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# Lung recruitment manoeuvres for reducing mortality and respiratory morbidity in mechanically ventilated neonates (Review)

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[Intervention Review]

# Lung recruitment manoeuvres for reducing mortality and respiratory morbidity in mechanically ventilated neonates

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## ABSTRACT

### Background

Preterm infants and neonates with respiratory conditions commonly require intubation and conventional mechanical ventilation (CMV) to maintain airway patency and support their respiration. Whilst this therapy is often lifesaving, it simultaneously carries the risk of lung injury. The use of lung recruitment manoeuvres (LRMs) has been found to reduce the incidence of lung injury, and improve oxygenation and lung compliance in ventilated adults. However, evidence pertaining to their use in neonates is limited, and there is no consensus of opinion as to whether LRMs are appropriate or effective in this population.

### Objectives

To determine the effects of LRMs on mortality and respiratory outcomes in mechanically ventilated neonates, when compared to no recruitment (routine care).

### Search methods

We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL 2020, Issue 4) in the Cochrane Library, MEDLINE via Ovid (1946 to 13 April 2020), and CINAHL via EBSCOhost (1989 to 13 April 2020). We also handsearched the reference lists of retrieved studies to source additional articles.

### Selection criteria

We included randomised controlled trials (RCTs), quasi-RCTs and randomised cross-over studies that compared the effect of LRMs to no recruitment (routine care) in mechanically ventilated neonates.

### Data collection and analysis

Two review authors independently assessed trial eligibility, extracted data and evaluated risk of bias in the included studies. When studies were sufficiently similar, we performed a meta-analysis using mean difference (MD) for continuous data and risk ratio (RR) for dichotomous data, with their respective 95% confidence intervals (CIs). We used the GRADE approach to assess the certainty of the evidence for key (clinically important) outcomes.

**Main results**

We included four studies (152 participants in total) in this review. Three of these studies, enrolling 56 participants, contributed data to our prespecified outcomes.

Two studies enrolling 44 participants on CMV for respiratory distress syndrome compared a stepwise LRM with positive end-expiratory pressure (PEEP) to routine care. Meta-analysis demonstrated no evidence of a difference between the LRM and routine care on mortality by hospital discharge (RR 1.00, 95% CI 0.17 to 5.77; low-certainty evidence), incidence of bronchopulmonary dysplasia (RR 0.25, 95% CI 0.03 to 2.07; low-certainty evidence), duration of supplemental oxygen (MD -7.52 days, 95% CI -20.83 to 5.78; very low-certainty evidence), and duration of ventilatory support (MD -3.59 days, 95% CI -12.97 to 5.79; very low-certainty evidence). The certainty of the evidence for these outcomes was downgraded due to risk of bias, imprecision, and inconsistency. Whilst these studies contributed data to four of our primary outcomes, we were unable to identify any studies that reported our other primary outcomes: duration of continuous positive airway pressure therapy, duration of neonatal intensive care unit stay, and duration of hospital stay.

The third study that contributed data to the review enrolled 12 participants on CMV for respiratory and non-respiratory causes, and compared two different LRMs applied after endotracheal tube suctioning to routine care. It was determined that both LRMs may slightly improve end-expiratory lung volume at 120 minutes' post-suctioning, when compared to routine care (incremental PEEP LRM versus routine care: MD -0.21, 95% CI -0.37 to -0.06; double PEEP LRM versus routine care: MD -0.18, 95% CI -0.35 to -0.02). It was also demonstrated that a double PEEP LRM may slightly reduce mean arterial pressure at 30 minutes' post-suctioning, when compared with routine care (MD -16.00, 95% CI -29.35 to -2.65).

**Authors' conclusions**

There is insufficient evidence to guide the use of LRMs in mechanically ventilated neonates. Well-designed randomised trials with larger sample sizes are needed to further evaluate the potential benefits and risks of LRM application in this population.

## PLAIN LANGUAGE SUMMARY

### Lung recruitment manoeuvres for reducing mortality and respiratory morbidity in mechanically ventilated neonates

**Review question**

In mechanically ventilated neonates, do lung recruitment manoeuvres (LRMs) help to reduce mortality and respiratory morbidity, compared to no recruitment?

**Background**

Critically ill neonates (infants from birth up to four weeks of age) commonly require intubation (placement of a breathing tube in the windpipe) and conventional mechanical ventilation (the use of a breathing machine) to support their breathing. Whilst this therapy is often lifesaving, it also carries the risk of lung injury. LRMs have been suggested to reduce the incidence of lung injury and improve respiratory outcomes in ventilated patients. A LRM involves deliberately increasing airway pressure for a brief period, which serves to reopen collapsed lung regions. LRMs have proved effective in ventilated adults; however, evidence regarding their use in neonates is limited. There is no consensus of opinion as to whether LRMs are appropriate or effective in this population.

**Study characteristics**

In a search up to 13 April 2020, we identified four studies that investigated LRM use in mechanically ventilated neonates. Two studies enrolling 44 preterm neonates (born before 30 weeks' gestational age) with respiratory distress syndrome compared a LRM within hours of birth to routine care. The third study involving 12 neonates compared two different types of LRMs applied directly after suctioning of the breathing tube to routine care. A fourth study enrolling 48 paediatric patients (including neonates) also compared a LRM after suctioning to routine care. This study did not contribute data to the review as the data pertaining to neonatal participants could not be isolated.

**Key results**

When data from the two studies involving preterm neonates was combined, we found no clear differences between the LRM and routine care for the outcomes of mortality, incidence of bronchopulmonary dysplasia (a chronic lung disease in preterm infants), duration of supplemental oxygen therapy, and duration of ventilatory support. Meanwhile, data from 12 neonates suggests that two different types of LRMs may help to restore lung volume after suctioning compared to routine care. One of the LRMs (named double PEEP (positive end-expiratory pressure)) may also cause a slight reduction in blood pressure, which can have negative consequences in neonates.

**Certainty of the evidence**

The certainty of the evidence for these results was low to very low as the included studies were small and vulnerable to bias from limitations in their methods. Evidence-based guidance for the use of LRMs in mechanically ventilated neonates continues to be limited. Our review should raise awareness of the lack of high-certainty evidence in this field and encourage further research. Additional research would be valuable given our findings of possible but uncertain benefit with LRMs in mechanically ventilated neonates.

## SUMMARY OF FINDINGS

### Summary of findings 1. Summary of findings for the main comparison

Lung recruitment manoeuvre compared to routine care in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome

**Patient or population:** preterm infants less than 30 weeks' gestational age requiring conventional mechanical ventilation for respiratory distress syndrome

**Setting:** neonatal intensive care units in Italy and China

**Intervention:** stepwise lung recruitment manoeuvre using positive end-expiratory pressure

**Comparison:** routine care

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with routine care | Risk with a lung recruitment manoeuvre | | | | |
| Mortality by hospital discharge | Study population | | RR 1.00 (0.17 to 5.77) | 44 (2 RCTs) | Low [ab] | - |
| | 91 per 1000 | 91 per 1000 (15 to 525) | | | | |
| Incidence of bronchopulmonary dysplasia | Study population | | RR 0.25 (0.03 to 2.07) | 44 (2 RCTs) | Low [ab] | - |
| | 136 per 1000 | 34 per 1000 (4 to 282) | | | | |
| Duration of supplemental oxygen (days) | The mean duration of supplemental oxygen ranged from 9.92 to 45 days | MD 7.52 days lower (20.83 lower to 5.78 higher) | - | 44 (2 RCTs) | Very low [acd] | - |
| Duration of ventilatory support (days) | The mean duration of ventilatory support ranged from 6.1 to 35 days | MD 3.59 days lower (12.97 lower to 5.79 higher) | - | 44 (2 RCTs) | Very low [ace] | - |
| Duration of continuous positive airway pressure therapy (hours or days) | - | - | - | - | - | None of the included studies reported on duration of continuous positive airway pressure therapy. |

| | | | | | | |
|---|---|---|---|---|---|---|
| Duration of neonatal intensive care unit stay (hours or days) | - | - | - | - | - | None of the included studies reported on duration of neonatal intensive care unit stay. |
| Duration of hospital stay (days) | - | - | - | - | - | None of the included studies reported on duration of hospital stay. |

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

**CI:** confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio

**GRADE Working Group grades of evidence**

**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low certainty:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect

**Very low certainty:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect

[a] Downgraded one level for serious risk of bias (unclear risk of selection bias, performance and detection bias, and reporting bias in included studies)
[b] Downgraded one level for serious imprecision (data derived from only two studies with small sample sizes; comparisons based on a small number of events, contributing to wide CIs around the effect estimates)
[c] Downgraded one level for serious imprecision (data derived from only two studies with small sample sizes)
[d] Downgraded one level for serious inconsistency (high heterogeneity between studies ($I^2$ = 77%, P = 0.04))
[e] Downgraded one level for serious inconsistency (moderate heterogeneity between studies ($I^2$ = 58%, P = 0.12))

# BACKGROUND

## Description of the condition

Preterm infants and neonates with respiratory conditions commonly require intubation and conventional mechanical ventilation (CMV) to maintain airway patency and support their respiration (Gardner 2009). Whilst this therapy is often lifesaving, it simultaneously carries the risk of lung injury (Slutsky 2013). CMV has been shown to aggravate proteinaceous lung oedema, which causes epithelial disruption, and results in marked changes in lung perfusion and compliance (Slutsky 2013). Furthermore, whilst endotracheal tube (ETT) suctioning is an essential component of care for intubated and ventilated patients, it can cause rapid, profound de-recruitment of alveoli, leading to a transient loss of lung volume (Hough 2014; Lindgren 2007).

In preterm infants, secondary lung injury as a result of CMV is considered one of the major precipitating factors for the development of bronchopulmonary dysplasia (BPD), a chronic lung disease associated with significant morbidity and mortality (Clark 2001; Davidson 2017).

## Description of the intervention

Lung recruitment manoeuvres (LRMs) are postulated to be a means of reducing lung injury in intubated and mechanically ventilated neonates (Duff 2007; Villagra 2002). A LRM is defined as a deliberate effort to transiently elevate airway pressures in a ventilated patient in order to reinflate collapsed lung regions and increase the number of alveoli participating in gas exchange (Hodgson 2016). LRMs may be implemented on a single occasion or routinely scheduled as a component of ventilation management. They can also be used post-suctioning to overcome the associated lung de-recruitment.

Several methods of administering LRMs have been described in the literature, with a consensus yet to be reached as to which is the most effective at reducing respiratory morbidity (Dyhr 2003; Maggiore 2003; Morrow 2007). Most LRM protocols either involve using sustained inflations or manipulating positive end-expiratory pressure (PEEP) (or a combination of these strategies) (Jauncey-Cooke 2009). In a sustained inflation manoeuvre, high positive pressure is applied to the lungs for a short duration before previous mean airway pressure is restored. The aim of this technique is to inflate alveoli with an elevated threshold opening pressure. By overcoming threshold opening pressure, alveoli literally 'pop' open and participate in gas exchange (Jauncey-Cooke 2009). Alternatively, higher levels of PEEP may be applied in order to alleviate end-expiratory alveolar collapse (Jauncey-Cooke 2009). Common methods of manipulating PEEP include a sharp increase for a short period, or progressive incremental increases followed by gradual decreases back to baseline (which is termed a ‘stepwise’ LRM) (Hodgson 2016; Jauncey-Cooke 2009). It has also been theorised that increasing the peak inspiratory pressure (PIP) along with PEEP may enhance effectiveness, as alveolar recruitment and de-recruitment are continuous processes throughout the breathing cycle – PIP will help to recruit alveoli during inspiration and PEEP preserves alveolar patency during expiration (Halter 2003; Jauncey-Cooke 2009).

Regardless of the method used, all LRMs can potentially cause harm to patients (Jauncey-Cooke 2009). LRMs increase intrathoracic pressure, which may transiently reduce venous return and cardiac output (Odenstedt 2005). They may also raise intracranial pressure (ICP), potentially leading to increased incidence and severity of intraventricular haemorrhage (IVH) (Duff 2007). The elevated pressures with LRMs can also cause barotrauma and air leak, leading to pneumothorax or pulmonary interstitial emphysema (Jauncey-Cooke 2009; Odenstedt 2005).

## How the intervention might work

Despite their potential complications, LRMs are thought to reduce the incidence of lung injury, increase lung compliance, and minimise the complications associated with ETT suctioning and disconnection from the ventilator (Dyhr 2003; Hodgson 2016; Jauncey-Cooke 2012a). By briefly elevating airway pressure to a higher level, LRMs serve to re-recruit collapsed lung regions, which helps to minimise physiological dead space and restore end-expiratory lung volume (EELV) (Brower 2003; Hodgson 2016; Jauncey-Cooke 2009). Improving EELV results in increased alveolar stability, and may reduce shearing injury to the alveoli associated with cyclic opening and closing (Jauncey-Cooke 2009).

## Why it is important to do this review

It has been reported that LRMs are effective in ventilated adults, when used specifically post-suctioning and also generally as a component of ventilation management for acute respiratory distress syndrome (ARDS) (Dyhr 2003; Goligher 2017; Maggiore 2003). However, evidence pertaining to LRM use in neonates is limited, and there is no consensus of opinion as to whether they are effective at reducing mortality and respiratory morbidity in this population.

# OBJECTIVES

To determine the effects of LRMs on mortality and respiratory outcomes in mechanically ventilated neonates, when compared to no recruitment (routine care).

# METHODS

## Criteria for considering studies for this review

### Types of studies

We accepted prospective randomised controlled trials (RCTs) (including individual and cluster-RCTs) as well as randomised cross-over studies that evaluated the effect of LRMs administered to mechanically ventilated neonates. We also accepted quasi-RCTs (in which treatment allocation was obtained by alternation, use of medical record numbers, date of birth, or other predictable methods), along with randomised trial data available only in conference abstract form.

### Types of participants

We included neonatal participants from birth, irrespective of gestational age (GA) (including term and preterm infants), up to four weeks of age, or participants that authors defined as neonates. Participants needed to be intubated and mechanically ventilated. In this review, we defined mechanical ventilation as any invasive method of positive pressure ventilation via either an ETT or tracheostomy tube. In instances where paediatric studies may have included neonates, we contacted the authors to determine if the neonatal data could be isolated.

### Types of interventions

We included studies that evaluated the effect of LRMs compared to no recruitment (routine care). In this review, a LRM was defined as a deliberate effort to transiently elevate airway pressures in order to increase the number of alveoli participating in gas exchange. Given this broad definition, we accepted all types of LRMs applied at any time point, including sustained inflations and manoeuvres involving PEEP manipulation.

### Types of outcome measures

#### *Primary outcomes*

- Mortality (death within 28 days of birth or mortality by hospital discharge)
- Incidence of BPD:
  - supplemental oxygen at 36 weeks' postmenstrual age
  - supplemental oxygen at 28 days of life
  - requirement for home oxygen therapy
- Duration of supplemental oxygen (days)
- Duration of ventilatory support (CMV) (hours or days)
- Duration of continuous positive airway pressure (CPAP) therapy (hours or days)
- Duration of neonatal intensive care unit (NICU) stay (hours or days)
- Duration of hospital stay (days)

#### *Secondary outcomes*

- Incidence of air leak (e.g. pneumothorax and pulmonary interstitial emphysema)
- Lung compliance as measured by respiratory mechanics monitor pre- and post-intervention
- Measures of oxygenation during or post-intervention, as reported in study:
  - partial pressure of oxygen in arterial blood ($PaO_2$)
  - peripheral oxygen saturation ($SpO_2$)
- Partial pressure of carbon dioxide in arterial blood ($PaCO_2$) during or post-intervention, as reported in study
- Heart rate (HR) during or post-intervention, as reported in study
- Measures of blood pressure (BP) during or post-intervention, as reported in study:
  - systolic and diastolic BP
  - mean arterial pressure (MAP)
- EELV as measured by computed tomography or electrical impedance tomography (EIT), or both, pre-, during and post-intervention
- Rates and types of intracranial lesions diagnosed by ultrasound scan:
  - IVH
  - periventricular leukomalacia
- Neurodevelopmental impairment: cerebral palsy, sensorineural hearing loss, visual impairment or developmental delay (e.g. Griffith's or Bayley Scales of Infant Development) assessed at 12 to 24 months corrected age, two years, or five years

## Search methods for identification of studies

### Electronic searches

We conducted a comprehensive search of electronic databases, including the Cochrane Central Register of Controlled Trials (CENTRAL 2020, Issue 4) in the Cochrane Library, MEDLINE via Ovid (1946 to 13 April 2020), and CINAHL via EBSCOhost (1989 to 13 April 2020), using the following search terms: ("recruitment manoeuvre*" OR "recruitment maneuver*" OR "recruitment technique*"), plus database-specific limiters for RCTs and neonates (see Appendix 1 for the full search strategies for each database). Ongoing or recently completed trials registered with ClinicalTrials.gov or The World Health Organization's International Clinical Trials Registry Platform (ICTRP) were included within the CENTRAL database search. We did not apply language restrictions. This search updates the search strategy found in the review protocol (Appendix 2).

### Searching other resources

We also handsearched the reference lists of retrieved studies in order to identify additional relevant articles.

## Data collection and analysis

We employed standard methods of Cochrane Neonatal, as well as of Cochrane, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

### Selection of studies

We exported records of the electronic database search results to Covidence to facilitate title and abstract screening (Covidence 2019). Two review authors (EB and JH) independently reviewed the search results by title and abstract, and excluded studies that clearly did not satisfy the inclusion criteria. We then obtained the full texts of potentially relevant studies. After full-text assessment, we listed the remaining excluded studies in the Characteristics of excluded studies table and described the reasons for exclusion. We discussed any disagreements until consensus was achieved. When we required additional information to determine study inclusion, we attempted to contact the corresponding study authors directly. We also attempted to obtain unpublished data from some authors.

### Data extraction and management

We used the standardised Cochrane data collection form to aid extraction of information on design, methods, participants, interventions, outcomes, and treatment effects from each included study. Two review authors (EB and JH) independently extracted data with identical results subsequently confirmed. We utilised Review Manager Web (RevMan Web) software for data entry, and construction of comparison tables and graphs (RevMan Web 2019).

### Assessment of risk of bias in included studies

Two review authors (EB and JH) independently assessed the risk of bias (low, high, or unclear) of all included studies using the Cochrane 'Risk of bias' tool for the following domains (Higgins 2011):

- Sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)

- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Any other bias

We resolved any disagreements by discussion. See Appendix 3 for a more detailed description of risk of bias for each domain.

### Measures of treatment effect

We analysed the results of the included studies using the statistical package in RevMan Web (RevMan Web 2019). For continuous data, we presented treatment effects as the mean difference (MD) with 95% confidence intervals (CIs) for individual studies and pooled estimates. If continuous outcomes were measured by different methods or by different scales, we planned to use standardised mean differences. For dichotomous data, we presented treatment effects as risk ratios (RRs) with 95% CIs for individual studies and pooled estimates.

### Unit of analysis issues

The unit of analysis was the participating neonate for individually randomised trials.

### Dealing with missing data

We contacted study authors to request information on missing or unclear data for outcomes of interest. If the authors did not respond or missing data could not be sourced, we still intended to include the study in question in the review. If we had concerns regarding the impact of including studies with high levels of missing data in the overall assessment of treatment effect, we planned to explore this through sensitivity analysis; however, this proved to be unnecessary as none of the included studies had high levels of missing data.

### Assessment of heterogeneity

Two review authors (EB and JH) assessed clinical and methodological heterogeneity across the included studies, with a meta-analysis conducted only when both authors agreed that study participants, interventions, and outcomes were sufficiently similar. We quantified the degree of heterogeneity among pooled data by applying the $I^2$ statistic together with a $Chi^2$ test as a measure of corresponding statistical significance, using a conservative P value of 0.1 for statistical significance. We used the following $I^2$ statistic thresholds as a guide to help interpret the degree of heterogeneity:

- Less than 25%: no heterogeneity
- 25% to 49%: low heterogeneity
- 50% to 74%: moderate heterogeneity
- 75% to 100%: high heterogeneity

We also visually inspected forest plots to identify obvious overlaps and outliers across pooled data. If we detected moderate or high heterogeneity ($I^2$ > 50%), we planned to explore potential sources of heterogeneity by performing a sensitivity analysis and subgroup analyses.

### Assessment of reporting biases

If more than 10 studies were included in a meta-analysis, we planned to assess for possible reporting or publication bias through visual examination of funnel plots.

### Data synthesis

We employed the following approaches for data synthesis and meta-analysis:

- For continuous data, we used an inverse-variance approach
- For dichotomous data, we used a Mantel-Haenszel approach

If we found no or low heterogeneity among trials, we used a fixed-effect model for meta-analysis. Conversely, if we found evidence of moderate or high heterogeneity among trials, we combined the data in a meta-analysis using a random-effects model.

### Subgroup analysis and investigation of heterogeneity

We originally planned to undertake subgroup analyses on data contributing to our primary outcomes. These subgroup analyses were to be stratified by:

- Chronological age
- GA
- Lung pathophysiology
- Pre-existing lung disease
- Mode and length of ventilation
- Timing and frequency of recruitment techniques

However, we ultimately did not conduct subgroup analyses as we felt that there were insufficient data for the analyses to be meaningful.

### Sensitivity analysis

If an adequate number of studies contributed data to our primary outcomes, we intended to perform a sensitivity analysis to explore the causes of heterogeneity and the robustness of the results. As part of our sensitivity analysis, we planned to separate studies according to:

- Quality of allocation concealment (adequate, inadequate, or unclear)
- Blinding (adequate, inadequate, unclear, or not performed)
- Analysis using both random-effects and fixed-effect models
- Intention-to-treat analysis and available case analysis (for dichotomous data only) (Higgins 2008)

Again, we did not conduct a sensitivity analysis as planned, as there were insufficient data to undertake meaningful analyses of this nature.

### Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the certainty of the evidence for the following primary outcomes: mortality, incidence of BPD, duration of supplemental oxygen, duration of ventilatory support, duration of CPAP therapy, duration of NICU stay, and duration of hospital stay.

Two review authors (EB and JH) independently assessed the certainty of the evidence for each of the outcomes above. We considered evidence from RCTs as high certainty but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias),

consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We used the GRADEpro GDT Guideline Development Tool to create a Summary of findings 1 to report the certainty of the evidence.

The GRADE approach results in an assessment of the certainty of a body of evidence as one of four grades.

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

# RESULTS

## Description of studies

### Results of the search

Refer to Figure 1 for a PRISMA flow diagram of the study selection process. Overall, our search strategy yielded 157 records. Of these, 156 were obtained from the CENTRAL, MEDLINE and CINAHL databases, while one was obtained via handsearching. We screened the titles and abstracts of 105 unique records, excluding 90 records in the process. Four additional records were identified as ongoing (ACTRN12617000609358; ChiCTR-INR-17013194; NCT02584023; NCT04289324). We assessed 11 full-text studies for eligibility, which led to the exclusion of seven further studies. Four studies in total were eligible for inclusion in this review.

**Figure 1. Review flow diagram**

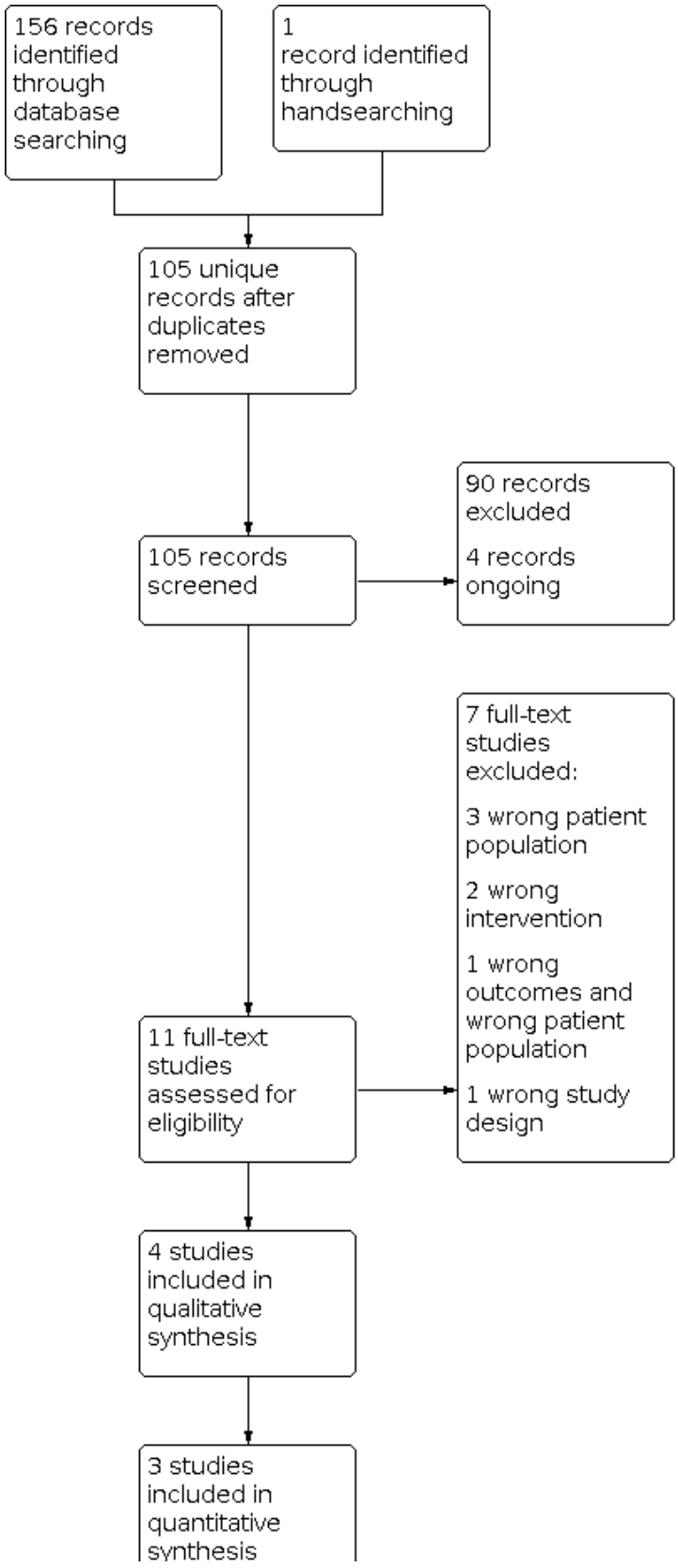
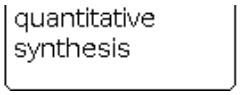


**Figure 1. (Continued)**




### Included studies

We included four studies in the review (Castoldi 2011; Jauncey-Cooke 2012a; Morrow 2007; Wu 2014). These studies are described in further detail in the Characteristics of included studies section.

Castoldi 2011 performed a two-arm parallel-group RCT that enrolled 20 preterm infants (GA less than 27 weeks) who required endotracheal intubation and CMV in the first hour of life due to severe respiratory distress syndrome (RDS). Notable exclusion criteria included lethal congenital abnormalities and IVH greater than grade 2. All participants received surfactant immediately after intubation and were supported with assist/control ventilation plus the volume guarantee option. The researchers randomly assigned the participants to either an intervention group or routine care group. Participants in the intervention group received a single LRM with PEEP as per the following protocol. After setting an initial PEEP level of 5 $cmH_2O$, the researchers incrementally increased the PEEP level by 0.2 $cmH_2O$ every five minutes while monitoring fraction of inspired oxygen ($FiO_2$) requirement and $SpO_2$ level. During the five minutes of monitoring, a reduction in $FiO_2$ requirement and increase in $SpO_2$ level were signals to continue with the manoeuvre and progressively increase PEEP. When $FiO_2$ reached 0.25, the PEEP level was subsequently reduced in a gradual stepwise manner until oxygenation worsened. Then, PEEP was increased again until (quote:) "stable oxygenation was achieved and the $FiO_2$ level reached levels prior to the fall in oxygenation" (during the PEEP reduction phase). Randomisation and interventions occurred within the first three hours of life. Eligible outcomes from this study included mortality by hospital discharge, incidence of BPD, duration of supplemental oxygen, duration of ventilatory support, and measure of oxygenation ($PaO_2$ at the end of the LRM).

Wu 2014 also performed a two-arm parallel-group RCT that enrolled 24 preterm infants (GA 28 to 30 weeks) who required endotracheal intubation and CMV in the first six hours of life due to severe RDS. The study methods were nearly identical to Castoldi 2011, with Wu 2014 basing their intervention on the earlier study. The only notable differences between the studies included: Wu 2014 specified a birth weight of 1000 to 1500 g as an inclusion criterion, and weak or absent spontaneous breathing as an exclusion criterion; participants in Wu 2014 were supported with a different mode of ventilation (proportional assist ventilation); and $SpO_2$ targets differed between studies (83% to 93% in Castoldi 2011; 85% to 93% in Wu 2014). Eligible outcomes from Wu 2014 were the same as Castoldi 2011 above, with the exception of $PaO_2$ at the end of the LRM.

Jauncey-Cooke 2012a performed a RCT with a cross-over design in the intervention arm. The study enrolled 60 children (aged zero to 16 years) who were mechanically ventilated for respiratory and non-respiratory causes. Postoperative cardiac patients were excluded. The participants' modes of ventilation and baseline PEEP levels were clinically managed and not altered for the purposes of the study. All participants had an arterial line in situ. The researchers randomly assigned the participants to either an intervention arm or routine care group. Participants in the intervention arm received two different LRMs in a cross-over fashion with the order randomised. The incremental PEEP LRM involved application of repeated increments of 4 $cmH_2O$ of PEEP every 60 seconds up to a maximum of 18 $cmH_2O$, followed by stepwise reductions back to baseline. The other LRM (named double PEEP) involved application of double baseline PEEP for two minutes before returning to baseline. The LRMs were performed immediately after open ETT suctioning and reconnection to the ventilator. After the participants received their first LRM, a two-hour washout period was adhered to before the next suction episode and administration of the second LRM. Participants in the routine care group received suctioning, minus recruitment. Eligible outcomes from this study included measures of oxygenation ($PaO_2$ and $SpO_2$), $PaCO_2$, HR, MAP, and EELV (as measured by EIT). As this study enrolled paediatric participants outside of our age range for inclusion, we intended to only include it if data pertaining to neonates could be isolated. Review author JJC, who is also the lead author of Jauncey-Cooke 2012a, was able to provide data for the outcomes above for all 12 neonatal participants (five in the intervention arm; seven in the control group). The Jauncey-Cooke 2012a data described in the Effects of interventions section reflects only the unpublished neonatal data sourced directly from JJC.

Morrow 2007 performed a two-arm parallel-group RCT that enrolled 48 paediatric patients with heterogenous lung pathology. All participants had ETTs in situ and were supported with pressure-limited, time-cycled CMV. Exclusion criteria included any cardiac abnormality or disease, raised ICP, haemodynamic instability, pneumothorax and coagulopathy, among others. Equal numbers of participants were randomised to an experimental group and control group. Five minutes after ETT suctioning, participants in the experimental group received a LRM comprising a single sustained inflation pressure of 30 $cmH_2O$ applied for 30 seconds. The LRM was performed manually using a one-litre anaesthetic bag. The control group underwent ETT suctioning, but did not receive a LRM. Measurements of ventilation and gas exchange were recorded on three occasions before and two occasions after the LRM. This study included neonatal and paediatric participants. Correspondence with the lead author established that the neonatal data could not be isolated as it was no longer available. Hence, this study did not contribute data to the review.

### Excluded studies

We excluded seven studies following full-text assessment. We excluded two studies because they enrolled non-neonatal participants (NCT01114009; Rodríguez-Moya 2017). We excluded Vento 2021 because the enrolled participants were not intubated and mechanically ventilated at time of inclusion to the study (they were breathing independently on nasal CPAP). Aleksandrovich 2014 was rejected as it was not a RCT. Kim 2010 and La Verde 2019 were rejected as they did not evaluate our prespecified intervention. We also excluded Song 2017 as it enrolled non-neonatal participants and did not report any of

our prespecified outcome measures. Refer to the Characteristics of excluded studies table for additional information regarding excluded studies.

### Risk of bias in included studies

All included studies had unclear risk of bias for at least two criteria. None of the included studies had a high risk of bias for any criterion. Refer to Figure 2 for a summary representation of the risk of bias across the review by criteria, and Figure 3 for risk of bias per criterion for each study. Further to this, a 'Risk of bias' table with additional details is included for each study in the Characteristics of included studies section.

**Figure 2. Risk of bias graph: review authors' judgements regarding each risk of bias item presented as percentages across all included studies**

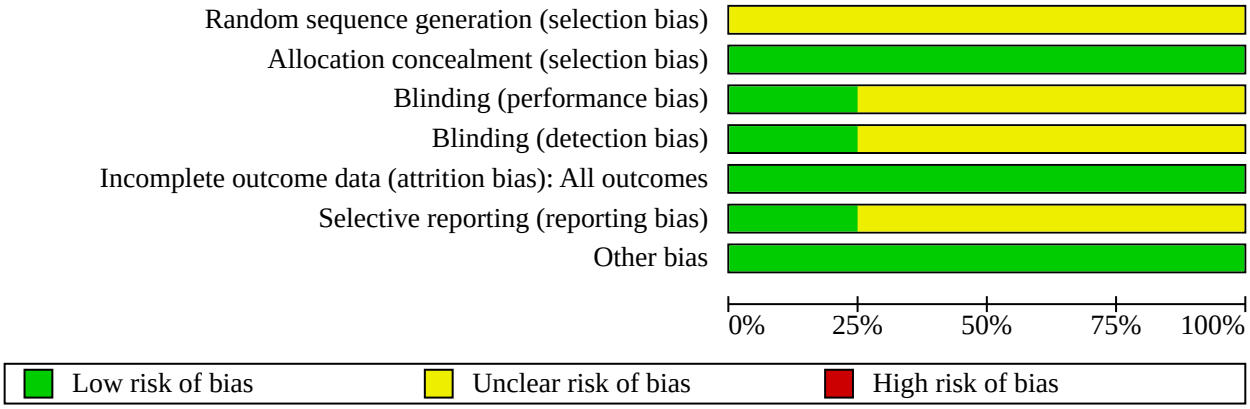
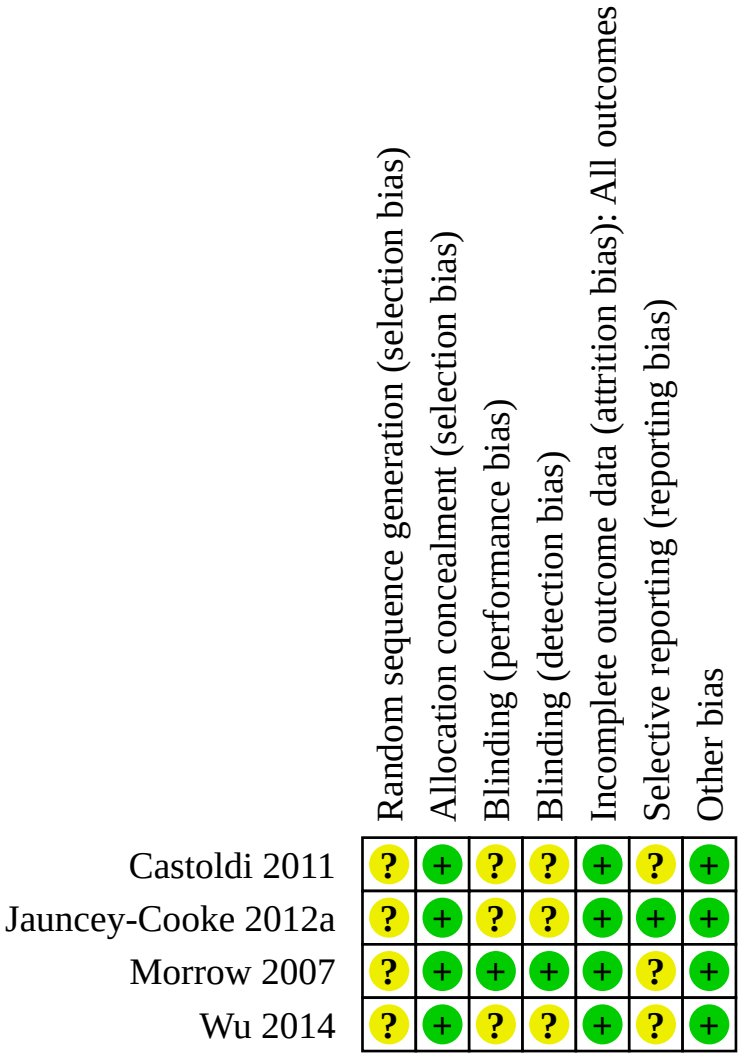


**Figure 3. Risk of bias summary: review authors' judgements regarding each risk of bias item for each included study**




### Allocation

All four studies reported that enrolled participants were randomly assigned to groups; however, the methods of random sequence generation were not described (unclear risk of bias). Adequate allocation concealment was achieved in all four studies through the use of sequentially numbered, sealed, opaque envelopes (low risk of bias).

### Blinding

Three studies were at unclear risk of performance bias as attempts to blind the study personnel and participants were not described (Castoldi 2011; Jauncey-Cooke 2012a; Wu 2014). Study personnel in Morrow 2007 were not blinded to group allocation due to the nature of the intervention and methods; however, adherence to the approved study protocol was ensured by a Safety Monitoring Committee (low risk of performance bias).

Morrow 2007 successfully achieved blinding of the outcome assessor, leading to a judgement of low risk of detection bias. Three studies were at unclear risk of detection bias as they did not mention if outcome assessors were aware of group allocation (Castoldi 2011; Jauncey-Cooke 2012a; Wu 2014).

### Incomplete outcome data

Castoldi 2011 and Wu 2014 both had complete outcome ascertainment and reporting (low risk of attrition bias). We deemed Jauncey-Cooke 2012a to also be at low risk of attrition bias as there were complete outcome data for all neonatal participants (for which we sought unpublished data), and for 58 out of 60 participants in the published study. In Morrow 2007, missing

outcome data were balanced in numbers across groups and the data were all excluded for the same reason, leading to a judgement of low risk of attrition bias.

### Selective reporting

We deemed Jauncey-Cooke 2012a to be at low risk of reporting bias as there did not appear to be any major deviations from the protocol (Jauncey-Cooke 2012c). We were unable to reliably assess whether selective reporting occurred in three studies as their protocols were unavailable (Castoldi 2011; Morrow 2007; Wu 2014).

### Other potential sources of bias

We did not identify any other potential sources of bias in the included studies.

## Effects of interventions

See: **Summary of findings 1** Summary of findings for the main comparison

Below, we detail three comparisons regarding the effect of LRMs in neonates. Comparison 1 concerns the application of a LRM within hours of birth versus routine care in preterm infants requiring CMV for RDS. Castoldi 2011 and Wu 2014 both contributed data to this comparison, and because these studies were sufficiently similar in regard to their methodology, their data could be combined in a meta-analysis for some outcomes. Comparisons 2 and 3 concern the application of different types of LRMs immediately after ETT suctioning versus routine care in neonates requiring CMV for respiratory and non-respiratory causes. Jauncey-Cooke 2012a contributed data to both of these comparisons.

We have only discussed outcomes for which any data were available. None of the included studies contributed data to the following outcomes: duration of CPAP therapy, duration of NICU stay, duration of hospital stay, incidence of air leak, lung compliance, rates and types of intracranial lesions, and neurodevelopment impairment.

### Comparison 1. LRM with PEEP versus routine care in preterm infants requiring CMV for RDS

Two studies enrolling 44 participants compared a LRM with PEEP to routine care in preterm infants requiring CMV for RDS (Castoldi 2011; Wu 2014). Both studies contributed data to the following four primary outcomes, while only Castoldi 2011 contributed data to one of our secondary outcomes.

#### *Primary outcomes*

##### 1.1 Mortality by hospital discharge

Our meta-analysis showed no evidence of a difference between a LRM and routine care on the outcome of mortality by hospital discharge (RR 1.00, 95% CI 0.17 to 5.77, P = 1.00, $I^2$ not applicable, studies = 2, participants = 44; Analysis 1.1). We graded the certainty of the evidence as low, due to risk of bias (unclear risk of selection, performance, detection, and reporting bias) and imprecision (comparison based on a small number of events, contributing to wide CIs around the effect estimate).

##### 1.2 Incidence of BPD

Our meta-analysis showed no evidence of a difference between a LRM and routine care on the outcome of incidence of BPD (RR 0.25, 95% CI 0.03 to 2.07, P = 0.20, $I^2$ = 0%, studies = 2, participants = 44; Analysis 1.2). We graded the certainty of the evidence as low, due to risk of bias (unclear risk of selection, performance, detection, and reporting bias) and imprecision (comparison based on a small number of events, contributing to wide CIs around the effect estimate).

##### 1.3 Duration of supplemental oxygen

Our meta-analysis showed no evidence of a difference between a LRM and routine care on the outcome of duration of supplemental oxygen (MD -7.52, 95% CI -20.83 to 5.78, P = 0.27, $I^2$ = 77%, studies = 2, participants = 44; Analysis 1.3). We graded the certainty of the evidence as very low, due to risk of bias (unclear risk of selection, performance, detection, and reporting bias), imprecision (data derived from only two small studies), and inconsistency (high heterogeneity between studies ($I^2$ = 77%, P = 0.04)).

##### 1.4 Duration of ventilatory support

Our meta-analysis showed no evidence of a difference between a LRM and routine care on the outcome of duration of ventilatory support (MD -3.59, 95% CI -12.97 to 5.79, P = 0.45, $I^2$ = 58%, studies = 2, participants = 44; Analysis 1.4). We graded the certainty of the evidence as very low, due to risk of bias (unclear risk of selection, performance, detection, and reporting bias), imprecision (data derived from only two small studies), and inconsistency (moderate heterogeneity between studies ($I^2$ = 58%, P = 0.12)).

#### *Secondary outcomes*

##### 1.5 Measure of oxygenation: $PaO_2$ at the end of the LRM

Only one study in this comparison measured $PaO_2$ (Castoldi 2011). There was no evidence of a difference between a LRM and routine care on the outcome of $PaO_2$ at the end of the LRM (MD 13.00, 95% CI -1.46 to 27.46, P = 0.08, participants = 20; Analysis 1.5). It is unclear how the timing of this measure was selected for participants in the routine care group.

### Comparison 2. Incremental PEEP LRM post-suctioning versus routine care in mechanically ventilated neonates

Only Jauncey-Cooke 2012a compared an incremental PEEP LRM post-suctioning to routine care in mechanically ventilated neonates. Unpublished data from all 12 neonatal participants contributed to the following six secondary outcomes.

#### *Secondary outcomes*

##### 2.1 Measure of oxygenation: $PaO_2$ at 120 minutes' post-suctioning

There was no evidence of a difference between an incremental PEEP LRM and routine care on the outcome of $PaO_2$ at 120 minutes' post-suctioning (MD -7.32, 95% CI -34.71 to 20.07, P = 0.60, participants = 12; Analysis 2.1).

##### 2.2 Measure of oxygenation: $SpO_2$ at 30 minutes' and 120 minutes' post-suctioning

At both 30 minutes' and 120 minutes' post-suctioning, there was no evidence of a difference between an incremental PEEP LRM and routine care on the outcome of $SpO_2$ (30 minutes' post-suctioning: MD 0.00, 95% CI -5.23 to 5.23, P = 1.00; 120 minutes' post-suctioning: MD 0.00, 95% CI -2.85 to 2.85, P = 1.00; participants = 12; Analysis 2.2).

#### 2.3 $PaCO_2$ at 120 minutes' post-suctioning

There was no evidence of a difference between an incremental PEEP LRM and routine care on the outcome of $PaCO_2$ at 120 minutes' post-suctioning (MD -2.27, 95% CI -17.46 to 12.92, P = 0.77, participants = 12; Analysis 2.3).

#### 2.4 HR at 30 minutes' and 120 minutes' post-suctioning

At both 30 minutes' and 120 minutes' post-suctioning, there was no evidence of a difference between an incremental PEEP LRM and routine care on the outcome of HR (30 minutes' post-suctioning: MD 7.00, 95% CI -23.29 to 37.29, P = 0.65; 120 minutes' post-suctioning: MD 14.00, 95% CI -13.33 to 41.33, P = 0.32; participants = 12; Analysis 2.4).

#### 2.5 MAP at 30 minutes' and 120 minutes' post-suctioning

There was no evidence of a difference between an incremental PEEP LRM and routine care on the outcome of MAP at both 30 minutes' and 120 minutes' post-suctioning (30 minutes' post-suctioning: MD -5.00, 95% CI -22.28 to 12.28, P = 0.57; 120 minutes' post-suctioning: MD -7.00, 95% CI -18.65 to 4.65, P = 0.24; participants = 12; Analysis 2.5).

#### 2.6 Change in EELV at 30 minutes' and 120 minutes' post-suctioning

There was no evidence of a difference between an incremental PEEP LRM and routine care on the outcome of EELV at 30 minutes' post-suctioning (MD 0.02, 95% CI -0.07 to 0.11; P = 0.71, participants = 12; Analysis 2.6). At 120 minutes' post-suctioning, the data suggest that an incremental PEEP LRM may slightly improve EELV, when compared with routine care (MD -0.21, 95% CI -0.37 to -0.06, P = 0.008, participants = 12; Analysis 2.6).

### Comparison 3. Double PEEP LRM post-suctioning versus routine care in mechanically ventilated neonates

Only Jauncey-Cooke 2012a compared a double PEEP LRM post-suctioning to routine care in mechanically ventilated neonates. Unpublished data from all 12 neonatal participants contributed to the following six secondary outcomes.

#### *Secondary outcomes*

#### 3.1 Measure of oxygenation: $PaO_2$ at 120 minutes' post-suctioning

There was no evidence of a difference between a double PEEP LRM and routine care on the outcome of $PaO_2$ at 120 minutes' post-suctioning (MD -7.84, 95% CI -32.14 to 16.46, P = 0.53, participants = 12; Analysis 3.1).

#### 3.2 Measure of oxygenation: $SpO_2$ at 30 minutes' and 120 minutes' post-suctioning

At both 30 minutes' and 120 minutes' post-suctioning, there was no evidence of a difference between a double PEEP LRM and routine care on the outcome of $SpO_2$ (30 minutes' post-suctioning: MD 2.00, 95% CI -2.56 to 6.56, P = 0.39; 120 minutes' post-suctioning: MD 0.00, 95% CI -2.93 to 2.93, P = 1.00; participants = 12; Analysis 3.2).

#### 3.3 $PaCO_2$ at 120 minutes' post-suctioning

There was no evidence of a difference between a double PEEP LRM and routine care on the outcome of $PaCO_2$ at 120 minutes' post-suctioning (MD -2.27, 95% CI -15.80 to 11.26, P = 0.74, participants = 12; Analysis 3.3).

#### 3.4 HR at 30 minutes' and 120 minutes' post-suctioning

At both 30 minutes' and 120 minutes' post-suctioning, there was no evidence of a difference between a double PEEP LRM and routine care on the outcome of HR (30 minutes' post-suctioning: MD 4.00, 95% CI -22.75 to 30.75, P = 0.77; 120 minutes' post-suctioning: MD 3.00, 95% CI -16.75 to 22.75, P = 0.77; participants = 12, Analysis 3.4).

#### 3.5 MAP at 30 minutes' and 120 minutes' post-suctioning

The data suggest that a double PEEP LRM may result in a slight reduction in MAP at 30 minutes' post-suctioning, when compared with routine care (MD -16.00, 95% CI -29.35 to -2.65, P = 0.02, participants = 12; Analysis 3.5). At 120 minutes' post-suctioning, there was no evidence of a difference between a double PEEP LRM and routine care on the outcome of MAP (MD -3.00, 95% CI -21.05 to 15.05, P = 0.74, participants = 12; Analysis 3.5).

#### 3.6 Change in EELV at 30 minutes' and 120 minutes' post-suctioning

There was no evidence of a difference between a double PEEP LRM and routine care on the outcome of EELV at 30 minutes' post-suctioning (MD -0.04, 95% CI -0.11 to 0.04, P = 0.37, participants = 12; Analysis 3.6). At 120 minutes' post-suctioning, the data suggest that a double PEEP LRM may slightly improve EELV, when compared with routine care (MD -0.18, 95% CI -0.35 to -0.02, P = 0.03, participants = 12; Analysis 3.6).

## DISCUSSION

### Summary of main results

We evaluated the efficacy of LRMs compared to routine care in mechanically ventilated neonates. Only three studies enrolling 56 participants contributed data to this review, which indicates that evidence-based guidance for the use of LRMs in this particular population continues to be limited.

Two small studies (Castoldi 2011; Wu 2014), enrolling 44 participants investigated the effect of a stepwise LRM within hours of birth compared to routine care in preterm infants on CMV for RDS (comparison 1). These studies contributed data to four of our primary (clinically important) outcomes, and as such, were included in our Summary of findings 1. Our meta-analysis demonstrated no evidence of a difference between the LRM and routine care for the outcomes of mortality by hospital discharge, incidence of BPD, duration of supplemental oxygen, and duration of ventilatory support. We believe that larger trials are warranted to more precisely measure the effect of early LRM application on clinically important outcomes in preterm infants requiring CMV.

Unpublished data from Jauncey-Cooke 2012a compared an incremental PEEP LRM to routine care (comparison 2) and a double PEEP LRM to routine care (comparison 3) in mechanically ventilated neonates following ETT suctioning. Data from all 12 neonatal participants contributed to several of our secondary outcomes, including measures of oxygenation ($PaO_2$ and $SpO_2$), $PaCO_2$, HR, MAP, and EELV. For most of these outcomes in comparisons 2 and 3, there was no evidence of a difference between groups. However, at 120 minutes' post-suctioning, the data suggest that both LRMs may slightly improve EELV, when compared with routine care. The limited data also suggest that a double PEEP LRM may result in a slight reduction in MAP at 30 minutes' post-suctioning, when compared with routine care, which is a potentially harmful complication. Neonatal hypotension has been associated with poor

outcomes, including IVH (Watkins 1989). This finding in neonates is consistent with existing literature regarding the haemodynamic effects of LRMs. Grasso 2002 found that LRM application in ventilated adults with ARDS caused a substantial reduction in MAP, while Lim 2004 and Odenstedt 2005 both shared similar findings in ventilated pigs. Again, larger trials are needed to further evaluate the potential benefits and risks of post-suctioning LRMs in neonates. Overall, we do not believe that our current findings have implications for clinical practice.

### Overall completeness and applicability of evidence

Our overall findings are insufficiently complete to guide clinical practice. Only three studies enrolling small sample sizes contributed data to the review, making our findings imprecise to draw conclusions. Whilst these studies contributed data to many of our primary and secondary outcomes, we have been unable to identify any data addressing the following outcomes: duration of CPAP therapy, duration of NICU stay, duration of hospital stay (primary outcomes); incidence of air leak, lung compliance, rates and types of intracranial lesions, and neurodevelopmental impairment (secondary outcomes).

The data from Castoldi 2011 and Wu 2014 are largely applicable to current practice. Both studies were published after 2010, enrolled participants frequently requiring CMV, and applied therapies consistent with modern practice, including surfactant therapy and attempts to limit invasive ventilatory support. The only major discrepancy that we noted was the lower $SpO_2$ targets employed by the study investigators (83% to 93% in Castoldi 2011; 85% to 93% in Wu 2014). Following findings from Askie 2018 and BOOST II 2013, targeting $SpO_2$ above 90% is often now preferred. Whilst applying higher $SpO_2$ targets may have influenced quantitative aspects of the LRM in each study (such as the $FiO_2$ or PEEP required to meet the $SpO_2$ targets), we deemed the overall rationale and process applied in these studies relevant to modern practice. The data from Jauncey-Cooke 2012a are also generally applicable to current practice, as the study was published after 2010, utilised a well-known ETT suctioning protocol, and adjusted participants' $FiO_2$ requirements to achieve a targeted $SpO_2$ range of 94% to 98%.

### Quality of the evidence

Using the GRADE approach, we graded the certainty of the evidence for two primary outcomes in the Summary of findings 1 (mortality by hospital discharge, and incidence of BPD) to be low, which reflects a limited confidence in the effect estimates (i.e. the true effect may be substantially different from the estimate of the effect) (Schünemann 2013). The certainty of the evidence for two other primary outcomes (duration of supplemental oxygen, and duration of ventilatory support) was graded as very low, which reflects a very limited confidence in the effect estimates (i.e. the true effect is likely to be substantially different from the estimate of the effect) (Schünemann 2013). We arrived at these conclusions by starting with a default of high certainty based on study design (RCT) and then downgrading due to a combination of factors, including risk of bias, imprecision, and inconsistency. Firstly, we downgraded the certainty of the evidence for all four outcomes one level due to risk of bias. We judged the studies contributing data (Castoldi 2011; Wu 2014) to have unclear risk of selection bias (no description of the method of random sequence generation), performance and detection bias (no description of attempts at blinding), and reporting bias (given the lack of available protocols). Whilst it is uncertain and perhaps even unlikely that these limitations influenced the outcomes, we erred on the side of caution. Secondly, all four outcomes were downgraded one further level for imprecision due to the small number of studies and small sample sizes. For mortality by hospital discharge, and incidence of BPD, comparisons were based on a small number of events, contributing to wide CIs around the effect estimates. Lastly, the certainty of the evidence for two outcomes was also further downgraded one level for inconsistency (duration of supplemental oxygen: high heterogeneity, $I^2$ = 77%; duration of ventilatory support: moderate heterogeneity, $I^2$ = 58%).

Whilst we did not formally grade the certainty of the evidence from Jauncey-Cooke 2012a, it is important to consider that the study's evidence is limited by its small sample size of only 12 participants. Although some slight differences were demonstrated favouring the incremental and double PEEP LRMs, these findings nonetheless reflect data from a very small number of participants and should be interpreted cautiously.

### Potential biases in the review process

We made a concerted effort throughout the review process to minimise bias. We used prespecified eligibility criteria, performed an extensive search of the literature, and ensured that two authors independently and reproducibly assessed trial eligibility, extracted data, evaluated risk of bias, and graded the certainty of the evidence (with differences resolved by discussion or by a third author). We are confident that our search strategy was sensitive enough to capture all presently available randomised trial evidence regarding LRM use in neonates. We would like to declare that four of our authors (JJC, CG, FB and CE) are also authors of one of the included studies (Jauncey-Cooke 2012a). To ensure that bias did not occur as a result of this, these authors did not participate in the screening process, data extraction, or 'Risk of bias' assessment for their study.

Despite these efforts, there remain some potential sources of bias in the review process. Firstly, Morrow 2007 could not contribute data to the review as its neonatal data could not be isolated. Our review is therefore missing a valuable source of information regarding the effect of LRMs post-suctioning in neonates. Similarly, we are also missing data from four ongoing trials. In the interest of obtaining higher quality evidence for the review, we chose to only include randomised trials. Consequently, we were unable to include some studies (namely Aleksandrovich 2014; Cruces 2013; Duff 2007) that assessed the effect of LRMs using a different study design. This criterion of restricting inclusion to only randomised trials may have excluded valuable, albeit lower quality, data from the review. Finally, our meta-analysis did not include sufficient trials to explore symmetry of funnel plots as a means of identifying possible publication or reporting bias.

### Agreements and disagreements with other studies or reviews

We are unaware of any other systematic reviews addressing the objectives of this review. However, a recent systematic review by Bamat and colleagues (Bamat 2019), which investigated the effects of different PEEP levels in ventilated preterm infants, also included Castoldi 2011 and Wu 2014. Our results for the outcomes

of mortality by hospital discharge and incidence of BPD from those studies match those reported in Bamat 2019.

## AUTHORS' CONCLUSIONS

### Implications for practice

There continues to be limited, low- to very low-certainty evidence to guide clinical use of LRMs in mechanically ventilated neonates. Current studies are unable to provide reliable evidence concerning the effectiveness of LRMs to reduce neonatal mortality and respiratory morbidity. Given the uncertainty of our results, a very cautious approach must be taken with LRM use in this population until further research is conducted.

### Implications for research

The findings of this review should raise awareness of the lack of evidence guiding LRM use in neonates and encourage further robust, well-designed trials. Adequately powered randomised trials should be undertaken to compare different types of LRMs (including incremental PEEP and/or double PEEP LRMs) with routine care in mechanically ventilated neonates, particularly for the outcomes of MAP and restoration of EELV following ETT suctioning. Larger studies are also warranted to further investigate the effect of LRM application early in life on clinically important outcomes (including mortality, incidence of BPD, and duration of ventilatory support, NICU stay and hospital stay) in preterm infants with RDS. Future studies should aim to utilise clear, reproducible LRM protocols and employ high-quality methodology, particularly with regard to sample size, random sequence generation and blinding.

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**NCT01114009** *{published data only}*

NCT01114009. Effects of recruitment maneuvers in early acute lung Injury (ALI) and acute respiratory distress syndrome (ARDS) patients [Effects of recruitment maneuvers in early ALI and ARDS patients]. clinicaltrials.gov/ct2/show/NCT01114009 (first received 30 April 2010).

**Rodríguez-Moya 2017** *{published data only}*

Rodríguez-Moya V, Gallo-Borrero C, Santos-Areas D, Prince-Martinez I, Diaz-Casanas E, Lopez-Herce J. Exogenous surfactant and alveolar recruitment in the treatment of the acute respiratory distress syndrome. *Clinical Respiratory Journal* 2017;**11**(6):1032-9. [DOI: 10.1111/crj.12462] [PMID: 26881996]

**Song 2017** *{published data only}*

Song IK, Kim EH, Lee JH, Ro S, Kim HS, Kim JT. Effects of an alveolar recruitment manoeuvre guided by lung ultrasound on anaesthesia-induced atelectasis in infants: a randomised, controlled trial. *Anaesthesia* 2017;**72**(2):214–22. [DOI: 10.1111/anae.13713] [PMID: 27804117]

**Vento 2021** *{published data only}*

Vento G, Ventura ML, Pastorino R, van Kaam AH, Carnielli V, Cools F, et al. Lung recruitment before surfactant administration in extremely preterm neonates with respiratory distress syndrome (IN-REC-SUR-E): a randomised, unblinded, controlled trial. *Lancet Respiratory Medicine* 2021;**9**(2):159-66. [DOI: 10.1016/S2213-2600(20)30179-X] [PMID: 32687801]

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**ACTRN12617000609358** *{published data only}*

ACTRN12617000609358. Normal saline instillation and lung recruitment with paediatric endotracheal suction [Feasibility of normal saline instillation and lung recruitment with paediatric endotracheal suction: a pilot, factorial, randomised controlled trial]. anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12617000609358 (first received 20 April 2017).

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**Jauncey-Cooke 2012b**

Jauncey-Cooke J, Bosgossian F, Hough JL, Schibler A, Davies MW, Grant CA, et al. Lung recruitment manoeuvres for reducing respiratory morbidity in mechanically ventilated neonates. *Cochrane Database of Systematic Reviews* 2012, Issue 7. Art. No: CD009969. [DOI: 10.1002/14651858.CD009969]

## CHARACTERISTICS OF STUDIES

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

**Castoldi 2011**

***Study characteristics***

**Castoldi 2011** *(Continued)*

| | |
|---|---|
| Methods | • 2-arm parallel-group RCT conducted in the NICU of "V. Buzzi" Children's Hospital of Milan, Italy<br>• Study period not stated<br>• Allocation concealment via sequentially numbered, sealed, opaque envelopes<br>• Blinding of intervention or outcome ascertainment not addressed |
| Participants | • Sample size: 20 infants with severe RDS diagnosed based on clinical and radiologic findings, and exclusion of other causes of respiratory failure (10 in LRM group; 10 in routine care group)<br>• Inclusion criteria: GA < 27 weeks; ≥ 1 course of prenatal glucocorticoids; requirement for endotracheal intubation and CMV in the 1st hour of life; written parental consent<br>• Exclusion criteria: lethal congenital abnormalities; severe IVH (> grade 2)<br>• All participants received surfactant immediately after intubation and were supported with assist/control ventilation + volume guarantee option. Starting parameters as follows: Vt = 6 mL/kg, inspiratory time = 0.3 seconds, respiratory rate = 60/min, PIP = 25 $cmH_2O$, PEEP = 5 $cmH_2O$ |
| Interventions | • Participants randomised to receive either a single LRM or no LRM (routine care)<br>• LRM consisted of a starting PEEP level of 5 $cmH_2O$, followed by application of repeated increments of 0.2 $cmH_2O$ of PEEP every 5 minutes while evaluating for improvements in oxygenation by monitoring $SpO_2$ levels (target: 83% to 93%) and $FiO_2$ requirement. PEEP level was progressively increased if oxygenation improved. When a $FiO_2$ of 0.25 was reached, a slow stepwise PEEP reduction was initiated. When oxygenation levels fell and $FiO_2$ administration consequently rose, the PEEP level was increased again until (quote:) "stable oxygenation was achieved and the $FiO_2$ level reached levels prior to the fall in oxygenation".<br>• Randomisation and interventions occurred within the 1st 3 hours of life. |
| Outcomes | • Primary study outcome/objective not explicitly stated, but hypothesis was that a LRM (quote:) "would lead to shorter need for $FiO_2$ and a more rapid achievement of better oxygenation, when compared with a similar cohort of infants not receiving the manoeuvre".<br>• Outcomes: $FiO_2$ at start of LRM; lowest $FiO_2$; time to lowest $FiO_2$; PEEP at start of LRM; maximum PEEP during LRM; final PEEP at the end of LRM; $a/AO_2$ ratio at start of LRM; $a/AO_2$ ratio final; $PaO_2$ at start of LRM; $PaO_2$ final; surfactant doses; extubation failure; length of respiratory support; length of tracheal intubation; PDA occurrence; maternal chorioamnionitis; sepsis; $O_2$ dependency; moderate or severe BPD; ROP grade > 2; mortality by hospital discharge |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Study stated that enrolled participants were randomly assigned to groups; however, the method of random sequence generation was not described. |
| Allocation concealment (selection bias) | Low risk | Sequentially numbered, sealed, opaque envelopes were used. |
| Blinding (performance bias) | Unclear risk | Not addressed, but unlikely given the nature of the intervention and methods |
| Blinding (detection bias) | Unclear risk | Not addressed, but unlikely given the nature of the intervention and methods |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Outcomes reported for all enrolled participants |

**Castoldi 2011** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available |
| Other bias | Low risk | Nil other sources of bias |

**Jauncey-Cooke 2012a**

| ***Study characteristics*** | |
|---|---|
| Methods | • RCT with a cross-over design in the intervention arm conducted in the PICU of the Mater Children's Hospital in Brisbane, Australia<br>• Study period: April 2007 to October 2010<br>• Allocation concealment via sequentially numbered, sealed, opaque envelopes<br>• Blinding of intervention or outcome ascertainment not addressed |
| Participants | • Sample size: 60 children (38 in intervention arm; 20 in routine care group)<br>• Inclusion criteria: 0 to 16 years of age; intubation and CMV for respiratory and non-respiratory causes; parental consent<br>• Exclusion criteria: postoperative cardiac patients<br>• All participants were intubated with a cuffed ETT and mechanically ventilated with various modes of ventilation, including SIMV, pressure control and pressure support.<br>• Modes of ventilation and baseline PEEP were clinically managed and not altered for the purposes of the study. |
| Interventions | • Participants randomised to either the intervention arm or routine care group<br>• Participants in the intervention arm received two different LRMs immediately after ETT suctioning in a cross-over fashion with the order randomised:<br>  ○ Incremental PEEP LRM: involved application of repeated increments of 4 $cmH_2O$ of PEEP every 60 seconds up to a maximum of 18 $cmH_2O$, followed by stepwise reductions back to baseline<br>  ○ Double PEEP LRM: involved application of double baseline PEEP for 2 minutes before returning to baseline<br>• A 2-hour washout period was adhered to between each manoeuvre.<br>• Participants in the routine care group received suctioning, minus recruitment. |
| Outcomes | • Primary study outcome/objective: to determine the impact of 2 different LRMs on oxygenation, oxygen delivery, haemodynamic status, EELV and regional gas distribution<br>• Outcomes: $PaO_2$; $PaCO_2$; $SaO_2$; $SpO_2$; $DaO_2$; HR; MAP; ICP; EELV; regional ventilation distribution |
| Notes | Review author JJC, who is also the lead author of Jauncey-Cooke 2012a, provided data for all 12 neonatal participants (5 in the intervention arm; 7 in the routine care group). |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Study stated that allocation to groups and the order of LRMs was randomised; however, the method of random sequence generation was not described. |
| Allocation concealment (selection bias) | Low risk | Sequentially numbered, sealed, opaque envelopes were used. |
| Blinding (performance bias) | Unclear risk | Not addressed, but unlikely given the nature of the intervention and methods |

**Jauncey-Cooke 2012a** *(Continued)*

| | | |
|---|---|---|
| Blinding (detection bias) | Unclear risk | Not addressed, but unlikely given the nature of the intervention and methods |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | • Complete outcome data for all neonatal participants<br>• Complete outcome data for 58/60 participants in the published study (2 participants in the intervention arm were excluded due to failure to obtain arterial blood gases) |
| Selective reporting (reporting bias) | Low risk | There did not appear to be any major deviations from the protocol (Jauncey-Cooke 2012c). |
| Other bias | Low risk | Nil other sources of bias |

**Morrow 2007**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | • 2-arm parallel-group RCT conducted in the PICU of Red Cross War Memorial Children's Hospital in Cape Town, South Africa<br>• Study period: May 2003 to October 2004<br>• Allocation concealment via concealed, opaque envelopes selected by independent physiotherapists<br>• Successful blinding of outcome assessor |
| Participants | • Sample size: 48 paediatric patients with heterogenous lung pathology (24 in experimental group; 24 in control group)<br>• Inclusion criteria: mechanically ventilated with ETTs ≤ 4 mm internal diameter; primary or secondary pulmonary disease<br>• Exclusion criteria: any cardiac abnormality or disease, either congenital or acquired; raised ICP, or the potential to develop pathologically raised ICP (including patients with meningitis, post-head injuries, intracranial tumours, hydrocephalus etc.); haemodynamic instability for the preceding 24 hours (changes ≥ 20% in MAP, HR or $SaO_2$); an average baseline $O_2$ saturation of < 85%; a pneumothorax, or a history of pneumothorax; coagulopathy, with a platelet count < 100 x $10^9$ /L; post-thoracic surgery; preterm or small for GA<br>• All participants were supported with pressure-limited, time-cycled CMV with constant through-flow of gas (allowing spontaneous non-triggered breaths). |
| Interventions | • Participants randomised to either the experimental group or control group<br>• Five minutes after ETT suctioning, the experimental group received a LRM comprising a single sustained inflation pressure of 30 $cmH_2O$ applied for 30 seconds. The LRM was performed manually using a 1 L anaesthetic bag, with 10 L/min gas flow of 100% $O_2$, connected to a pressure manometer. Immediately after LRM application, the ventilator was reconnected on its original settings.<br>• The control group underwent ETT suctioning, but did not receive a LRM. |
| Outcomes | • Primary study question: (quote:) "does a recruitment manoeuvre after suctioning have any immediate or short-term effect on ventilation and gas exchange in mechanically-ventilated paediatric patients?"<br>• Outcomes: dynamic lung compliance; expiratory airway resistance; mechanical expired Vt; spontaneous expired Vt; RR; $SaO_2$ |
| Notes | This study included neonatal and paediatric participants. Correspondence with the lead author established that the neonatal data could not be isolated as it was no longer available. Hence, this study did not contribute data to the review. |
| ***Risk of bias*** | |

**Morrow 2007** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Study stated that enrolled participants were randomly assigned to groups; however, the method of random sequence generation was not described. |
| Allocation concealment (selection bias) | Low risk | Concealed, opaque envelopes were used and selected by independent physiotherapists. |
| Blinding (performance bias) | Low risk | The physiotherapists who performed the ETT suctioning and LRMs were not blinded to group allocation due to the nature of the intervention and methods; however, (quote:) "the approved protocol was followed for the duration of the study under observation of the Safety Monitoring Committee." Blinding of participants not addressed. |
| Blinding (detection bias) | Low risk | Successful blinding of outcome assessor |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Missing outcome data balanced in numbers across groups, with the same reason for missing data across groups (all participants completed the trial; however, 7 participants in each group with ETT leaks > 20% were excluded from the analysis) |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available |
| Other bias | Low risk | Nil other sources of bias |

**Wu 2014**

| ***Study characteristics*** | |
|---|---|
| Methods | • 2-arm parallel-group RCT conducted in the NICU of Huaian Maternity and Child Healthcare Hospital, China<br>• Study period not stated<br>• Allocation concealment via sequentially numbered, sealed, opaque envelopes<br>• Blinding of intervention or outcome ascertainment not addressed |
| Participants | • Sample size: 24 infants with severe RDS diagnosed based on clinical and radiologic findings (12 in LRM group; 12 in routine care group)<br>• Inclusion criteria: GA 28 to 30 weeks; BW 1000 to 1500 grams; ≥ 1 course of prenatal glucocorticoids; requirement for endotracheal intubation and CMV in the 1st 6 hours of life; written parental consent<br>• Exclusion criteria: lethal congenital abnormalities; severe IVH (> grade 2); weak or absent spontaneous breathing<br>• All participants received surfactant immediately after intubation and were supported with proportional assist ventilation. Starting parameters as follows: Vt = 4 to 6 mL/kg, PEEP = 5 $cmH_2O$, backup ventilation (SIMV mode) automatically initiated after 10 seconds without spontaneous breathing and suppressed with re-initiation of spontaneous breaths |
| Interventions | • Participants randomised to receive either a single LRM or no LRM (routine care)<br>• LRM consisted of a starting PEEP level of 5 $cmH_2O$, followed by application of repeated increments of 0.2 $cmH_2O$ of PEEP every 5 minutes while evaluating for improvements in oxygenation by monitoring $SpO_2$ levels (target: 85% to 93%) and $FiO_2$ requirement. PEEP level was progressively increased if oxygenation improved. When a $FiO_2$ of 0.25 was reached, a slow stepwise PEEP reduction was initiated. When oxygenation levels fell and $FiO_2$ administration consequently rose, the PEEP level was increased |

**Wu 2014** *(Continued)*

| | |
|---|---|
| | again until (quote:) "stable oxygenation was achieved and the $FiO_2$ level reached levels prior to the fall in oxygenation".<br>• Randomisation and intervention occurred within the (quote:) "second 2 h of life". |
| Outcomes | • Primary study outcome/objective: primary outcome not stated. Objective was to investigate effects of LRM with PEEP on (quote:) "oxygenation and outcomes".<br>• Outcomes: $FiO_2$ at the start of LRM; lowest $FiO_2$; time to the lowest $FiO_2$; PEEP at the start of LRM; maximum PEEP during LRM; final PEEP at the end of LRM; $a/AO_2$ ratio at the start of LRM; $a/AO_2$ ratio at the end of LRM; surfactant doses; extubation failure; length of respiratory support; length of tracheal intubation; PDA occurrence; sepsis; ROP grade > 2; moderate or severe BPD; mortality by hospital discharge; $O_2$ dependency |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Study stated that enrolled participants were randomly assigned to groups; however, the method of random sequence generation was not described. |
| Allocation concealment (selection bias) | Low risk | Sequentially numbered, sealed, opaque envelopes were used. |
| Blinding (performance bias) | Unclear risk | Not addressed, but unlikely given the nature of the intervention and methods |
| Blinding (detection bias) | Unclear risk | Not addressed, but unlikely given the nature of the intervention and methods |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Outcomes reported for all enrolled participants |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available |
| Other bias | Low risk | Nil other sources of bias |

$a/AO_2$: arterial/alveolar oxygen
BPD: bronchopulmonary dysplasia
BW: birth weight
CMV: conventional mechanical ventilation
$DaO_2$: oxygen delivery
EELV: end-expiratory lung volume
ETT: endotracheal tube
$FiO_2$: fraction of inspired oxygen
GA: gestational age
HR: heart rate
ICP: intracranial pressure
IVH: intraventricular haemorrhage
LRM: lung recruitment manoeuvre
MAP: mean arterial pressure
NICU: neonatal intensive care unit
$O_2$: oxygen
$PaCO_2$: partial pressure of carbon dioxide in arterial blood
$PaO_2$: partial pressure of oxygen in arterial blood

PDA: patent ductus arteriosus
PEEP: positive end-expiratory pressure
PICU: paediatric intensive care unit
PIP: peak inspiratory pressure
RCT: randomised controlled trial
RDS: respiratory distress syndrome
ROP: retinopathy of prematurity
RR: respiratory rate
$SaO_2$: arterial haemoglobin saturation of oxygen
SIMV: synchronised intermittent mechanical ventilation
$SpO_2$: peripheral oxygen saturation
Vt: tidal volume

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

| Study | Reason for exclusion |
|---|---|
| Aleksandrovich 2014 | Not a RCT |
| Kim 2010 | Researchers did not investigate the effect of a LRM compared to control (both groups received a LRM). |
| La Verde 2019 | Researchers did not investigate the effect of a LRM compared to control (both groups received a LRM). |
| NCT01114009 | Included non-neonatal participants (outside age range for inclusion in this review) |
| Rodríguez-Moya 2017 | Included non-neonatal participants (outside age range for inclusion in this review) |
| Song 2017 | Researchers included non-neonatal participants (outside age range for inclusion in this review) and did not report any of our prespecified outcome measures (study only reported lung ultrasound scores for consolidation and B-lines). |
| Vento 2021 | Participants were not intubated and mechanically ventilated at time of inclusion to the study (they were breathing independently with only nasal CPAP for respiratory support). |

CPAP: continuous positive airway pressure
LRM: lung recruitment manoeuvre
RCT: randomised controlled trial

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

**ACTRN12617000609358**

| | |
|---|---|
| Study name | Normal saline instillation and lung recruitment with paediatric endotracheal suction |
| Methods | • Single-centre pilot RCT<br>• Randomisation via computer-generated randomisation schedule<br>• Nil blinding due to nature of interventions and methods |
| Participants | • Sample size:<br>  ○ Target: 100<br>  ○ Final: 58<br>• Inclusion criteria: 0 (> 37 weeks' gestation) to 16 years of age (15 years + 364 days); oral or nasal ETT; CMV using volume control mode; likely to be ventilated for > 24 hours |

**ACTRN12617000609358** *(Continued)*

| | |
|---|---|
| | • Exclusion criteria: cardiac surgery in this admission; air leak syndrome; ventilated for > 48 hours prior to screening; previous study enrolment in this hospital admission; current diagnosis of VAP; tracheal reconstruction; CF; pulmonary hypoplasia; TBI or raised ICP |
| Interventions | • Group 1 (no NSI and no LRM): ETS will be performed by the PICU clinician as clinically indicated and as per standard practice. No NSI and no LRM is to be used.<br>• Group 2 (no NSI and LRM): ETS will be performed by the PICU clinician as clinically indicated and as per standard practice. No normal saline is to be instilled during the ETS episode. For LRM, at the completion of the ETS episode, the patient will be reconnected to the ventilator and the baseline PEEP setting will be doubled (to a maximum of 18 $cmH_2O$ for 2 minutes).<br>• Group 3 (NSI and no LRM): ETS will be performed by the PICU clinician as clinically indicated and as per standard practice. Upon disconnection of the patient from the ventilator, 0.1 mL/kg of normal saline will be instilled directly into the ETT before connecting the anaesthetic bag and proceeding with the ETS procedure. On completion of the ETS procedure, the patient will be reconnected to the ventilator. Ventilator settings will not change from baseline.<br>• Group 4 (NSI and LRM): ETS will be performed by the PICU clinician as clinically indicated and as per standard practice. Upon disconnection of the patient from the ventilator, 0.1 mL/kg of normal saline will be instilled directly into the ETT before connecting the anaesthetic bag and proceeding with the ETS procedure. For LRM, at the completion of the ETS episode, the patient will be reconnected to the ventilator and the baseline PEEP setting will be doubled (to a maximum of 18 $cmH_2O$) for 2 minutes. |
| Outcomes | • Primary outcome: feasibility<br>• Feasibility assessment will include:<br>  ◦ Eligibility: 75% of patients screened are eligible.<br>  ◦ Recruitment: 70% of eligible patients are recruited.<br>  ◦ Retention: less than 15% of patients withdraw or are lost to follow-up.<br>  ◦ Protocol adherence: 80% of participants will receive their allocated treatment throughout their study participation.<br>  ◦ Missing data: there will be less than 10% missing data.<br>• Secondary outcomes: $SpO_2/FiO_2$; lung compliance; VAP; EEL; regional Vt |
| Starting date | October 2017 |
| Contact information | Ms Jessica Schults<br>jessica.schults@health.qld.gov.au |
| Notes | • Recruitment status: completed<br>• No results posted |

**ChiCTR-INR-17013194**

| | |
|---|---|
| Study name | Lung protective ventilation strategy in infants undergoing congenital heart disease operation with cardiopulmonary bypass |
| Methods | Single-centre 3-arm parallel-group RCT |
| Participants | • Target sample size: 120<br>• Inclusion criteria: participants 0 to 1 years of age, undergoing a congenital heart disease operation through median sternotomy with cardiopulmonary bypass<br>• Exclusion criteria: participants' statutory guardians refuse to sign informed consent perioperatively; residual intracardiac shunt right to left diagnosed by TEE intraoperatively or by ECG postoperatively; left ventricular dysfunction (defined as LVEF < 50% diagnosed by ECG postoperatively); severe complications during protective lung ventilation intervention (defined as complica- |

**ChiCTR-INR-17013194** *(Continued)*

| | |
|---|---|
| | tions that cannot be relieved with the conventional dose of vasoactive agents or chest drainage, and last at least 3 minutes), including hypotension, bradycardia, arrhythmia, pneumothorax and pneumomediastinum |
| Interventions | • Group 1: small Vt ventilation<br>• Group 2: LRM using incremental PEEP<br>• Group 3: ventilation with optimal PEEP |
| Outcomes | • Primary outcome: $PaO_2/FiO_2$<br>• Secondary outcomes: Ppeak; lung compliance; $A\text{-}aDO_2$; $Pa\text{-}ETCO_2$ |
| Starting date | November 2017 |
| Contact information | Sun Yuan<br>sunyuan01@xinhuamed.com.cn |
| Notes | • Recruitment status: recruiting<br>• We attempted to contact the lead investigator to obtain an update on the status of the trial; however, we did not receive a reply. |

**NCT02584023**

| | |
|---|---|
| Study name | Lung ultrasound and alveolar recruitment in mechanically ventilated infants |
| Methods | • Single-centre 2-arm parallel-group RCT<br>• Blinding of participants only |
| Participants | • Sample size: 40<br>• Inclusion criteria: 0 to 1 years of age; minor surgery < 2 hours under general anaesthesia; mechanically ventilated after endotracheal intubation<br>• Exclusion criteria: history of lung surgery; laparoscopic surgery; abnormal preoperative chest radiograph findings including atelectasis, pneumothorax, pleural effusion, and pneumonia; considered inappropriate by the investigator |
| Interventions | • Alveolar recruitment arm: perform lung ultrasound twice during the perioperative period after the endotracheal intubation and at the end of surgery. Conduct alveolar RM after first lung ultrasound assessment<br>• Control arm: no intervention during the perioperative period. Perform lung ultrasound twice only for the diagnostic purpose after the endotracheal intubation and at the end of surgery |
| Outcomes | • Primary outcome: postoperative incidence of pulmonary atelectasis (time frame: within the 1st day after surgery)<br>• Secondary outcomes: intraoperative incidence of pulmonary atelectasis after intubation (time frame: from the moment of intubation until the end of surgery, up to 6 hours); intraoperative incidence of pulse oximetry ($SpO_2$) ≤ 95% (or 10% below the baseline value) (time frame: from the induction of general anaesthesia until the end of the surgery, up to 6 hours); postoperative incidence of pulse oximetry ($SpO_2$) ≤ 95% (or 10% below the baseline value) (time frame: within the 1st day after the surgery) |
| Starting date | October 2015 |
| Contact information | Jin-Tae Kim |

**NCT02584023** *(Continued)*

| | |
|---|---|
| | jintae73@snu.ac.kr |
| Notes | • Recruitment status: completed<br>• No results posted<br>• We attempted to contact the lead investigator to obtain an update on the status of the trial; however, we did not receive a reply. |

**NCT04289324**

| | |
|---|---|
| Study name | Open lung maneuvers during high frequency oscillatory ventilation in preterm infants (OPEN4H-FOV) |
| Methods | • Single-centre, 2-arm, parallel-group RCT<br>• Nil blinding due to nature of interventions and methods |
| Participants | • Target sample size: 36<br>• Inclusion criteria: preterm infants born below 28 weeks of gestational age; not older than 29 weeks of postmenstrual age; receiving HFOV<br>• Exclusion criteria: known congenital anomalies of the heart, of the lung, and/or of the CNS; known chromosomal abnormalities; participation in other intervention trials |
| Interventions | • Experimental group: stepwise oxygenation-guided LRM at regular (12 hour) intervals during HFOV<br>• Control group: no regular LRM during HFOV |
| Outcomes | • Primary outcome: HFOV oxygen saturation index (oxygen saturation index averaged over HFOV for not more than 7 consecutive days)<br>• Secondary outcomes: BPD (respiratory support at 36 weeks' postmenstrual age); days of ventilation (days on conventional and HFOV); overall oxygen saturation index (oxygen saturation index averaged over ventilation time) |
| Starting date | 25 February 2020 |
| Contact information | Tobias Werther<br>tobias.werther@meduniwien.ac.at |
| Notes | • Recruitment status: recruiting<br>• Estimated study completion date: 30 June 2022 |

$A\text{-}aDO_2$: alveolar-arterial oxygen gradient
BPD: bronchopulmonary dysplasia
CF: cystic fibrosis
CMV: conventional mechanical ventilation
CNS: central nervous system
ECG: electrocardiogram
EEL: end-expiratory level
ETS: endotracheal suction
ETT: endotracheal tube
$FiO_2$: fraction of inspired oxygen
HFOV: high frequency oscillatory ventilation
ICP: intracranial pressure
LRM: lung recruitment manoeuvre
LVEF: left ventricular ejection fraction
NSI: normal saline instillation
$Pa\text{-}ETCO_2$: end-tidal carbon dioxide

$PaO_2$: partial pressure of oxygen in arterial blood
PEEP: positive end-expiratory pressure
PICU: paediatric intensive care unit
Ppeak: peak inspiratory airway pressure
RCT: randomised controlled trial
RM: recruitment manoeuvre
$SpO_2$: peripheral oxygen saturation
TBI: traumatic brain injury
TEE: transoesophageal ultrasonic examination
VAP: ventilator associated pneumonia
Vt: tidal volume.

## DATA AND ANALYSES

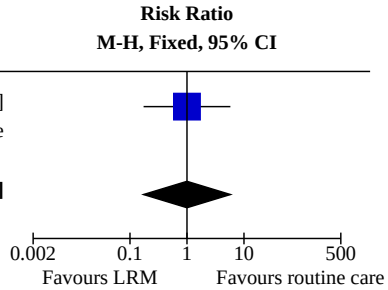
### Comparison 1. LRM with PEEP versus routine care in preterm infants requiring CMV for RDS

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.1 Mortality by hospital discharge | 2 | 44 | Risk Ratio (M-H, Fixed, 95% CI) | 1.00 [0.17, 5.77] |
| 1.2 Incidence of BPD | 2 | 44 | Risk Ratio (M-H, Fixed, 95% CI) | 0.25 [0.03, 2.07] |
| 1.3 Duration of supplemental oxygen | 2 | 44 | Mean Difference (IV, Random, 95% CI) | -7.52 [-20.83, 5.78] |
| 1.4 Duration of ventilatory support | 2 | 44 | Mean Difference (IV, Random, 95% CI) | -3.59 [-12.97, 5.79] |
| 1.5 Measure of oxygenation: $PaO_2$ at the end of the LRM | 1 | 20 | Mean Difference (IV, Fixed, 95% CI) | 13.00 [-1.46, 27.46] |

### Analysis 1.1. Comparison 1: LRM with PEEP versus routine care in preterm infants requiring CMV for RDS, Outcome 1: Mortality by hospital discharge

| Study or Subgroup | LRM Events | LRM Total | Routine care Events | Routine care Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Castoldi 2011 | 2 | 10 | 2 | 10 | 100.0% | 1.00 [0.17 , 5.77] |
| Wu 2014 | 0 | 12 | 0 | 12 | | Not estimable |
| **Total (95% CI)** | | **22** | | **22** | **100.0%** | **1.00 [0.17 , 5.77]** |
| Total events: | 2 | | 2 | | | |

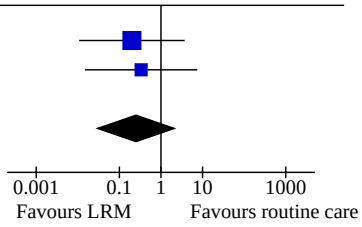
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



### Analysis 1.2. Comparison 1: LRM with PEEP versus routine care in preterm infants requiring CMV for RDS, Outcome 2: Incidence of BPD

| Study or Subgroup | LRM Events | LRM Total | Routine care Events | Routine care Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Castoldi 2011 | 0 | 10 | 2 | 10 | 62.5% | 0.20 [0.01 , 3.70] |
| Wu 2014 | 0 | 12 | 1 | 12 | 37.5% | 0.33 [0.01 , 7.45] |
| **Total (95% CI)** | | **22** | | **22** | **100.0%** | **0.25 [0.03 , 2.07]** |
| Total events: | 0 | | 3 | | | |

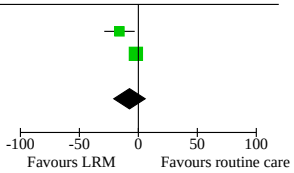
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: Not applicable




### Analysis 1.3. Comparison 1: LRM with PEEP versus routine care in preterm infants requiring CMV for RDS, Outcome 3: Duration of supplemental oxygen

| Study or Subgroup | LRM Mean [days] | LRM SD [days] | LRM Total | Routine care Mean [days] | Routine care SD [days] | Routine care Total | Weight | Mean Difference IV, Random, 95% CI [days] |
|---|---|---|---|---|---|---|---|---|
| Castoldi 2011 | 29 | 12 | 10 | 45 | 17 | 10 | 39.1% | -16.00 [-28.90 , -3.10] |
| Wu 2014 | 7.83 | 2.04 | 12 | 9.92 | 2.78 | 12 | 60.9% | -2.09 [-4.04 , -0.14] |
| **Total (95% CI)** | | | **22** | | | **22** | **100.0%** | **-7.52 [-20.83 , 5.78]** |

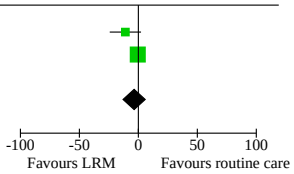
Heterogeneity: Tau² = 74.60; Chi² = 4.37, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Not applicable




### Analysis 1.4. Comparison 1: LRM with PEEP versus routine care in preterm infants requiring CMV for RDS, Outcome 4: Duration of ventilatory support

| Study or Subgroup | LRM Mean [days] | LRM SD [days] | LRM Total | Routine care Mean [days] | Routine care SD [days] | Routine care Total | Weight | Mean Difference IV, Random, 95% CI [days] |
|---|---|---|---|---|---|---|---|---|
| Castoldi 2011 | 24 | 13 | 10 | 35 | 17 | 10 | 29.5% | -11.00 [-24.26 , 2.26] |
| Wu 2014 | 5.6 | 1.4 | 12 | 6.1 | 2 | 12 | 70.5% | -0.50 [-1.88 , 0.88] |
| **Total (95% CI)** | | | **22** | | | **22** | **100.0%** | **-3.59 [-12.97 , 5.79]** |

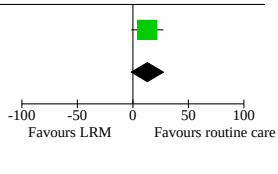
Heterogeneity: Tau² = 31.98; Chi² = 2.38, df = 1 (P = 0.12); I² = 58%
Test for overall effect: Z = 0.75 (P = 0.45)
Test for subgroup differences: Not applicable




### Analysis 1.5. Comparison 1: LRM with PEEP versus routine care in preterm infants requiring CMV for RDS, Outcome 5: Measure of oxygenation: $PaO_2$ at the end of the LRM

| Study or Subgroup | LRM Mean [mm Hg] | LRM SD [mm Hg] | LRM Total | Routine care Mean [mm Hg] | Routine care SD [mm Hg] | Routine care Total | Weight | Mean Difference IV, Fixed, 95% CI [mm Hg] |
|---|---|---|---|---|---|---|---|---|
| Castoldi 2011 | 79 | 20 | 10 | 66 | 12 | 10 | 100.0% | 13.00 [-1.46 , 27.46] |
| **Total (95% CI)** | | | **10** | | | **10** | **100.0%** | **13.00 [-1.46 , 27.46]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.76 (P = 0.08)
Test for subgroup differences: Not applicable



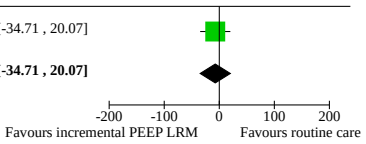
**Comparison 2. Incremental PEEP LRM post-suctioning versus routine care in mechanically ventilated neonates**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.1 Measure of oxygenation: $PaO_2$ at 120 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | -7.32 [-34.71, 20.07] |
| 2.2 Measure of oxygenation: $SpO_2$ at 30 minutes' and 120 minutes' post-suctioning | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 2.2.1 30 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | 0.00 [-5.23, 5.23] |
| 2.2.2 120 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | 0.00 [-2.85, 2.85] |
| 2.3 $PaCO_2$ at 120 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | -2.27 [-17.46, 12.92] |
| 2.4 HR at 30 minutes' and 120 minutes' post-suctioning | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 2.4.1 30 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | 7.00 [-23.29, 37.29] |
| 2.4.2 120 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | 14.00 [-13.33, 41.33] |
| 2.5 MAP at 30 minutes' and 120 minutes' post-suctioning | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 2.5.1 30 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | -5.00 [-22.28, 12.28] |
| 2.5.2 120 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | -7.00 [-18.65, 4.65] |
| 2.6 Change in EELV at 30 minutes' and 120 minutes' post-suctioning | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 2.6.1 30 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | 0.02 [-0.07, 0.11] |
| 2.6.2 120 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | -0.22 [-0.37, -0.06] |

## Analysis 2.1. Comparison 2: Incremental PEEP LRM post-suctioning versus routine care in mechanically ventilated neonates, Outcome 1: Measure of oxygenation: $PaO_2$ at 120 minutes' post-suctioning

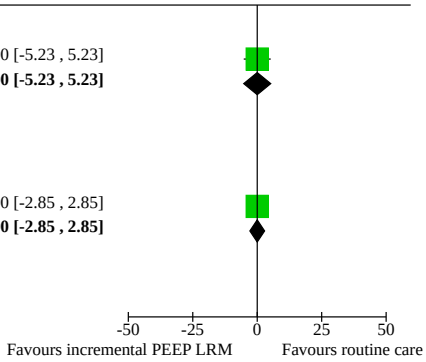
| Study or Subgroup | Incremental PEEP LRM Mean [mm Hg] | SD [mm Hg] | Total | Routine care Mean [mm Hg] | SD [mm Hg] | Total | Weight | Mean Difference IV, Fixed, 95% CI [mm Hg] |
|---|---|---|---|---|---|---|---|---|
| Jauncey-Cooke 2012a | 82.02 | 26.45 | 5 | 89.34 | 19.7 | 7 | 100.0% | -7.32 [-34.71 , 20.07] |
| **Total (95% CI)** | | | **5** | | | **7** | **100.0%** | **-7.32 [-34.71 , 20.07]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.60)
Test for subgroup differences: Not applicable




## Analysis 2.2. Comparison 2: Incremental PEEP LRM post-suctioning versus routine care in mechanically ventilated neonates, Outcome 2: Measure of oxygenation: $SpO_2$ at 30 minutes' and 120 minutes' post-suctioning

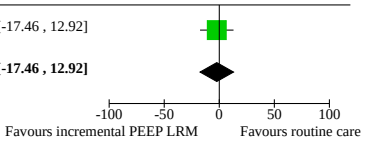
| Study or Subgroup | Incremental PEEP LRM Mean [%] | SD [%] | Total | Routine care Mean [%] | SD [%] | Total | Weight | Mean Difference IV, Fixed, 95% CI [%] |
|---|---|---|---|---|---|---|---|---|
| **2.2.1 30 minutes' post-suctioning** | | | | | | | | |
| Jauncey-Cooke 2012a | 95 | 3.96 | 5 | 95 | 5.28 | 7 | 100.0% | 0.00 [-5.23 , 5.23] |
| **Subtotal (95% CI)** | | | **5** | | | **7** | **100.0%** | **0.00 [-5.23 , 5.23]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.00 (P = 1.00) | | | | | | | | |
| **2.2.2 120 minutes' post-suctioning** | | | | | | | | |
| Jauncey-Cooke 2012a | 97 | 2.17 | 5 | 97 | 2.87 | 7 | 100.0% | 0.00 [-2.85 , 2.85] |
| **Subtotal (95% CI)** | | | **5** | | | **7** | **100.0%** | **0.00 [-2.85 , 2.85]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.00 (P = 1.00) | | | | | | | | |




## Analysis 2.3. Comparison 2: Incremental PEEP LRM post-suctioning versus routine care in mechanically ventilated neonates, Outcome 3: $PaCO_2$ at 120 minutes' post-suctioning

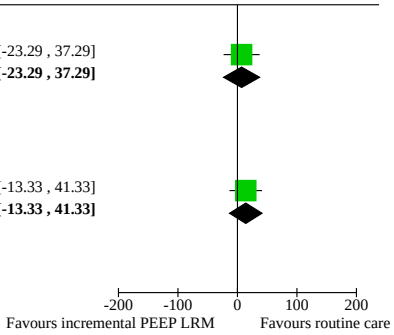
| Study or Subgroup | Incremental PEEP LRM Mean [mm Hg] | SD [mm Hg] | Total | Routine care Mean [mm Hg] | SD [mm Hg] | Total | Weight | Mean Difference IV, Fixed, 95% CI [mm Hg] |
|---|---|---|---|---|---|---|---|---|
| Jauncey-Cooke 2012a | 57 | 13.63 | 5 | 59.27 | 12.67 | 7 | 100.0% | -2.27 [-17.46 , 12.92] |
| **Total (95% CI)** | | | **5** | | | **7** | **100.0%** | **-2.27 [-17.46 , 12.92]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.29 (P = 0.77)
Test for subgroup differences: Not applicable



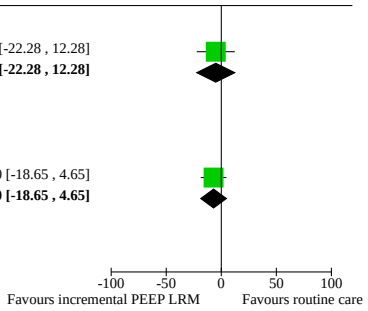
## Analysis 2.4. Comparison 2: Incremental PEEP LRM post-suctioning versus routine care in mechanically ventilated neonates, Outcome 4: HR at 30 minutes' and 120 minutes' post-suctioning

| Study or Subgroup | Incremental PEEP LRM Mean [bpm] | SD [bpm] | Total | Routine care Mean [bpm] | SD [bpm] | Total | Weight | Mean Difference IV, Fixed, 95% CI [bpm] |
|---|---|---|---|---|---|---|---|---|
| **2.4.1 30 minutes' post-suctioning** | | | | | | | | |
| Jauncey-Cooke 2012a | 129 | 27.16 | 5 | 122 | 25.29 | 7 | 100.0% | 7.00 [-23.29 , 37.29] |
| **Subtotal (95% CI)** | | | **5** | | | **7** | **100.0%** | **7.00 [-23.29 , 37.29]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.45 (P = 0.65) | | | | | | | | |
| **2.4.2 120 minutes' post-suctioning** | | | | | | | | |
| Jauncey-Cooke 2012a | 132 | 26.39 | 5 | 118 | 19.64 | 7 | 100.0% | 14.00 [-13.33 , 41.33] |
| **Subtotal (95% CI)** | | | **5** | | | **7** | **100.0%** | **14.00 [-13.33 , 41.33]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 1.00 (P = 0.32) | | | | | | | | |



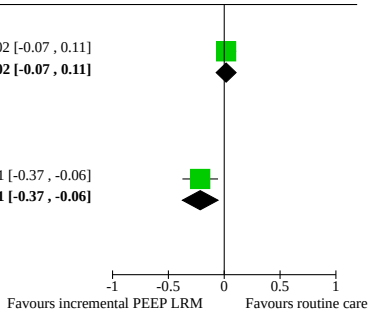

## Analysis 2.5. Comparison 2: Incremental PEEP LRM post-suctioning versus routine care in mechanically ventilated neonates, Outcome 5: MAP at 30 minutes' and 120 minutes' post-suctioning

| Study or Subgroup | Incremental PEEP LRM Mean [mm Hg] | SD [mm Hg] | Total | Routine care Mean [mm Hg] | SD [mm Hg] | Total | Weight | Mean Difference IV, Fixed, 95% CI [mm Hg] |
|---|---|---|---|---|---|---|---|---|
| **2.5.1 30 minutes' post-suctioning** | | | | | | | | |
| Jauncey-Cooke 2012a | 65 | 16.48 | 5 | 70 | 12.79 | 7 | 100.0% | -5.00 [-22.28 , 12.28] |
| **Subtotal (95% CI)** | | | **5** | | | **7** | **100.0%** | **-5.00 [-22.28 , 12.28]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.57 (P = 0.57) | | | | | | | | |
| **2.5.2 120 minutes' post-suctioning** | | | | | | | | |
| Jauncey-Cooke 2012a | 57 | 8.09 | 5 | 64 | 12.48 | 7 | 100.0% | -7.00 [-18.65 , 4.65] |
| **Subtotal (95% CI)** | | | **5** | | | **7** | **100.0%** | **-7.00 [-18.65 , 4.65]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 1.18 (P = 0.24) | | | | | | | | |




## Analysis 2.6. Comparison 2: Incremental PEEP LRM post-suctioning versus routine care in mechanically ventilated neonates, Outcome 6: Change in EELV at 30 minutes' and 120 minutes' post-suctioning

| Study or Subgroup | Incremental PEEP LRM Mean [delta Z] | SD [delta Z] | Total | Routine care Mean [delta Z] | SD [delta Z] | Total | Weight | Mean Difference IV, Fixed, 95% CI [delta Z] |
|---|---|---|---|---|---|---|---|---|
| **2.6.1 30 minutes' post-suctioning** | | | | | | | | |
| Jauncey-Cooke 2012a | 0.037 | 0.074 | 5 | 0.02 | 0.083 | 7 | 100.0% | 0.02 [-0.07 , 0.11] |
| **Subtotal (95% CI)** | | | **5** | | | **7** | **100.0%** | **0.02 [-0.07 , 0.11]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.37 (P = 0.71) | | | | | | | | |
| **2.6.2 120 minutes' post-suctioning** | | | | | | | | |
| Jauncey-Cooke 2012a | -0.038 | 0.019 | 5 | 0.177 | 0.214 | 7 | 100.0% | -0.21 [-0.37 , -0.06] |
| **Subtotal (95% CI)** | | | **5** | | | **7** | **100.0%** | **-0.21 [-0.37 , -0.06]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 2.64 (P = 0.008) | | | | | | | | |



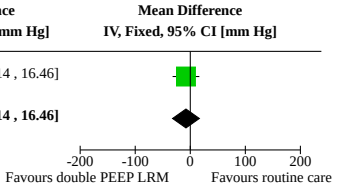
**Comparison 3. Double PEEP LRM post-suctioning versus routine care in mechanically ventilated neonates**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.1 Measure of oxygenation: $PaO_2$ at 120 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | -7.84 [-32.14, 16.46] |
| 3.2 Measure of oxygenation: $SpO_2$ at 30 minutes' and 120 minutes' post-suctioning | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 3.2.1 30 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | 2.00 [-2.56, 6.56] |
| 3.2.2 120 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | 0.00 [-2.93, 2.93] |
| 3.3 $PaCO_2$ at 120 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | -2.27 [-15.80, 11.26] |
| 3.4 HR at 30 minutes' and 120 minutes' post-suctioning | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 3.4.1 30 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | 4.00 [-22.75, 30.75] |
| 3.4.2 120 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | 3.00 [-16.75, 22.75] |
| 3.5 MAP at 30 minutes' and 120 minutes' post-suctioning | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 3.5.1 30 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | -16.00 [-29.35, -2.65] |
| 3.5.2 120 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | -3.00 [-21.05, 15.05] |
| 3.6 Change in EELV at 30 minutes' and 120 minutes' post-suctioning | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 3.6.1 30 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | -0.04 [-0.11, 0.04] |
| 3.6.2 120 minutes' post-suctioning | 1 | 12 | Mean Difference (IV, Fixed, 95% CI) | -0.18 [-0.35, -0.02] |

## Analysis 3.1. Comparison 3: Double PEEP LRM post-suctioning versus routine care in mechanically ventilated neonates, Outcome 1: Measure of oxygenation: $PaO_2$ at 120 minutes' post-suctioning

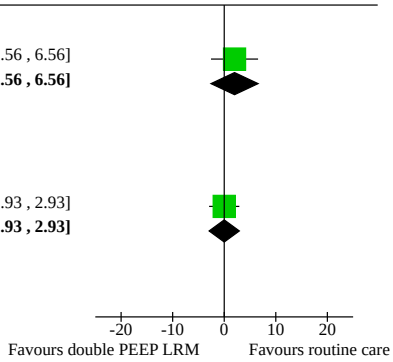
| Study or Subgroup | Double PEEP LRM Mean [mm Hg] | SD [mm Hg] | Total | Routine care Mean [mm Hg] | SD [mm Hg] | Total | Weight | Mean Difference IV, Fixed, 95% CI [mm Hg] |
|---|---|---|---|---|---|---|---|---|
| Jauncey-Cooke 2012a | 81.5 | 22.16 | 5 | 89.34 | 19.7 | 7 | 100.0% | -7.84 [-32.14 , 16.46] |
| **Total (95% CI)** | | | **5** | | | **7** | **100.0%** | **-7.84 [-32.14 , 16.46]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable




## Analysis 3.2. Comparison 3: Double PEEP LRM post-suctioning versus routine care in mechanically ventilated neonates, Outcome 2: Measure of oxygenation: $SpO_2$ at 30 minutes' and 120 minutes' post-suctioning

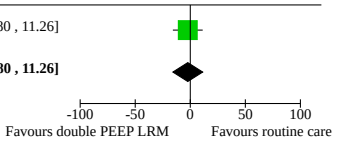
| Study or Subgroup | Double PEEP LRM Mean [%] | SD [%] | Total | Routine care Mean [%] | SD [%] | Total | Weight | Mean Difference IV, Fixed, 95% CI [%] |
|---|---|---|---|---|---|---|---|---|
| **3.2.1 30 minutes' post-suctioning** | | | | | | | | |
| Jauncey-Cooke 2012a | 97 | 2.68 | 5 | 95 | 5.28 | 7 | 100.0% | 2.00 [-2.56 , 6.56] |
| **Subtotal (95% CI)** | | | **5** | | | **7** | **100.0%** | **2.00 [-2.56 , 6.56]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.86 (P = 0.39) | | | | | | | | |
| **3.2.2 120 minutes' post-suctioning** | | | | | | | | |
| Jauncey-Cooke 2012a | 97 | 2.3 | 5 | 97 | 2.87 | 7 | 100.0% | 0.00 [-2.93 , 2.93] |
| **Subtotal (95% CI)** | | | **5** | | | **7** | **100.0%** | **0.00 [-2.93 , 2.93]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.00 (P = 1.00) | | | | | | | | |




## Analysis 3.3. Comparison 3: Double PEEP LRM post-suctioning versus routine care in mechanically ventilated neonates, Outcome 3: $PaCO_2$ at 120 minutes' post-suctioning

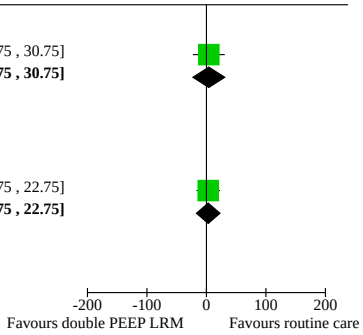
| Study or Subgroup | Double PEEP LRM Mean [mm Hg] | SD [mm Hg] | Total | Routine care Mean [mm Hg] | SD [mm Hg] | Total | Weight | Mean Difference IV, Fixed, 95% CI [mm Hg] |
|---|---|---|---|---|---|---|---|---|
| Jauncey-Cooke 2012a | 57 | 11.12 | 5 | 59.27 | 12.67 | 7 | 100.0% | -2.27 [-15.80 , 11.26] |
| **Total (95% CI)** | | | **5** | | | **7** | **100.0%** | **-2.27 [-15.80 , 11.26]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable



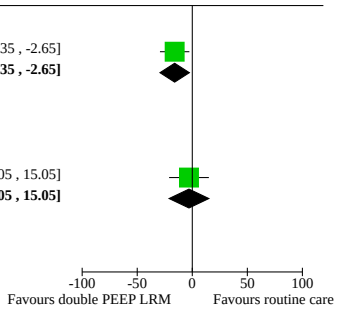
## Analysis 3.4. Comparison 3: Double PEEP LRM post-suctioning versus routine care in mechanically ventilated neonates, Outcome 4: HR at 30 minutes' and 120 minutes' post-suctioning

| Study or Subgroup | Double PEEP LRM Mean [bpm] | SD [bpm] | Total | Routine care Mean [bpm] | SD [bpm] | Total | Weight | Mean Difference IV, Fixed, 95% CI [bpm] |
|---|---|---|---|---|---|---|---|---|
| **3.4.1 30 minutes' post-suctioning** | | | | | | | | |
| Jauncey-Cooke 2012a | 126 | 21.79 | 5 | 122 | 25.29 | 7 | 100.0% | 4.00 [-22.75 , 30.75] |
| **Subtotal (95% CI)** | | | **5** | | | **7** | **100.0%** | **4.00 [-22.75 , 30.75]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.29 (P = 0.77) | | | | | | | | |
| **3.4.2 120 minutes' post-suctioning** | | | | | | | | |
| Jauncey-Cooke 2012a | 121 | 15.24 | 5 | 118 | 19.64 | 7 | 100.0% | 3.00 [-16.75 , 22.75] |
| **Subtotal (95% CI)** | | | **5** | | | **7** | **100.0%** | **3.00 [-16.75 , 22.75]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.30 (P = 0.77) | | | | | | | | |



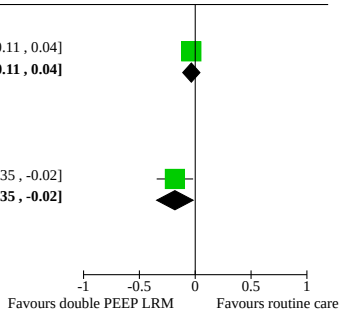

## Analysis 3.5. Comparison 3: Double PEEP LRM post-suctioning versus routine care in mechanically ventilated neonates, Outcome 5: MAP at 30 minutes' and 120 minutes' post-suctioning

| Study or Subgroup | Double PEEP LRM Mean [mm Hg] | SD [mm Hg] | Total | Routine care Mean [mm Hg] | SD [mm Hg] | Total | Weight | Mean Difference IV, Fixed, 95% CI [mm Hg] |
|---|---|---|---|---|---|---|---|---|
| **3.5.1 30 minutes' post-suctioning** | | | | | | | | |
| Jauncey-Cooke 2012a | 54 | 10.73 | 5 | 70 | 12.79 | 7 | 100.0% | -16.00 [-29.35 , -2.65] |
| **Subtotal (95% CI)** | | | **5** | | | **7** | **100.0%** | **-16.00 [-29.35 , -2.65]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 2.35 (P = 0.02) | | | | | | | | |
| **3.5.2 120 minutes' post-suctioning** | | | | | | | | |
| Jauncey-Cooke 2012a | 61 | 17.69 | 5 | 64 | 12.48 | 7 | 100.0% | -3.00 [-21.05 , 15.05] |
| **Subtotal (95% CI)** | | | **5** | | | **7** | **100.0%** | **-3.00 [-21.05 , 15.05]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.33 (P = 0.74) | | | | | | | | |




## Analysis 3.6. Comparison 3: Double PEEP LRM post-suctioning versus routine care in mechanically ventilated neonates, Outcome 6: Change in EELV at 30 minutes' and 120 minutes' post-suctioning

| Study or Subgroup | Double PEEP LRM Mean [delta Z] | SD [delta Z] | Total | Routine care Mean [delta Z] | SD [delta Z] | Total | Weight | Mean Difference IV, Fixed, 95% CI [delta Z] |
|---|---|---|---|---|---|---|---|---|
| **3.6.1 30 minutes' post-suctioning** | | | | | | | | |
| Jauncey-Cooke 2012a | -0.015 | 0.053 | 5 | 0.02 | 0.083 | 7 | 100.0% | -0.04 [-0.11 , 0.04] |
| **Subtotal (95% CI)** | | | **5** | | | **7** | **100.0%** | **-0.04 [-0.11 , 0.04]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.89 (P = 0.37) | | | | | | | | |
| **3.6.2 120 minutes' post-suctioning** | | | | | | | | |
| Jauncey-Cooke 2012a | -0.005 | 0.044 | 5 | 0.177 | 0.214 | 7 | 100.0% | -0.18 [-0.35 , -0.02] |
| **Subtotal (95% CI)** | | | **5** | | | **7** | **100.0%** | **-0.18 [-0.35 , -0.02]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 2.19 (P = 0.03) | | | | | | | | |



# APPENDICES

## Appendix 1. Review search strategy

The RCT filters have been created using Cochrane's highly sensitive search strategies for identifying randomised trials (Higgins 2019). The neonatal filters were created and tested by the Cochrane Neonatal Information Specialist.

**CENTRAL via CRS Web**

#1: MeSH descriptor: [Infant, Newborn] explode all trees

#2: infant or infants or infant's or "infant s" or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW or ELBW or NICU

#3: #1 OR #2

#4: "recruitment manoeuvre*" OR "recruitment maneuver*" OR "recruitment technique*"

#5: randomized controlled trial OR controlled clinical trial OR randomized OR randomised OR placebo OR randomly OR trial

#6: MeSH descriptor: [Clinical Trials as Topic] this term only

#7: (clinical trial):pt

#8: #5 OR #6 OR #7

#9: #3 AND #4 AND #8

**MEDLINE via Ovid**

1: exp infant, newborn/

2: (newborn* or new born or new borns or newly born or baby* or babies or premature or prematurity or preterm or pre term or low birth weight or low birthweight or VLBW or LBW or infant or infants or 'infant s' or infant's or infantile or infancy or neonat*).ti,ab.

3: 1 or 2

4: randomized controlled trial.pt.

5: controlled clinical trial.pt.

6: randomized.ab.

7: placebo.ab.

8: drug therapy.fs.

9: randomly.ab.

10: trial.ab.

11: groups.ab.

12: or/4-11

13: exp animals/ not humans.sh.

14: 12 not 13

15: 3 and 14

16: randomi?ed.ti,ab.

17: randomly.ti,ab.

18: trial.ti,ab.

19: groups.ti,ab.

20: ((single or doubl* or tripl* or treb*) and (blind* or mask*)).ti,ab.

21: placebo*.ti,ab.

22: 16 or 17 or 18 or 19 or 20 or 21

23: 2 and 22

24: limit 23 to yr="1946 -Current"

25: 15 or 24

26: (recruitment manoeuvre* or recruitment maneuver* or recruitment technique*).mp.

27: 25 and 26

**CINAHL via EBSCOhost**

S1: infant or infants or infant's or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW

S2: "recruitment manoeuvre*" OR "recruitment maneuver*" OR "recruitment technique*"

S3: randomized controlled trial OR controlled clinical trial OR randomized OR randomised OR placebo OR randomly OR trial

S4: (MH "Clinical Trials")

S5: PT clinical trial

S6: S3 OR S4 OR S5

S7: S1 AND S2 AND S6

## Appendix 2. Protocol search strategy

**CENTRAL via CRS Web**

#1 MeSH descriptor Positive-Pressure Respiration explode all trees
#2 MeSH descriptor Continuous Positive Airway Pressure explode all trees
#3 MeSH descriptor Intermittent Positive-Pressure Breathing explode all trees
#4 MeSH descriptor Respiration, Artificial, this term only
#5 recruit* near (manoeuv* or manouev* or manuev* or techniq* or airway*)
#6 ((artificial* or mechanical*) near (respirat* or ventilat*)):ti,ab
#7 (Positive pressure or (sustained near inflation)):ti,ab
#8 (recruitment or derecruitment or PEEP or CPAP):ti,ab
#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10 MeSH descriptor Lung Injury explode all trees
#11 MeSH descriptor Acute Lung Injury explode all trees
#12 MeSH descriptor Lung, this term only
#13 MeSH descriptor Respiratory Insufficiency explode all trees
#14 MeSH descriptor Respiratory Distress Syndrome, Adult explode all trees
#15 MeSH descriptor Respiratory Distress Syndrome, Newborn explode all trees
#16 MeSH descriptor Pulmonary Atelectasis explode all trees
#17 lung and (injur* or collaps* or consolidat*)
#18 (respirator* near distress):ti,ab
#19 (hypox?emia or hypoxic or oxygenation):ti,ab
#20 (#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21 (#9 AND #20)
#22 neonat* or infant* or pre-term

**MEDLINE via Ovid**

1. exp Positive-Pressure Respiration/ or exp Continuous Positive Airway Pressure/ or exp Intermittent Positive-Pressure Breathing/ or Respiration, Artificial/ or ((recruit* adj5 (manoeuv* or manouev* or manuev* or techniq* or airway*)) or ((artificial* or mechanical*) adj5 (respirat* or ventilat*))).mp. or (Positive pressure or (sustained adj3 inflation) or (recruitment or derecruitment or PEEP or CPAP)).ti,ab.

2. exp Lung Injury/ or exp Acute Lung Injury/ or exp Lung/ or exp Respiratory Insufficiency/ or exp Respiratory Distress Syndrome, Newborn/ or exp Respiratory Distress Syndrome, Adult/ or exp Pulmonary Atelectasis/ or ((lung adj4 (injur* or collaps* or consolidat*)) or (respirator* adj3 distress)).mp. or (hypox?emia or hypoxic or oxygenation).ti,ab.
3. 1 and 2
4. exp Pediatrics/ or exp Children/ or exp Child/ or exp Infant/ or exp Pre-term/ or exp Child, Preschool/ or (p?ediatric or infant* or child* or neonat*).mp.
5. exp Adult/ or adult*.mp.
6. 5 not (4 and 5)
7. 3 not (6 or pre?term.mp.)
8. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
9. 8 and 7

**Embase**

1. exp positive end expiratory pressure/ or artificial ventilation/ or exp positive end expiratory pressure/ or exp intermittent positive pressure ventilation/ or ((recruit* adj5 (manoeuv* or manouev* or manuev* or techniq* or airway*)) or ((artificial* or mechanical*) adj5 (respirat* or ventilat*))).mp. or (Positive pressure or (sustained adj3 inflation) or (recruitment or derecruitment or PEEP or CPAP)).ti,ab.
2. exp acute lung injury/ or exp lung injury/ or exp lung/ or exp lung collapse/ or exp respiratory failure/ or exp respiratory distress syndrome/ or exp atelectasis/ or piratory Distress Syndrome, Newborn/ or exp Respiratory Distress Syndrome, Adult/ or exp Pulmonary Atelectasis/ or ((lung adj4 (injur* or collaps* or consolidat*)) or (respirator* adj3 distress)).mp. or (hypox?emia or hypoxic or oxygenation).ti,ab.
3. 1 and 2
4. exp pediatrics/ or exp adult child/ or exp child/ or exp infant/ or exp adolescent/ or (p?ediatric or infant* or child* or adoles* or teenage* or neonat*).mp.
5. exp adult/ or adult*.mp.
6. 5 not (4 and 5)
7. 3 not (6 or pre?term.mp.)
8. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab.) not (animals not (humans and animals)).sh.
9. 7 and 8

**CINAHL via EBSCOhost**

S1 (MM "Positive-Pressure Respiration, Intrinsic") or (MH "Positive Pressure Ventilation+") or (MM "Continuous Positive Airway Pressure") or (MH "Intermittent Positive Pressure Breathing") or (MM "Intermittent Positive Pressure Ventilation") or (MM "Positive End-Expiratory Pressure")
S2 TX recruit* and (manoeuv* or manouev* or manuev* or techniq* or airway*)
S3 TX (artificial* or mechanical*) and (respirat* or ventilat*)
S4 S1 or S2 or S3
S5 (MM "Atelectasis") or (MH "Respiratory Distress Syndrome+") or (MH "Respiratory Failure+") or (MH "Lung+")
S6 TX lung and (injur* or collaps* or consolidat*)
S7 TX (respirator* and distress)
S8 TI ( hypox?emia or hypoxic or oxygenation ) or AB ( hypox?emia or hypoxic or oxygenation )
S9 S5 or S6 or S7 or S8
S10 S4 and S9
S11 TX p?ediatric or infant* or child* or adoles* or teenage* or neonat*
S12 S10 and S11
S13 TX random* or trial*
S14 (MH "Random Assignment") or (MH "Clinical Trials+") or (MM "Double-Blind Studies") or (MM "Single-Blind Studies") or (MM "Triple-Blind Studies") or (MM "Placebos") or (MM "Multicenter Studies")
S15 S13 or S14
S16 S12 and S15

**LILACS**

((‘recruit$ or derecruit$” or “respiration, artificial” or “positive pressure ventil$”)) and (“oxygenation” or “hypoxic” or “hypoxemia”) or “atelecta$” or “alveoli$ collapse” or “alveolar consoled$” or “lung injury” or “respiratory distress syndrome” and (“paediatric” or “pediatric” or “child$” or pre-term$")

## Appendix 3. 'Risk of bias' tool

**Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?**

For each included study, we categorised the method used to generate the allocation sequence as:

- low risk (any truly random process, e.g. random number table, computer random number generator);
- high risk (any non-random process, e.g. odd or even date of birth, hospital or clinic record number); or
- unclear risk.

**Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?**

For each included study, we categorised the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomisation, consecutively numbered sealed opaque envelopes);
- high risk (open random allocation, unsealed or non-opaque envelopes, alternation, date of birth); or
- unclear risk.

**Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?**

For each included study, we categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk, high risk or unclear risk for participants; and
- low risk, high risk or unclear risk for personnel.

**Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?**

For each included study, we categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

**Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?**

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised the methods as:

- low risk (< 20% missing data);
- high risk (≥ 20% missing data); or
- unclear risk

**Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?**

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we compared prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we contacted study authors to gain access to the study protocol. We assessed the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

**Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?**

For each included study, we described any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

- low risk;

- high risk; or
- unclear risk.

If needed, we explored the impact of the level of bias by undertaking sensitivity analyses.

## HISTORY

Protocol first published: Issue 7, 2012
Review first published: Issue 3, 2021

## CONTRIBUTIONS OF AUTHORS

EB was responsible for undertaking the database searches, organising retrieval of studies, screening retrieved studies against eligibility criteria, extracting data from included studies, evaluating risk of bias in included studies, assessing the certainty of the evidence, managing data for the review, entering review data into RevMan Web, analysing data, interpreting data, corresponding with study authors, and primary writing and editing of the review.

CE was responsible for co-authoring the original protocol (Jauncey-Cooke 2012b), and editing the review.

JJC was responsible for conceiving the review, and writing the original protocol (Jauncey-Cooke 2012b).

FB was responsible for co-authoring the original protocol (Jauncey-Cooke 2012b), confirming data and editing the review.

CG was responsible for co-authoring the original protocol (Jauncey-Cooke 2012b), and editing the review.

JH was responsible for screening retrieved studies against eligibility criteria, extracting data from included studies, evaluating risk of bias in included studies, assessing the certainty of the evidence, analysing data, interpreting data, corresponding with study authors, and editing the review.

## DECLARATIONS OF INTEREST

EB has no interest to declare.

CE is an author of one of the included studies (Jauncey-Cooke 2012a). She was not involved in data extraction or interpretation in this review.

JJC is the lead author of one of the included studies (Jauncey-Cooke 2012a). She was not involved in data extraction or interpretation in this review.

FB is an author of one of the included studies (Jauncey-Cooke 2012a). She was not involved in data extraction or interpretation in this review.

CG is an author of one of the included studies (Jauncey-Cooke 2012a). She was not involved in data extraction or interpretation in this review.

JH has no interest to declare.

## SOURCES OF SUPPORT

### Internal sources

- No sources of support supplied

### External sources

- Vermont Oxford Network, USA

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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- The Background of the review was slightly modified from the protocol (Jauncey-Cooke 2012b), to include updated literature.
- We updated our eligibility criteria to include cluster-RCTs and data available only in conference abstract form.
- Also within our eligibility criteria, we converted the following secondary outcomes from dichotomous to continuous outcomes so that they aligned with those typically included and reported in contemporary neonatal trials: measures of oxygenation, $PaCO_2$, HR, and BP.

- Our search strategy was updated to be in accordance with the standard search strategy of Cochrane Neonatal.
  - As of July 2019, Cochrane Neonatal no longer searches Embase for its reviews. RCTs and controlled clinical trials (CCTs) from Embase are added to the Cochrane Central Register of Controlled Trials (CENTRAL) via a robust process (see How CENTRAL is created). Cochrane Neonatal has validated their searches to ensure that relevant Embase records are found while searching CENTRAL.
  - Also as of July 2019, Cochrane Neonatal no longer searches for RCTs and CCTs on the following platforms: ClinicalTrials.gov or The WHO ICTRP, as records from both platforms are added to CENTRAL on a monthly basis (see How CENTRAL is created). Comprehensive search strategies are executed in CENTRAL to retrieve relevant records. The ISRCTN (at www.isrctn.com/, formerly Controlled-trials.com), is searched separately.
- We updated the Selection of studies section to include the use of Covidence to facilitate screening of retrieved studies.
- We included a PRISMA flow diagram to illustrate the study selection process, and also a Summary of findings 1, both of which were not discussed in the original protocol (Jauncey-Cooke 2012b).
- In keeping with current Cochrane guidelines, we incorporated the use of the GRADE approach to assess the certainty of the evidence for primary outcomes, and decided to only conduct subgroup and sensitivity analyses on primary outcomes (not secondary outcomes), if appropriate.
- A/Prof Kristen Gibbons and Prof Mark Davies were credited as authors of our protocol (Jauncey-Cooke 2012b); however, they were not involved in the subsequent review process.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Bias; Bronchopulmonary Dysplasia [*epidemiology]; Confidence Intervals; Incidence; Infant, Premature; Oxygen [administration & dosage]; Positive-Pressure Respiration [adverse effects] [methods]; Respiration, Artificial [*adverse effects] [methods] [statistics & numerical data]; Respiratory Distress Syndrome, Newborn [*therapy]; Ventilator-Induced Lung Injury [*mortality] [prevention & control]

### MeSH check words

Humans; Infant, Newborn