experience with VTV means that volume targeting in neonatal intensive care should no longer be considered experimental. The studies included in the systematic review were conducted by researchers with expertise in these modes. Careful education is important in units considering the use of VTV. Some of the available VTV modes are under represented in this review.

Implications for research

Further randomised controlled trials, powered to assess effects on important outcomes such as death and neurodevelopmental outcome are still required, although these will be increasing difficult to conduct as increasing numbers of clinicians lose equipoise for the use of VTV modes. As death and long term morbidity are the most important long term outcomes, further research may be best conducted by units that currently do not use volume targeting as their main ventilation modality. We note the some data have been presented at conferences and urge researchers to complete and publish these studies.

Future research should compare different volume targeting strategies. Future specific areas of research should include further understanding the respiratory patterns of infants ventilated using these modes, optimising algorithms for tidal volume measurement, and

the selection of optimum VT. Comparisons should be made of different modes and different ventilators and the selection of associated parameters (e.g. maximum/minimum PIP settings). The tailoring of VTV modes to individual patients needs further examination. Increased understanding of the interaction between ventilator parameters and patient respiratory effort is required, and as infants vary tidal volume during spontaneous breathing, research should also assess whether the targeting of a fixed VT is optimum. Ventilator manufacturers can assist researchers and clinicians by making all specifications of their VTV modes freely available.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Piotrowski 1997

Methods	Randomisation procedure: Not further specified. Blinding of randomisation: Sealed envelopes. Blinding of intervention: No. Blinding of outcome measurements: No. Follow up: Complete.
Participants	Single centre; 57 infants. Eligible if: BW < 2500 g, postnatal age < 72 hours, and need for mechanical ventilation for lung disease at randomisation and Servo ventilator available. Excluded if: Sepsis/pneumonia, congenital malformation, pneumothorax or any other air leak, meconium aspiration.
Interventions	Ventilator: Different ventilators were used for experimental group (Siemens Sevo 300 ventilator) and control group (Bear Cub or Sechrist ventilator). Both groups were ventilated using PEEP 3-5 cm H_2O and inflation time 0.5 sec. Target: SpO_2 88-95%, pCO_2 < 55 mm Hg. Infants extubated once ventilator rate < 12/min, FiO_2 < 0.25, and after a 30-60 min trial of ETT-CPAP. Experimental group (n=27): PRVC mode, a synchronized, pressure-limited AC-mode that sequentially varied the delivered pressure to approximate a target inspiratory VT_{target} of 5-6 ml/kg plus 4-5 ml of compressible volume. VT_{target} adjusted to achieve "normal excursion of the chest". Control group (n=30): Non-synchronised IMV mode. PIP set to achieve "normal excursion of the chest". Duration of intervention: Until extubation.
Outcomes	Death in hospital, oxygen at 28 days, any air leak, pneumothorax, PIE, any IVH, IVH grade 3- 4, PDA, sepsis, use of muscle relaxants, duration of ventilation.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomisation procedure: Not further specified.
Allocation concealment?	Yes	Blinding of randomisation: Sealed envelopes.
Blinding? All outcomes	No	Blinding of intervention: No. Blinding of outcome measurements: No.

Piotrowski 1997 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	Follow up: Complete.
Free of selective reporting?	Yes	
Free of other bias?	No	The intervention and control groups used different ventilator models, modes and synchronisation settings.

Sinha 1997

Methods	Randomisation procedure: Not further specified. Blinding of randomisation: Sealed envelopes. Blinding of intervention: No. Blinding of outcome: Was done for chest x-ray findings, but not for other outcome. Follow-up: Complete.
Participants	Single centre; 50 infants. Eligible if: BW > 1200 g and had RDS requiring mechanical ventilation. Excluded if: Confirmed/suspected sepsis/pneumonia, congenital malformation, or lack of arterial access.
Interventions	Ventilator: Both groups used VIP Bird ventilator in AC-mode with inflation time at 0.3-0.5 sec. Target: pH 7.27-7.40, $paCO_2$ 4.5 to 6 kPa, paO_2 8-11 kPa. Experimental group (n=25): Volume controlled ventilation (pressure triggered) with inspired VT_{target} set at 5-8 ml/kg. Control group (n=25): Time-cycled, pressure-limited ventilation (flow triggered) with PIP adjusted to achieve inspired VT 5-8 ml/kg. Duration of intervention: Until weaning from ventilation.
Outcomes	"Success" criteria outcome: Time from entry into the study until achievement of either $AaDO_2$< 13 kPa for more than 12 hours or MAP < 8.0 cm H_2O for more than 12 hours or extubation. Other outcome criteria: Death in hospital, failed allocated treatment, IVH or PVL (not reported separately), BPD (in oxygen at 36 weeks), pneumothorax, PDA.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomisation procedure: Not further specified.
Allocation concealment?	Yes	Blinding of randomisation: Sealed envelopes.

Sinha 1997 (*Continued*)

Blinding? All outcomes	No	Blinding of intervention: No. Blinding of outcome: Was done for chest x-ray findings, but not for other outcome.
Incomplete outcome data addressed? All outcomes	Yes	Follow-up: Complete.
Free of selective reporting?	No	
Free of other bias?	Unclear	VTV mode was pressure triggered, PLV mode flow triggered.

Herrera 2002

Methods	Randomisation procedure: Not further specified. Blinding of randomisation: Sealed envelopes. Blinding of intervention: No. Blinding of outcome measurements: No. Follow up: Complete.
Participants	Single centre; 17 infants. Eligible if: Appropriate for gestational age (AGA) infants of 600-1200 g, ventilated for RDS, > 48 hours of age and clinically stable. Excluded if: Congenital malformations, sepsis, pneumothorax, other air leak, meconium aspiration and terminal state.
Interventions	Ventilator: Both groups used Draeger Babylog 8000plus. Pre-study settings, SIMV rate 16/min, PIP 15 cm H_2O. Cross over study: VTV epoch: SIMV+VG with expired VT_{target} 4.5ml//kg. Maximum PIP set 10 cm H_2O above pre-ventilation PIP. PLV epoch: SIMV Duration of intervention: 60 minutes.
Outcomes	Airflow, pressure, FiO_2, $TcCO_2$, minute volume.
Notes	The last 8 infants (of 17) were randomised to an additional third VTV-epoch of SIMV-VG 3.0 ml/kg. For meta-analysis, only the SIMV-VG 4.5 ml/kg versus SIMV data of all 17 infants has been used.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomisation procedure: Not further specified.

Herrera 2002 (*Continued*)

Allocation concealment?	Yes	Blinding of randomisation: Sealed envelopes.
Blinding? All outcomes	No	Blinding of intervention: No. Blinding of outcome measurements: No.
Incomplete outcome data addressed? All outcomes	Yes	Data complete.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Lista 2004

Methods	Randomisation procedure: By random number sequencing, stratified by GA (25-28 weeks and 29-32 weeks). Blinding of randomisation: Not specified. Blinding of intervention: No. Blinding of outcome measurements: No. Follow up: Complete to discharge.
Participants	Two centres; 53 infants. Eligible if: Between 25-32 weeks of gestation, received at least 1 course of antenatal steroids, ventilated for RDS in first 24 hours, treated with surfactant within 3 hours. Excluded: lethal anomalies, receiving muscle relaxants at entry, IVH greater than grade 2, actual or suspected sepsis.
Interventions	Ventilator: Both groups used. Draeger Babylog 8000plus with set back up rate 40/min, PEEP 3.5-4 cm H_2O. Mean inflation time 0.4-0.5 sec (upper limit in PSV-mode). Target FiO_2 to maintain oxygen saturations 90-96%. Target blood gas parameters: pH > 7.25, pO_2 50-75 mm Hg, pCO_2 40-65 mm Hg). Experimental group (n=30): PSV + VG with expired VT_{target} 5 ml/kg throughout study. Control group (n=23): PSV with PIP set manually to achieve expired VT of around 5 ml/kg, and PIP weaned to achieve blood gas goals. Duration of intervention: Until extubation.
Outcomes	Death in hospital, PDA, receiving oxygen at 28 days and 36 weeks, IVH, PVL, ROP, PIE, PVL, need for postnatal steroids. The study was also designed to compare inflammatory markers in the two groups.
Notes	

Risk of bias

Item	Authors' judgement	Description

Lista 2004 (*Continued*)

Adequate sequence generation?	Yes	Randomisation procedure: By random number sequencing, stratified by GA (25-28 weeks and 29-32 weeks).
Allocation concealment?	Unclear	Blinding of randomisation: Not specified.
Blinding? All outcomes	No	Blinding of intervention: No. Blinding of outcome measurements: No.
Incomplete outcome data addressed? All outcomes	Yes	Follow up: Complete to discharge.
Free of selective reporting?	Unclear	The primary outcome of this study was inflammatory cytokines. After randomisation, seven infants were excluded because placental histology identified chorioamnionitis (supplemental data), which could have influenced the primary outcome of this study. After the post-randomisation exclusions data from 30 infants in the VTV group and 23 infants in the PLV group were reported.
Free of other bias?	Unclear	In the post hoc subgroup of infants < 1000 g identified from supplemental data, 12/30 (40%) patients in the VTV group were <1000 g compared with 5/23 (22%) in the PLV group.

Keszler 2004a

Methods	Randomisation procedure: Not further specified. Blinding of randomisation: Sealed envelopes. Blinding of intervention: No. Blinding of outcome measurements: No. Follow up: Complete.
Participants	Single centre; 18 infants. Eligible if: GA < 34 weeks, ventilated for RDS before 6 hours of age. Excluded: Congenital cardiac, respiratory or CNS anomalies, paralysis or sedation or ETT leak > 30 %.
Interventions	Ventilator: Both groups used Drager Babylog 8000plus with set backup rate of 40/min. Target pCO_2 of 35-45 torr. Experimental group (n=9): AC-VG with expired VT_{target} 5 ml/kg, adjusted by 0.5 ml/kg to maintain target pCO_2 . Control group (n=9): AC with PIP set to achieve 4-6 ml/kg expired VT, using PIP changes of 1-2 cm H_2O to maintain target pCO_2.

Keszler 2004a (*Continued*)

	Duration of intervention: 72 hours or until extubation.	
Outcomes	(Including supplemental data): Blood gas results, pneumothorax, PIE, mortality, cranial ultrasound scan.	
Notes		

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomisation procedure: Not further specified.
Allocation concealment?	Yes	Blinding of randomisation: Sealed envelopes.
Blinding? All outcomes	No	Blinding of intervention: No. Blinding of outcome measurements: No.
Incomplete outcome data addressed? All outcomes	Yes	Follow up: Complete.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

D'Angio 2005

Methods	Randomisation procedure: Block randomisation (8 participants per block). Stratified by centre and birth weight. Blinding of randomisation: Sealed, opaque envelopes. Blinding of intervention: No. Blinding of outcome measurements: No. Follow up: Complete to discharge. 64 infants in each group were also assessed at 6-18 months corrected age (neurodevelopmental outcome).
Participants	Two centres; 213 infants enrolled. Eligible if: BW 500-1249 g, GA $\geq$ 24 weeks and in need of mechanical ventilation. Excluded if: Not specified.
Interventions	Ventilator: Both groups used primarily the Siemens Servo 300 ventilator. However, patients in the SIMV group were changed over to a VIP Bird ventilator (SIMV mode) if requiring a ventilator rate over 40/min. Enrolled before 6 h of age. Target paO_2 (mm Hg): 45-60 (GA 24-26 w), 50-70 (GA 27-28 w), 60-80 (GA > 28 w) . Target pCO_2: 45-55 mm Hg (all GA's). Experimental group (n =105): PRVC; a synchronized, pressure-limited AC-mode that

D'Angio 2005 (*Continued*)

	sequentially varied the delivered pressure to approximate a target inspiratory VT (measured at ventilator). Target VT values not specified in the publication. Control group (n=108): SIMV with only PEEP support between synchronized inflations. Duration of intervention: Remained on randomised method until extubated, died or met failure criteria (hypoxia, hypercapnia or hypocapnia or decision of clinical team).
Outcomes	Primary: Proportion of infants alive and extubated at 14 days. Other: FiO_2, ventilator rate, PIP, VT, $PaCO_2$, PaO_2, oxygenation index, $AaDO_2$, proportion alive and extubated at 28 days, or 36 weeks, proportion died before discharge, age at final extubation, proportion extubated at 14 days without requiring subsequent re-intubation.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation procedure: Block randomisation (8 participants per block). Stratified by centre and birth weight.
Allocation concealment?	Yes	Blinding of randomisation: Sealed, opaque envelopes.
Blinding? All outcomes	No	Blinding of intervention: No. Blinding of outcome measurements: No.
Incomplete outcome data addressed? All outcomes	Yes	Follow up: Complete to discharge. 64 infants in each group were also assessed at 6-18 months corrected age (neurodevelopmental outcome).
Free of selective reporting?	Yes	
Free of other bias?	Unclear	Different trigger modes in VTV and PLV groups.

Nafday 2005

Methods	Randomisation procedure: Block randomisation, stratified by weight (500 - 750 g, 751 - 1000 g, 1001-1250 g, 1251-1500 g). Blinding of randomisation: Sealed envelopes. Blinding of intervention: No. Blinding of outcome measurements: No. Follow up: Complete to discharge.

Nafday 2005 (*Continued*)

Participants	Single centre; 34 infants. Eligable if: BW < 1500 g, clinical and radiographic RDS, < 12 hrs old, about to receive surfactant. Excluded if: Major congenital malformations, congenital heart disease, confirmed/suspected sepsis/pneumonia, pneumothorax, other air leak, requiring paralysis/heavy sedation, moribund.
Interventions	Ventilator: Both groups used Drager Babylog 8000plus. Ventilator rate adjusted to target blood gas values. Targeted arterial blood pH 7.25-7.35, $PaCO_2$ 45-55 mm Hg, PaO_2 50-70 mm Hg, SpO_2 88-95%. Experimental group (n=16): PSV-VG with expired VT_{target} 5ml/kg. Control group (n=18): SIMV. The measured VT was not used to adjust pressures during the intervention. Duration of intervention: 24 hours.
Outcomes	Primary: Ventilatory pressures during the first 24 hours after surfactant administration or randomisation. Others: Survival to discharge, BPD (36 weeks), IVH, PDA (requiring indomethacin or ligation), NEC (Bell 2 or greater), air leak (PIE, pneumothorax, pneumomediastinum).
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation procedure: Block randomisation, stratified by weight (500-750 g, 751-1000 g, 1001-1250 g, 1251-1500 g).
Allocation concealment?	Yes	Blinding of randomisation: Sealed envelopes.
Blinding? All outcomes	No	Blinding of intervention: No. Blinding of outcome measurements: No.
Incomplete outcome data addressed? All outcomes	Yes	Follow up: Complete to discharge.
Free of selective reporting?	Yes	
Free of other bias?	Unclear	The intervention and control groups used different synchronisation modes.

Polimeni 2006

Methods	Randomisation procedure: Not further specified. Blinding of randomisation: Sealed, opaque envelopes. Blinding of intervention: No. Blinding of outcome measurements: No. Follow up: Complete.
Participants	Single centre; 12 Infants. Eligible if: BW <1500 g, recovered from RDS, presenting with hypoxaemic episodes.
Interventions	Ventilator: Both groups used Draeger Babylog 8000plus. Crossover study: 12 infants with expired VT_{target} 4.5 ml/kg. 20 infants with expired VT_{target} 6.0 ml/kg. 1st group (n=12) VTV epoch: SIMV-VG (4.5 ml/kg). Maximum PIP set 10 cm H_2O above pre-randomisation PIP. PLV epoch: SIMV as previous ventilation. 2nd group (n=20) VTV epoch: SIMV-VG (6.0 ml/kg). Maximum PIP set 10 cm H_2O above pre-randomisation PIP. PLV epoch: SIMV as previous ventilation. Duration of intervention: 2 hours.
Outcomes	Primary: Frequence and severity of hypoxaemic episodes. Other: PIP, distribution of VT, frequency and duration of hypoxaemia (SpO_2 <88,%, <75%), FiO_2.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomisation procedure: Not further specified.
Allocation concealment?	Yes	Blinding of randomisation: Sealed, opaque envelopes.
Blinding? All outcomes	No	Blinding of intervention: No. Blinding of outcome measurements: No.
Incomplete outcome data addressed? All outcomes	Yes	Data complete.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Singh 2006+2009

Methods	Randomisation procedure: Random block randomisation. Stratified by birth weight. Blinding of randomisation: Sealed, opaque envelopes. Blinding of intervention: No. Blinding of outcome measurements: No. Follow up: Complete to discharge (Singh 2006). Follow-up data of 85 from 94 infants discharged home alive reported separately (Singh 2009).
Participants	Initially two centres, but reduced to one; 109 infants. Eligible if: BW 600-1500 g, GA 24-31 weeks with RDS requiring mechanical ventilation. Excluded if: Severe congenital malformations. All patients included as intention to treat. Some analyses only performed for patients from main centre.
Interventions	Ventilator: Both groups used VIP Bird Gold. Experimental group (n = 57): Volume controlled ventilation, inspired VT_{target} 4-6ml/kg. Pmax setting not described. Control group (n = 52): PLV. PIP was manually adjusted to target VT 4-6 ml/kg. Duration of intervention: Until infants were recovering from their acute respiratory illness. At that point the ventilatory mode was changed to SIMV with pressure support ("weaning mode") for patients in both groups.
Outcomes	Primary outcome criteria: Time from entry into the study until achievement of either $AaDO_2$< 13 kPa for more than 12 hours or MAP < 8.0 cm H_2O for more than 12 hours. Other: total duration of mechanical ventilation (MV), duration of MV+CPAP, survival to discharge, frequency of complications: BPD (36 weeks), IVH, PVL, PDA (requiring treatment), NEC (Bell stage II or greater). Follow up (Singh 2009): Home oxygen, cough, wheeze, inhaler use, rate of hospital readmission, rate of respiratory readmission, neuro disability (cerebral palsy, deaf, behavioural problems, blindness) by questionnaire.
Notes	109 infants were enrolled, of whom 94 survived to discharge. Three infants died post-discharge. (Singh 2009). 85 of 91 (93%) infants eligible for follow-up were assessed at a median of 22 months corrected age; 45 in the VTV group 40 in the PLV group (Singh 2009).

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation procedure: Random block randomisation. Stratified by birthweight.
Allocation concealment?	Yes	Blinding of randomisation: Sealed, opaque envelopes.
Blinding? All outcomes	No	Blinding of intervention: No. Blinding of outcome measurements to discharge: No. Follow up investigators blinded to original

Singh 2006+2009 (*Continued*)

		treatment modality.
Incomplete outcome data addressed? All outcomes	Yes	Follow up: Complete to discharge. 85 of 91 (93%) infants eligible for follow-up were assessed at a median of 22 months corrected age.
Free of selective reporting?	Yes	
Free of other bias?	Unclear	VTV group weaned using PLV mode.

Hummler 2006

Methods	Randomisation procedure: Not further specified. Blinding of randomisation: Sealed envelopes. Blinding of intervention: No. Blinding of outcome measurements: No.
Participants	Single centre; 15 infants. Eligible if: Infants $\leq$1500 g. Ventilator dependent with a ventilator rate $\geq$ 10/min and having recurrent hypoxaemic episodes (study definition).
Interventions	All patients: Stephanie ventilator. Pressure controlled SIMV prior to study. Target SpO_2 82-90%. Standardised protocols for FiO_2 adjustment. Crossover study: VTV epoch: Volume controlled-SIMV. Maximum PIP limit up to 40 H_2O. Inspired VT_{target} set from pre-study VT (7.8+/-1.4 ml/kg). PLV epoch: Pressure controlled SIMV. Rate 39 (+/-13) /min. Duration of intervention: 4 hours.
Outcomes	Primary: Time with SpO_2 below lower limit of target range (80-92%). Other: Time with SpO_2 above/within target range, incidence/duration/severity of desaturation episodes, FiO_2, number of FiO_2 adjustment necessary to target SpO_2, VT, compliance, resistance.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomisation procedure: Not further specified.
Allocation concealment?	Yes	Blinding of randomisation: Sealed envelopes.

Hummler 2006 (*Continued*)

Blinding? All outcomes	No	Blinding of intervention: No. Blinding of outcome measurements: No.
Incomplete outcome data addressed? All outcomes	Yes	Data complete.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Piotrowski 2007

Methods	Randomisation procedure: Sequential numbers. Stratified by gestational age (24-28 weeks and 29-33 weeks). Blinding of randomisation: Sealed envelopes. Blinding of intervention: No. Blinding of outcome measurements: No. Follow up: Complete to discharge.
Participants	Single centre; 56 infants. Eligible if: GA 24-32 weeks with RDS, requiring ventilation for at least 24 hours. Excluded if: Severe congenital malformation, lack of parental consent and pulmonary air leak on admission.
Interventions	Ventilator: Experimental group used Siemens Servo 300 providing PRVC as the VTV mode. Control group (SIMV) used one of the 4 different ventilators (depending on availability): Bear Cub (CEM)/Bear 750 PSV, Sechrist Millenium, Draeger Babylog 8000 plus or SLE 5000. Both groups: Inflation time 0.4 sec, inflation rate 40/min, PEEP 3-5 cm H_2O. Experimental group (n = 30): PRVC; a synchronized, pressure-limited AC-mode that sequentially varied the delivered pressure to approximate a target inspiratory VT_{target} 8-10 ml/kg (included allowance for circuit compliance). Control Group (n = 26): SIMV. Duration of intervention: Until extubation.
Outcomes	Primary outcome: 12 or more hours with "effective ventilation" (SpO_2 > 90 % pCO2 < 50 mm Hg) with FiO_2 < 0.23 and PIP < 15 cm H_2O. Secondary outcomes: Time to extubation, BPD (28 days), air leak, , IVH and PDA.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation procedure: Sequential numbers. Stratified by gestational age (24-28 weeks and 29-33 weeks).

Piotrowski 2007 (*Continued*)

Allocation concealment?	Yes	Blinding of randomisation: Sealed envelopes.
Blinding? All outcomes	No	Blinding of intervention: No. Blinding of outcome measurements: No.
Incomplete outcome data addressed? All outcomes	Yes	Follow up: Complete to discharge.
Free of selective reporting?	Yes	
Free of other bias?	No	Although randomised, infants in the PRVC group had increased surfactant use and increased FiO_2 in the first 6 hours after admission.

Cheema 2007

Methods	Randomisation procedure: Permuted blocks within strata (<1250 g and > 1250 g blocks) . Blinding of randomisation: Sealed envelopes. Blinding of intervention: No. Blinding of outcomes measurements: Outcome measure defines end of intervention period.
Participants	Two centres; 40 infants. Eligible if: GA < 34 weeks and ventilated for RDS. Excluded if: Major surgical or congenital anomalies.
Interventions	Ventilator: Both groups used Drager Babylog 8000plus in SIPPV (AC) mode. Experimental group (n=19): SIPPV-VG, expired VT_{target} 4.0 ml/kg. Maximum PIP described as, "a balance between enabling the ventilator to deliver the desired tidal volume and preventing excessive PIP".. Control group (n=21): SIPPV (AC). PIP determined by clinical team. Duration of intervention: From onset of mechanical ventilation after admission in the neonatal until first blood gas result (median age 95 min).
Outcomes	Primary: pCO_2 and proportion within target range (5-7 kPa). Others: First pH, paO_2. Post hoc subgroup analysis 23-25, 26-33 weeks.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**

Cheema 2007 (*Continued*)

Adequate sequence generation?	Yes	Randomisation procedure: Permuted blocks within strata (<1250 g and > 1250 g blocks).
Allocation concealment?	Yes	Blinding of randomisation: Sealed envelopes.
Blinding? All outcomes	No	Blinding of intervention: No. Blinding of outcomes measurements: Outcome measure defines end of intervention period.
Incomplete outcome data addressed? All outcomes	Yes	Follow up: Complete to discharge.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

AC: assist control
AGA: appropriate for gestational age
BPD: bronchopulmonary dysplasia
BW: birth weight
GA: gestational age
RDS: respiratory distress syndrome
ETT: endotracheal tube

VG: volume guarantee
PIP: peak inspiratory pressure
IT: inflation time
MAP: mean airway pressure
PTX: pneumothorax
PIE: pulmonary interstitial emphysema
PEEP: positive end-expiratory pressure
PRVC: pressure-regulated volume-controlled
PSV: pressure support ventilation
PDA: patent ductus arteriosus
RDS. respiratory distress syndrome

IVH: intraventricular haemorrhage
PVL: periventricular leukomalacia
ROP: retinopathy of prematurity
SIPPV: synchronised intermittent positive pressure ventilation, the same as AC
SIMV: synchronised intermittent mandatory ventilation
VT: Tidal volume

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

Study	Reason for exclusion
Abd El-Moneim 2005	Journal publication. Crossover study, but not randomised.
Abubakar 2001	Journal publication.The order of ventilatory modes was not randomised in this crossover study which means that an effect of fatigue cannot be excluded. Additionally, this study did not report outcomes specified in this Cochrane review protocol.
Abubakar 2006	Abstract presentation. A study investigating time to recovery after ETT suction in infants randomised to ventilation with/without VG mode. The study did not report the outcomes specified in this Cochrane review protocol.
Cheema 2001	Journal publication.This short term crossover study did not address any of the outcome measurements of this Cochrane review protocol. Also, the crossover was made from PLV to volume guarantee mode without changing the maximum PIP (Pmax), which may have interfered with the ventilator's capacity to deliver the set VT and hence affected the outcomes.
Colnaghi 2006	Abstract presentation. This study was a randomised trial comparing 3 groups ventilated with Draeger Babylog 8000plus: Group 1: PSV. Group 2: PSV+VG. Group 3: AC+VG. However, the outcomes were biochemical assays of inflammatory markers in serum and tracheal aspirates. This study did not report the outcomes specified in this Cochrane review protocol. Despite randomisation, there were also inception differences in the study group characteristics
Dotta 2004	Abstract presentation. Randomised study, but authors do not report the outcomes specified in this Cochrane review protocol.
Keszler 2004b	Abstract presentation. Abstract does not report whether interventions randomised. The study outcomes do not include those specified in this Cochrane review protocol.
Lista 2000	Journal publication (in Italian). A non-randomised study.
Olsen 2002	Journal publication. A crossover study that did not discuss the outcome measurements of this Cochrane review protocol.
Ramirez-Del Valle 2006	Abstract presentation. Randomised study, but authors do not report the outcomes specified in this Cochrane review protocol.
Sinha 2008	Abstract presentation. Outcomes do not include those specified in this Cochrane review protocol.
Wach 2003	Abstract presentation. No information in the abstract whether intervention was randomised. The study outcomes do not include those specified in this Cochrane review protocol.

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

Salvia 2006

Trial name or title	Effect of VG combined with SIMV vs SIMV in the extremely premature infant
Methods	Randomisation (unspecified)
Participants	60 VLBW infants
Interventions	Intervention Group: SIMV+VG Control Group: SIMV
Outcomes	PIP, MAP, VT, CO_2 , FiO_2/SpO_2 Duration of mechanical ventilation, oxygen therapy, duration of admission, PDA, IVH, PVL, BPD, 2 year follow up data
Starting date	Not reported
Contact information	MD Silvia
Notes	Studied from 30 minutes after first surfactant dose. Study is ongoing and collecting 2 year follow up data

TARDIS

Trial name or title	A randomised controlled trial of modes of ventilatory support in preterm babies from point of delivery to the neonatal intensive care unit
Methods	Randomisation (sealed enveloped)
Participants	Preterm infants < 32 weeks, ventilated in delivery room
Interventions	Intervention group: Triggered VG mode Control group: IMV
Outcomes	PaCO2, PaO2, cerebral blood flow, grade 3/4 IVH, PVL, BPD, neurodevelopmental impairment at 1 and 3 years
Starting date	29/11/2006
Contact information	M Tracy, Nepean Hospital, Penrith. Australia
Notes	Studied from intubation in DR

DATA AND ANALYSES

Comparison 1. Volume-targeted vs pressure limited ventilation - subgroup by mode of ventilation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death in hospital	7	554	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.53, 1.20]
1.1 Strict Studies	3	180	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.28, 1.11]
1.2 Hybrid Studies	4	374	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.58, 1.62]
2 Death or BPD (28 days)	2	109	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.60, 1.39]
2.1 Strict Studies	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.28, 1.58]
2.2 Hybrid Studies	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.66, 1.69]
3 Death or BPD (36 weeks)	5	439	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.57, 0.93]
3.1 Strict Studies	3	180	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.47, 0.96]
3.2 Hybrid Studies	2	259	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.56, 1.08]
4 Failure of mode of ventilation	4	405	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.43, 0.94]
4.1 Strict studies	1	109	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.29, 1.52]
4.2 Hybrid Studies	3	296	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.40, 0.97]
5 Need for muscle relaxant	2	75	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.07, 1.40]
5.1 Strict studies	1	18	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2 Hybrid Stuides	1	57	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.07, 1.40]
6 Duration of intermittent positive pressure ventilation (days)	6	431	Mean Difference (IV, Fixed, 95% CI)	-2.36 [-3.90, -0.83]
6.1 Strict Studies	3	152	Mean Difference (IV, Fixed, 95% CI)	-3.18 [-5.36, -0.99]
6.2 Hybrid Studies	3	279	Mean Difference (IV, Fixed, 95% CI)	-1.56 [-3.73, 0.60]
7 Duration of IPPV (log data)	5	381	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.16, -0.00]
7.1 Strict studies	3	152	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.24, -0.04]
7.2 Hybrid studies	2	229	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.12, 0.15]
8 Inspired oxygen concentration % (study definition)	4	168	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-1.54, 1.34]
9 Any pH < 7.25	2	58	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.23, 4.70]
10 Hypocarbia pCO2 <4.7 kPa	2	58	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.33, 0.96]
11 Resp acidosis pH < 7.25 and pCO2 > 8 kPa	2	58	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.28, 8.78]
12 Incidence of hypocarbia or resp acidosis	2	58	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.42, 1.12]
13 Patent ductus arteriosus	6	537	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.85, 1.25]
13.1 Strict Studies	2	162	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.69, 1.24]
13.2 Hybrid Studies	4	375	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.85, 1.41]
14 Air leak (any)	5	374	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.44, 1.43]
14.1 Strict studies	2	71	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.09, 2.81]
14.2 Hybrid Studies	3	303	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.45, 1.58]
15 Pneumothorax	8	589	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.25, 0.84]
15.1 Strict studies	3	180	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.07, 1.15]
15.2 Hybrid Studies	5	409	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.26, 1.02]
16 Pulmonary interstitial emphysema	6	430	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.63, 2.30]
16.1 Strict studies	2	71	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.12, 5.04]
16.2 Hybrid Studies	4	359	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.64, 2.57]

17 Any IVH	5	441	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.71, 1.18]
17.1 Strict Studies	2	125	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.74, 1.67]
17.2 Hybrid Studies	3	316	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.60, 1.14]
18 Grade 3/4 IVH	6	494	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.45, 1.11]
18.1 Strict Studies	3	178	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.26, 1.81]
18.2 Hybrid Studies	3	316	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.43, 1.19]
19 Periventricular leukomalacia	4	351	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.15, 1.16]
19.1 Strict studies	3	178	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.10, 1.38]
19.2 Hybrid Studies	1	173	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.09, 2.63]
20 Any IVH or PVL	3	298	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.58, 1.18]
20.1 Strict Studies	2	125	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.52, 1.35]
20.2 Hybrid Studies	1	173	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.48, 1.39]
21 Grade 3/4 IVH or PVL	5	401	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.28, 0.84]
21.1 Strict studies	3	178	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.26, 1.14]
21.2 Hybrid	2	223	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.19, 0.96]
22 BPD (supplemental oxygen at 28 days)	3	166	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.61, 1.62]
22.1 Strict Studies	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.14, 2.32]
22.2 Hybrid Studies	2	113	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.66, 1.85]
23 BPD (supplemental oxygen at 36 weeks)	5	413	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.53, 1.00]
23.1 Strict Studies	3	178	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.45, 1.18]
23.2 Hybrid Studies	2	235	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.48, 1.10]

Comparison 2. Volume-targeted vs pressure limited ventilation - infants less than 1000g

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death in hospital	5	246	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.42, 1.21]
1.1 Strict Studies	4	226	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.46, 1.39]
1.2 Hybrid Studies	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 1.86]
2 Died or CLD (28 days)	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.22, 3.18]
3 Died or BPD (36 weeks)	4	224	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.62, 1.01]
3.1 Strict Studies	3	81	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.52, 1.10]
3.2 Hybrid Studies	1	143	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.59, 1.12]
4 Duration of Mechanical Ventilation (days, survivors)	5	198	Mean Difference (IV, Fixed, 95% CI)	-0.82 [-4.43, 2.80]
4.1 Strict Studies	3	63	Mean Difference (IV, Fixed, 95% CI)	-0.32 [-4.53, 3.89]
4.2 Hybrid Studies	2	135	Mean Difference (IV, Fixed, 95% CI)	-2.21 [-9.29, 4.87]
5 Duration of Mechanical Ventilation (Log(days), Survivors)	5	198	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.12, 0.10]
5.1 Strict Studies	3	63	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.23, 0.14]
5.2 Hybrid Studies	2	135	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.12, 0.14]
6 Any pH < 7.25	2	26	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.27, 6.53]
7 Hypocarbia pCO2 <4.7 kPa	2	26	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.11, 1.51]
8 Respiratory Acidosis pH < 7.25 and pCO2 > 8 kPa	2	26	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [0.32, 11.61]

9 Hypocarbia or respiratory acidosis	2	26	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.26, 2.03]
10 Patent ductus arteriosus	4	241	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.85, 1.39]
10.1 Strict Studies	2	75	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.77, 1.57]
10.2 Hybrid Studies	2	166	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.78, 1.50]
11 Air leak (any)	4	189	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.55, 2.23]
11.1 Strict Studies	2	23	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.10, 7.24]
11.2 Hybrid Studies	2	166	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.54, 2.40]
12 Pneumothorax	5	247	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.29, 1.37]
12.1 Strict Studies	3	81	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.11, 1.90]
12.2 Hybrid Studies	2	166	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.28, 1.86]
13 Pulmonary interstitial emphysema	4	189	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.58, 3.67]
13.1 Strict Studies	2	23	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.10, 7.24]
13.2 Hybrid Studies	2	166	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.58, 4.53]
14 Any IVH	4	225	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.55, 1.16]
14.1 Strict Studies	2	62	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.62, 2.08]
14.2 Hybrid Studies	2	163	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.40, 1.06]
15 Grade 3/4 IVH	4	184	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.27, 1.04]
15.1 Strict Studies	3	164	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.28, 1.36]
15.2 Hybrid Studies	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.09, 1.27]
16 Periventricular leukomalacia	4	203	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.15, 1.24]
16.1 Strict Studies	3	79	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.10, 1.53]
16.2 Hybrid Studies	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.10, 2.63]
17 Any IVH or PVL	3	186	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.60, 1.35]
17.1 Strict Studies	2	62	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.61, 1.80]
17.2 Hybrid Studies	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.43, 1.42]
18 Grade 3/4 IVH or PVL	3	145	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.20, 0.99]
18.1 Strict Studies	2	21	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.03, 0.95]
18.2 Hybrid Studies	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.23, 1.55]
19 BPD (supplemental oxygen at 28 days)	2	37	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.24, 1.78]
19.1 Strict Studies	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.10, 7.24]
19.2 Hybrid Studies	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.19, 1.86]
20 BPD (36 weeks)	4	202	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.59, 1.12]
20.1 Strict Studies	3	79	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.49, 1.50]
20.2 Hybrid Studies	1	123	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.53, 1.18]

Comparison 3. Miscellaneous post-hoc analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Steroids for BPD	1	203	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.65, 1.31]
2 Home Oxyggen (Survivors)	2	270	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.30, 1.36]
3 Home Oxygen in Survivors (Infants < 1000 g)	1	123	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.25, 2.23]
4 Severe Disability (any definition)	2	209	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.47, 1.59]
5 Severe Disability (any definition) or Death	1	109	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.27, 1.06]

6 Gross Motor Developmental Issue (any definition)	1	128	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.47, 2.14]

WHAT'S NEW

Last assessed as up-to-date: 30 June 2010.

Date	Event	Description
27 September 2010	New search has been performed	This updates the review "Volume-targeted versus pressure-limited ventilation in the neonate" published in the Cochrane Database of Systematic Reviews, Issue 3, 2005 (McCallion 2005). The searches were conducted in January 2010. At total of six new trials (seven publications) were added: Piotrowski 2007, Singh 2006 and 2009, D'Angio 2005, Polimeni 2006, Hummler 2006, Cheema 2007. Supplemental data from authors has been included to facilitate analysis of duration of ventilation and outcomes of infants < 1000 g. Pooled meta-analysis identified a statistically significant reduction in the primary combined outcome of death and bronchopulmonary dysplasia favouring volume targeted ventilation. The conclusions have been revised.
27 September 2010	New citation required and conclusions have changed	Wheeler K, Klingenberg C added to authorship. The conclusions have been revised.

HISTORY

Protocol first published: Issue 2, 2002

Review first published: Issue 3, 2005

Date	Event	Description
1 April 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Naomi McCallion wrote the protocol with assistance from Colin Morley and Peter Davis.

For the 2005 review, Naomi McCallion wrote the review with assistance from Peter Davis and Colin Morley.

For the 2010 update, Kevin Wheeler and Claus Klingenberg performed the search, assessed articles, liaised with study authors regarding supplemental information, extracted and analysed data.

Kevin Wheeler wrote the review with assistance from Claus Klingenberg, and supervision from Peter Davis and Colin Morley.

DECLARATIONS OF INTEREST

Colin Morley has been a consultant to Drager Medical since 2009

SOURCES OF SUPPORT

Internal sources

- Royal Women's Hospital Foundation, Melbourne, Australia.
- Murdoch Children's Research Institute, Melbourne, Australia.

External sources

- NMHRC Program Grant, Australia.

Part of Dr Wheeler's salary

- Monash Universary, Melbourne, Australia.

Research Scholarship for Dr Kevin Wheeler

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol limited PLV to time-cycled modes. In view of development of modern PLV-modes that may be flow cycled (e.g. PSV mode with the Draeger Babylog Plus ventilator) we have chosen to include all trials comparing VTV with PLV, independent of PLV being provided in a time-cycled or flow-cycled fashion.

The following **subgroup analysis** was performed, which was not specified in the initial protocol

Subgroup analysis for strict vs hybrid trial designs, within Analyses 1 and 2 where applicable.

The following **outcomes** included above were not included in the original protocol for this review.

Analysis 3.1 Steroids for BPD

Analysis 3.2 Home oxygen (survivors)

Analysis 3.3 Home oxygen (survivors <1000g)

Analysis 3.5 Severe disability (arbitrary definition) or death

Analysis 3.4 Severe disability (arbitrary)

Analysis 3.6 Gross motor developmental issue (arbitrary definition)

INDEX TERMS

Medical Subject Headings (MeSH)

Bronchopulmonary Dysplasia [etiology]; Infant, Newborn; Infant, Premature; Intermittent Positive-Pressure Ventilation [*methods; mortality]; Randomized Controlled Trials as Topic

MeSH check words

Humans