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[Intervention Review]

Surfactant therapy for bronchiolitis in critically ill infants

Kana R Jat¹, Deepak Chawla²¹Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India. ²Department of Pediatrics, Government Medical College and Hospital, Chandigarh, India**Contact address:** Kana R Jat, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, Delhi, 110029, India. drkanaram@gmail.com.**Editorial group:** Cochrane Acute Respiratory Infections Group.**Publication status and date:** New search for studies and content updated (no change to conclusions), published in Issue 8, 2015.**Citation:** Jat KR, Chawla D. Surfactant therapy for bronchiolitis in critically ill infants. *Cochrane Database of Systematic Reviews* 2015, Issue 8. Art. No.: CD009194. DOI: [10.1002/14651858.CD009194.pub3](https://doi.org/10.1002/14651858.CD009194.pub3).

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ABSTRACT

Background

Bronchiolitis is one of the most frequent causes of respiratory failure in infants; some infants will require intensive care and mechanical ventilation. There is lack of evidence regarding effective treatment for bronchiolitis other than supportive care. Abnormalities of surfactant quantity or quality (or both) have been observed in severe cases of bronchiolitis. Exogenous surfactant administration appears to favourably change the haemodynamics of the lungs and may be a potentially promising therapy for severe bronchiolitis. This is an update of a review published in Issue 9, 2012. We did not identify any new studies for inclusion, and our conclusions remain unchanged.

Objectives

To evaluate the efficacy of exogenous surfactant administration (i.e. intratracheal administration of surfactant of any type (whether animal-derived or synthetic), at any dose and at any time after start of ventilation) compared to placebo, no intervention or standard care in reducing mortality and the duration of ventilation in infants and children with bronchiolitis requiring mechanical ventilation.

Search methods

We searched the Cochrane Central Register of Controlled Studies (CENTRAL; 2015, Issue 5) which contains the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (1948 to June week 3, 2015); EMBASE (1974 to June 2015); CINAHL (1982 to June 2015); LILACS (1985 to June 2015); and Web of Science (1985 to June 2015).

Selection criteria

We considered prospective, randomised controlled trials (RCTs) and quasi-RCTs evaluating the effect of exogenous surfactant in infants and children with bronchiolitis requiring mechanical ventilation.

Data collection and analysis

Two review authors selected studies independently. We extracted the data using a predefined proforma, independently analysed the data, and performed meta-analyses.

Main results

We included three small RCTs enrolling 79 participants. Two trials did not use a placebo in the control arms and the third trial used air placebo. Two included studies reported no mortality. We judged all three of the included studies to be at low risk or unclear risk across all risk of bias categories; we did not judge any of the studies to be at high risk of bias in any category. Our pooled analysis of the three trials revealed that duration of mechanical ventilation was not significantly different between the groups (mean difference (MD) -63.04, 95% confidence interval (CI) -130.43 to 4.35 hours) but duration of intensive care unit (ICU) stay was less in the surfactant group compared to the control group: MD -3.31, 95% CI -6.38 to -0.25 days. After excluding one trial which produced significant heterogeneity, the duration of

mechanical ventilation and duration of ICU stay were significantly lower in the surfactant group compared to the control group: MD -28.99, 95% CI -40.10 to -17.87 hours; and MD -1.81, 95% CI -2.42 to -1.19 days, respectively. Use of surfactant had favourable effects on oxygenation and CO₂ elimination. No adverse effects and no complications were observed in any of the three included studies. The level of evidence for duration of mechanical ventilation, duration of intensive care unit stay, oxygenation parameters, and carbon dioxide parameters was of moderate quality.

Authors' conclusions

Use of surfactant had favourable effects on duration of mechanical ventilation, duration of ICU stay, oxygenation, and CO₂ elimination. However, the studies are few and small (n = 79) so available evidence is insufficient to establish the effectiveness of surfactant therapy for bronchiolitis in critically ill infants who require mechanical ventilation. There is a need for larger trials with adequate power and a cost-effectiveness analysis to evaluate the effectiveness of exogenous surfactant therapy for infants with bronchiolitis who require intensive care management.

PLAIN LANGUAGE SUMMARY

Usefulness of surfactant for bronchiolitis in seriously ill infants and children

Review question

Will use of exogenous surfactant (a material made of lipid and protein that is produced by the lungs) in infants and children with bronchiolitis, who require mechanical ventilation, decrease mortality and duration of mechanical ventilation?

Background

Bronchiolitis (infection of small airways in the lungs) is one of the most common causes of respiratory failure in infants. There are no established treatment options for bronchiolitis. Surfactant may be useful in bronchiolitis because of its favourable effect on lung mechanics. We wanted to evaluate the efficacy of exogenous surfactant in reducing mortality and the duration of ventilation in infants and children with bronchiolitis, requiring mechanical ventilation.

Study characteristics

The evidence is current to June 2015. Three small randomised controlled trials (RCTs) enrolling 79 participants were included in the review. All studies included children younger than 2.5 years with a diagnosis of bronchiolitis who required mechanical ventilation. Two studies did not include a placebo (a substance having no active effect) for comparison. None of the included studies provided a source of funding.

Key results

Two included studies reported no mortality. Use of surfactant for mechanically ventilated infants and children with bronchiolitis did not decrease the duration of mechanical ventilation. However, the intervention decreased duration of stay in the intensive care unit and had favourable effects on oxygenation and carbon dioxide removal. No complications were observed in any of the three included studies.

Quality of the evidence

The level of evidence for duration of mechanical ventilation, duration of intensive care unit stay, oxygenation parameters, and carbon dioxide parameters was of moderate quality. The limited number of studies with small numbers of participants was the reason for moderate quality, and are limitations of this review. There is a need for larger trials to establish any benefits of surfactant for bronchiolitis in critically ill infants and children.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Surfactant for critically ill infants with bronchiolitis

Surfactant for critically ill infants with bronchiolitis

Patient or population: critically ill infants with bronchiolitis

Settings: intensive care unit

Intervention: surfactant

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Surfactant				
Duration of mechanical ventilation (hours)	The mean duration of mechanical ventilation (hours) in the control groups was 170 to 213.6 ¹	The mean duration of mechanical ventilation (hours) in the intervention groups was 63.04 lower (130.43 lower to 4.35 higher)		79 (3 studies)	⊕⊕⊕⊖ moderate ²	Duration of mechanical ventilation was highest among controls in Luchetti 1998 where blinding was not mentioned
Duration of ICU stay (days)	The mean duration of ICU stay (days) in the control group was 8.2 to 15.7 days ¹	The mean duration of ICU stay (days) in the intervention groups was 3.31 lower (6.38 to 0.25 lower)		79 (3 studies)	⊕⊕⊕⊖ moderate ²	Duration of ICU stay was highest among controls in Luchetti 1998 where blinding was not mentioned
PO₂/FiO₂ ratio at 12 hours	The mean PO₂/FiO₂ ratio at 12 hours in the control group was 140 to 148.1 ³	The mean PO₂/FiO₂ ratio at 12 hours in the intervention groups was 99.08 higher (57.43 to 140.72 higher)		60 (2 studies)	⊕⊕⊕⊖ moderate ²	SD was not available for Luchetti 2002; it was imported from Luchetti 1998

PO₂/FiO₂ ratio at 24 hours	The mean PO₂/FiO₂ ratio at 24 hours in the control group was 136 to 145.9 ³	The mean PO₂/FiO₂ ratio at 24 hours in the intervention group was 109.64 higher (63.29 to 155.99 higher)	60 (2 studies)	⊕⊕⊕⊕ moderate ²	SD was not available for Luchetti 2002; it was imported from Luchetti 1998
PCO₂ at 12 hours (mmHg)	The mean PCO₂ at 12 hours (mmHg) in the control group was 42.2 to 45 mmHg ³	The mean PCO₂ at 12 hours (mmHg) in the intervention group was 7.63 lower (8.99 to 6.28 lower)	60 (2 studies)	⊕⊕⊕⊕ moderate ²	SD was not available for Luchetti 2002; it was imported from Luchetti 1998
PCO₂ at 24 hours (mmHg)	The mean PCO₂ at 24 hours (mmHg) in the control group was 42.6 to 45 mmHg ³	The mean PCO₂ at 24 hours (mmHg) in the intervention group was 7.9 lower (9.42 to 6.38 lower)	60 (2 studies)	⊕⊕⊕⊕ moderate ²	SD was not available for Luchetti 2002; it was imported from Luchetti 1998

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Range of means in control groups in all three studies.

²Total number of participants is less than 400.

³Range of means in control groups from two studies.

CI: confidence interval

GRADE: Grading of Recommendations: Assessment, Development and Evaluation

ICU: intensive care unit

PO₂/FiO₂ ratio: ratio of partial pressure of arterial oxygen and fractional inspired oxygen

SD: standard deviation

PCO₂: partial pressure of arterial carbon dioxide

BACKGROUND

Description of the condition

Bronchiolitis is one of the most frequent causes of respiratory failure in infants and yet no effective therapy is available except for supportive care. Acute bronchiolitis (inflammation of the small airways in the lung) is predominantly a viral disease and respiratory syncytial virus (RSV) is the most common cause (CDC 2010). Bronchiolitis is more common in non-breast fed male infants and in those living in crowded conditions (Meates-Dennis 2005). In the USA, approximately 2% to 3% of all infants in the first 12 months of life are hospitalised (more than 125,000 hospitalisations annually) because of an RSV infection (Meissner 2009). From 1979 to 1997 there were 1806 (annual mean 95 deaths; range 66 to 127) bronchiolitis-associated deaths in the USA (Shay 2001). Risk factors for severe morbidity and mortality in bronchiolitis are: low and very low birth weight infants, prematurity, chronic pulmonary disease (most often bronchopulmonary dysplasia), congenital heart disease, immune deficiency, increasing birth order, low five-minute Apgar score, young maternal age, unmarried mother and tobacco use during pregnancy (Holman 2003; Navas 1992). Primary RSV infection occurs later in infants from higher socioeconomic groups and there is less risk of developing severe disease in these infants (Handforth 2000).

Clinical features of bronchiolitis begin as sneezing, rhinorrhoea and fever. It may then gradually progress to paroxysmal wheezy cough, respiratory distress and irritability. A physical examination will find wheezing, with or without fine crackles. Chest X-ray usually reveals hyperinflated lungs with patchy atelectasis. The diagnosis of bronchiolitis is clinical, particularly in a previously healthy infant presenting with first-time viral symptoms and wheezing. About 10% to 15% of infants and children hospitalised with bronchiolitis require intensive care for worsening respiratory distress and about half of these develop respiratory failure, requiring mechanical ventilation (Navas 1992). The case-fatality rate is usually 0.5% to 1.5% in high-income countries and causes may be apnoea, respiratory failure or severe dehydration (Levy 1997). There was a declining trend in post-neonatal mortality rate due to bronchiolitis in the UK, where figures fell from 21.47 per 100,000 in 1979 to 1.82 per 100,000 live births in 2000 (Panickar 2005). There are limited epidemiological data from low-income countries. A study from Bangladesh (Kabir 2003) reported a mortality rate of 2% in children admitted to hospital with a diagnosis of bronchiolitis.

Description of the intervention

The mainstay of bronchiolitis treatment is supportive measures, such as adequate fluid intake, antipyretics and oxygen supplement if necessary. Humidified oxygen is indicated for hospitalised infants with hypoxia (Davison 2004). Many therapeutic interventions other than supportive measures have been used to treat bronchiolitis but their effectiveness is not well documented.

Hypertonic nebulised saline may have a role in the management of bronchiolitis (Zhang 2013). In a recent review, nebulised adrenaline has been shown to be beneficial in acute bronchiolitis (Hartling 2011a; Hartling 2011b). Other adjunctive therapies for bronchiolitis, for example, bronchodilators (Gadomski 2014), heliox inhalation therapy (Liet 2010), chest physiotherapy (Roqué i Figuls 2012), nebulised recombinant human deoxyribonuclease (Mercus 2001;

Nasr 2001) and steam inhalation (Umoren 2011) have no definitive role in the management of bronchiolitis.

Corticosteroids (Fernandes 2013) and antibiotics (Farley 2014) are usually not recommended for bronchiolitis. Ribavirin, an antiviral agent administered by aerosol, has no clear beneficial effect in bronchiolitis caused by RSV (Ventre 2007). There is no support for RSV immunoglobulin administration during acute episodes of RSV bronchiolitis (Davison 2004). Palivizumab, an intramuscular monoclonal antibody to the RSV F protein, is recommended for infants younger than two years of age with chronic lung disease (bronchopulmonary dysplasia), prematurity or symptomatic congenital heart disease, before and during the RSV season, to reduce the severity and incidence of acute bronchiolitis due to RSV (Meissner 2009).

Pulmonary surfactant is a highly surface active (preventing alveolar collapse) lipoprotein complex that is synthesised and secreted by type II alveolar cells and the airway Clara cell (Goerke 1998). A natural surfactant contains about 80% phospholipids (mainly dipalmitoylphosphatidylcholine), 8% neutral lipids and 12% proteins (Wood 1993). There are four types of surfactant-associated proteins: SP-A, SP-B, SP-C and SP-D (Griese 1999). Pulmonary surfactants reduce surface tension at the air-liquid interface of the lung and prevent alveolar collapse (Possmayer 1990). There are two types of surfactants available for clinical use: animal surfactants (for example, beractant and poractant) and synthetic surfactants (for example, colfosceril palmitate) (Logan 2009; Ramanathan 2009; Appendix 1). Surfactants (especially SP-A and SP-D) also have some immunological functions and protect the lungs from injuries and infections caused by inhaled particles and micro-organisms (Wright 2003). A genetic association has been reported between SP-A (Löfgren 2002) and SP-D (Lahti 2002) gene locus and severe RSV infection. Use of exogenous surfactants in preterm babies with respiratory distress syndrome (RDS)/hyaline membrane disease (HMD) has been extensively studied and is now the standard management for this condition (Ardell 2015; Seger 2009; Soll 1998).

How the intervention might work

Dargaville 1996 reported deficiency of SP-A and disaturated phosphatidylcholine and impaired surfactant functional activity during acute viral bronchiolitis that resolved as the disease improved. In another study, severe viral bronchiolitis requiring mechanical ventilation was associated with an absence of surfactant activity and phosphatidylglycerol which resolved by clinical recovery (Skelton 1999). These abnormalities may represent one of the pathophysiological mechanisms causing airway obstruction in acute bronchiolitis. Barr 2000 revealed that SP-A enhanced binding and uptake of RSV by peripheral blood monocytes and U937 macrophages (a human macrophage cell line known to express SP-A receptors) and, further, the SP-A mediated uptake of RSV reversed the effects of RSV on TNF-alpha and IL-10 production by both monocytes and U937 macrophages). These findings suggest that RSV clearance from the human lung may be enhanced by SP-A.

Why it is important to do this review

Acute bronchiolitis is one of the most frequent causes of hospitalisation in infants. A few of those affected require intensive care and mechanical ventilation. However, no effective treatment

is available, except for supportive therapy. Abnormalities of surfactant have been observed in severe cases of bronchiolitis; exogenous surfactant administration appears to favourably change the haemodynamics of the lungs and may be a promising therapy for severe bronchiolitis.

OBJECTIVES

To evaluate the efficacy of exogenous surfactant administration (i.e. intratracheal administration of surfactant of any type (whether animal-derived or synthetic), at any dose and at any time after start of ventilation) compared to placebo, no intervention or standard care in reducing mortality and the duration of ventilation in infants and children with bronchiolitis requiring mechanical ventilation.

METHODS

Criteria for considering studies for this review

Types of studies

Prospective, randomised controlled trials (RCTs) and quasi-RCTs evaluating the effect of exogenous surfactant in infants and children with bronchiolitis, requiring mechanical ventilation.

Types of participants

Infants and children (0 to 60 months of age) in an intensive care unit (ICU) with a diagnosis of bronchiolitis, requiring mechanical ventilation. There is no standard diagnostic criteria for bronchiolitis; diagnosis is usually clinical. We included studies of children with a diagnosis of bronchiolitis.

Types of interventions

Comparison of exogenous surfactant with placebo, no intervention or standard care (humidified oxygen or adrenaline nebulisation, or both). We included intratracheal administration of surfactant of any type (for example, animal-derived or synthetic), at any dose and at any time after start of ventilation.

Types of outcome measures

Primary outcomes

1. Mortality.
2. Duration of mechanical ventilation (hours).
3. Adverse effects (desaturation, change in heart rate, change in blood pressure and bronchospasm) or complications (pneumothorax) or both.

Secondary outcomes

1. Duration of ICU stay.
2. Duration of hospital stay.
3. Gas exchange [effects on oxygenation (pO_2/FiO_2 ratio) and CO_2 elimination (pCO_2)].
4. Respiratory mechanics (effects on pulmonary compliance and airways resistance).

5. Recurrent lower respiratory tract disease.

Search methods for identification of studies

Electronic searches

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 5) which contains the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (January 2012 to June week 3, 2015); EMBASE (January 2012 to June 2015); CINAHL (January 2012 to June 2015); LILACS (2011 to June 2015); and Web of Science (2012 to June 2015).

Previously we searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2012, Issue 4) which contains the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (1948 to May week 1, 2012); EMBASE (1974 to May 2012); CINAHL (1982 to May 2012); LILACS (1985 to May 2012); and Web of Science (1985 to May 2012).

We used the search strategy in [Appendix 2](#) to search CENTRAL and MEDLINE. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format ([Lefebvre 2011](#)). We adapted the search strategy to search EMBASE ([Appendix 3](#)), CINAHL ([Appendix 4](#)), LILACS ([Appendix 5](#)), and Web of Science ([Appendix 6](#)). We imposed no language or publication restrictions. We excluded non-RCTs.

Searching other resources

We searched ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (<http://apps.who.int/trialsearch/>) for completed and ongoing trials. We ran the latest search on 25 June 2015.

One review author (KRJ) contacted experts in the field to determine if they knew of any additional ongoing RCTs, or completed published or unpublished articles. KRJ contacted companies that supply surfactant in order to identify possible ongoing trials of surfactant in bronchiolitis.

Data collection and analysis

Selection of studies

Two review authors (KRJ, DC) independently assessed the studies for inclusion. We independently reviewed the reference lists of all available review articles and primary studies to identify references not found in the computerised searches. Two review authors (KRJ, DC) independently screened the title and abstract of search results to identify studies which might be relevant to this review. We retrieved the full-text of potentially relevant studies and independently assessed them for inclusion in the review. We recorded the selection process in a PRISMA flow diagram ([Moher 2009](#)) ([Figure 1](#)). We corresponded with investigators, where appropriate, to clarify study eligibility. We listed excluded studies with reason(s) for exclusion (see [Characteristics of excluded studies](#)). We resolved disagreements by discussion.

Figure 1. Study flow diagram.

Data extraction and management

Two review authors (KRJ, DC) independently extracted data using a standardised data collection form in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011), which included the following data: source, eligibility, methods, participants and settings, interventions, outcomes, results, adverse outcomes and miscellaneous (funding source of the study, or potential conflicts of interest). We resolved disagreements by discussion.

Assessment of risk of bias in included studies

Two review authors (KRJ, DC) independently assessed the risk of bias in included studies using the criteria described in the

Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). This comprised a judgement for each specific feature of the study as 'low risk', 'high risk' or 'unclear risk' of bias ('unclear' indicating either lack of information or uncertainty over the potential for bias). The specific features were random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. We created a 'Risk of bias' graph (Figure 2) using Review Manager 5 software (RevMan 2014).

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

Measures of treatment effect

We analysed dichotomous outcomes by calculating the risk ratio (RR) and risk difference (RD). We analysed continuous outcome data as mean differences (MDs). We expressed the overall results with 95% confidence intervals (CIs).

Unit of analysis issues

We only included RCTs in the review. We found no quasi-RCTs, cluster-RCTs or cross-over trials.

Dealing with missing data

We considered one or more of the following steps for any missing data.

1. We contacted the trial investigators to request missing data whenever possible.
2. We performed sensitivity analyses to assess how sensitive results were to reasonable changes in the assumptions that were made.
3. We addressed the potential impact of missing data on the findings of the review in the [Discussion](#).
4. We calculated the standard deviation (SD) from study statistics (for example, standard errors and P values) for missing SDs of continuous outcome data. If SD calculation was still not possible, then we imputed from other studies in the meta-analysis as per the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Deeks 2011](#)).

There were no losses to follow-up in the included studies and we did not need to perform an intention-to-treat (ITT) analysis.

Assessment of heterogeneity

We assessed both clinical and methodological heterogeneity before pooling. We carried out assessment for statistical heterogeneity visually, using a Chi² test and using the I² statistic. Using the Chi² test, a low P value (< 0.1) (or a large Chi² test relative to its degree of freedom) provided evidence of

heterogeneity of intervention effects (variation in effect estimates beyond chance). We interpreted the values of the I² statistic as follows: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% represents considerable heterogeneity ([Deeks 2011](#)).

Assessment of reporting biases

There were an insufficient number of included studies to assess publication bias using funnel plots in [RevMan 2014](#).

Data synthesis

We carried out the meta-analyses using [RevMan 2014](#). We used a fixed-effect model for pooled data analysis unless there was important statistical heterogeneity among studies, in which case we considered a random-effects meta-analysis. We created [Summary of findings for the main comparison](#) using GRADEproGDT software ([GRADEproGDT 2015](#)).

Subgroup analysis and investigation of heterogeneity

Insufficient data did not allow us to conduct a subgroup analysis for different age groups and for risk factors for severe bronchiolitis.

However, we performed subgroup analyses to investigate statistical heterogeneity to determine the possible reason(s) for this. Further, we performed subgroup analysis to explore whether the heterogeneity was a result of low quality trials or not.

Sensitivity analysis

We performed sensitivity analyses to test the robustness of the decisions if sufficient numbers of trials were found. We:

1. repeated meta-analysis after exclusion of studies with inadequate concealment of allocation;
2. repeated meta-analysis after exclusion of studies in which the outcome evaluation was not blinded;
3. repeated meta-analysis, imputing missing data as best possible and worst possible outcome(s); and

4. compared the difference of pooled analysis results by using a fixed-effect model and a random-effects model.

RESULTS

Description of studies

All the results are based on published data only. We attempted to contact study authors of included studies through emails to provide additional details but received no replies.

Results of the search

We retrieved records from CENTRAL (5), MEDLINE (12), EMBASE (21), CINAHL (15), LILACS (1), and Web of Science (24); after removing duplicates there was a total of 56 records. We identified three additional records through other sources. Thus, we screened a total of 59 records for eligibility (Figure 1). Out of these, we excluded 53 and assessed the remaining six full-text articles for eligibility. We excluded three full-text articles and included the remaining three trials for qualitative and quantitative synthesis.

Included studies

We included three studies, enrolling 79 participants. Details of these studies are provided in the [Characteristics of included studies](#) tables. All three studies were RCTs; two from Italy ([Luchetti 1998](#); [Luchetti 2002](#)) and one from the UK ([Tibby 2000](#)). One study was multicentric (six centres) ([Luchetti 2002](#)). We summarised extracted data from included studies in [Appendix 7](#). The age of included participants ranged from 1 week to 2.5 years, as provided in studies by [Luchetti 1998](#) and [Luchetti 2002](#). The children were younger in the [Tibby 2000](#) study, with a median (inter-quartile range, IQR) age of 2 (1.5 to 3.1) months and 1.4 (1 to 2.1) months in the surfactant and control group, respectively. The children in the [Luchetti 1998](#) study were older with a mean (standard deviation, SD) age of 10.4 (1.8) and 11.2 (2.0) months in the surfactant and control group, respectively ([Appendix 7](#)). Overall there were 40 males and 39 females, with no major difference in sex distribution among the studies ([Appendix 7](#)). The majority of participants had RSV-induced

respiratory failure except for the [Luchetti 1998](#) study where viral aetiology was known only in four out of a total 20 cases and these were RSV-positive. The [Luchetti 1998](#) study enrolled patients when they were on mechanical ventilation for 24 hours without significant improvement of their clinical status (used predefined oxygenation and PaCO₂ (partial pressure of arterial CO₂) criteria) and used surfactant 50 mg/kg in two to three doses. [Luchetti 2002](#) included participants who had mechanical ventilation for at least 12 hours without significant improvement and used surfactant 50 mg/kg in two aliquots over about five minutes. The [Tibby 2000](#) study enrolled participants who were ventilated for less than 24 hours with an oxygenation index above five and a ventilation index above 20 and surfactant was administered in two doses (100 mg/kg), 24 hours apart. Participants with uncorrected congenital heart disease and neuromuscular diseases were excluded by two studies ([Luchetti 2002](#); [Tibby 2000](#)). The [Luchetti 2002](#) study excluded children with chronic lung disease, whereas the [Tibby 2000](#) study did not exclude children with chronic lung disease and with a history of prematurity. Intervention included porcine surfactant (Curosurf) in [Luchetti 1998](#) and [Luchetti 2002](#) trials and bovine surfactant (Survanta) in the [Tibby 2000](#) trial. The exogenous surfactant was administered through an endotracheal tube in all studies. [Luchetti 1998](#) and [Luchetti 2002](#) used no placebo, whereas air placebo was used in [Tibby 2000](#). The primary outcomes vary among the included studies as depicted in the [Characteristics of included studies](#) tables.

Excluded studies

We excluded three RCTs ([Moller 2003](#); [Willson 1999](#); [Willson 2005](#)) for the reasons given in the [Characteristics of excluded studies](#) table. All three studies used surfactants but none of them enrolled participants with bronchiolitis.

Risk of bias in included studies

The risk of bias rated for each criteria for included studies is shown in the [Characteristics of included studies](#) and 'Risk of bias' graph ([Figure 2](#)) and 'Risk of bias' summary ([Figure 3](#)).

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

	Random 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)	Other bias
Luchetti 1998	?	+	?	?	+	+	?
Luchetti 2002	?	+	+	+	+	+	?
Tibby 2000	?	?	+	?	?	+	?

Allocation

The method of random sequence generation was not described by any of the included studies ([Characteristics of included studies](#)). Sealed envelopes were used for allocation concealment in studies by [Luchetti 1998](#) and [Luchetti 2002](#) and it was not described in the study by [Tibby 2000](#).

Blinding

Participants and health care providers were blinded in the study by [Tibby 2000](#); blinding of health care providers was attempted in the study by [Luchetti 2002](#) and it was not mentioned in the [Luchetti 1998](#) study. Outcome assessors were blinded in the [Luchetti 2002](#) trial, whereas it was not mentioned in the studies by [Luchetti 1998](#) and [Tibby 2000](#).

Incomplete outcome data

Mortality data were not reported in the [Tibby 2000](#) study; apart from this study, there were no incomplete outcome data.

Selective reporting

None of the included studies had selective reporting based on the outcomes mentioned in the methods section; although a study protocol was not available for any of these studies.

Other potential sources of bias

None of the included studies mentioned funding or conflict of interest.

Effects of interventions

See: [Summary of findings for the main comparison](#) Surfactant for critically ill infants with bronchiolitis

Primary outcomes

1. Mortality

Mortality data were described for 60 participants in two included studies; there was no mortality in either study (Luchetti 1998; Luchetti 2002).

2. Duration of mechanical ventilation (hours)

The data regarding duration of mechanical ventilation were available for 79 participants in all three included studies. Duration

of mechanical ventilation was significantly less in two studies (Luchetti 1998; Luchetti 2002) but there was no significant difference in the study by Tibby 2000. When data from three studies were pooled, the duration of mechanical ventilation was no different in the surfactant group compared to the control group (mean difference (MD) -63.04 hours, 95% confidence interval (CI) -130.43 to 4.35) but there was a trend towards beneficial effects of surfactant (Analysis 1.2; Figure 4).

Figure 4. Forest plot of comparison: 1 Primary outcome: 1.2 Duration of mechanical ventilation (hours).

There was statistically significant heterogeneity for duration of mechanical ventilation (I^2 statistic 97%) that was attributed to the Luchetti 1998 study, where blinding was not attempted and controls had comparatively higher duration of mechanical ventilation. After excluding the Luchetti 1998 study from the meta-analysis, the duration of mechanical ventilation was significantly lower in the surfactant group (MD -28.99 hours, 95% CI -40.10 to -17.87).

3. Adverse effects (desaturation, change in heart rate, change in blood pressure and bronchospasm) or complications (pneumothorax) or both

Luchetti 1998 reported that no adverse haemodynamic effects (no significant change in heart rate and blood pressure) and no complications were noted. Luchetti 1998 reported no other specific adverse effects and complications. Luchetti 2002 stated that they observed no significant change in heart rate and no complications, without mentioning specific adverse effects and complications.

Tibby 2000 stated that no complications were noted, again without mentioning specific adverse effects and complications.

Secondary outcomes

1. Duration of ICU stay

The data regarding duration of intensive care unit (ICU) stay were available from all three included studies (79 participants). The Tibby 2000 study had non-significant difference in duration of ICU stay between the experimental and control group; duration of ICU stay in the control group was just significantly less for the Luchetti 1998 and Luchetti 2002 studies (Analysis 2.1; Figure 5). After combining the data, the duration of ICU stay was significantly less in the surfactant group compared to the control group (MD -3.31 days, 95% CI -6.38 to -0.25) (Analysis 2.1; Figure 5). There was statistically significant heterogeneity for duration of ICU stay (I^2 statistic = 94%), again attributable to the Luchetti 1998 study. The results were still significant after excluding the Luchetti 1998 study from the analysis (MD -1.81 days, 95% CI -2.42 to -1.19).

Figure 5. Forest plot of comparison: 2 Secondary outcome: 2.1 Duration of ICU stay (days).

2. Duration of hospital stay

Duration of hospital stay was available from Tibby 2000 only and it was not significantly different between the groups (13 days versus 17 days; $P = 0.3$).

3. Gas exchange (effects on oxygenation (PO_2/FiO_2 ratio) and CO_2 elimination (pCO_2))

The effect of oxygenation was measured as PO_2/FiO_2 ratio (ratio of partial pressure of arterial oxygen and fractional inspired oxygen) in two studies (Luchetti 1998; Luchetti 2002) and as oxygenation index ($OI = \text{mean airway pressure (cm H}_2\text{O)} \times FiO_2 \times 100/\text{arterial}$

PO₂(mm Hg)) and alveolar arterial gradient (Aa) by the third study (Tibby 2000). In the Luchetti 1998 and Luchetti 2002 studies, the PO₂/FiO₂ ratio was significantly higher in the surfactant group at 1, 3, 12 and 24 hours and at 1, 3, 6, 12, 24 and 48 hours, respectively. In the Tibby 2000 study, the mean OI and Aa gradient changed from 6.3 to 9.3 and 198 to 246, respectively, following the first dose, and from 6.8 to 7.6 and 191 to 225, respectively, after the second dose;

but all changes were not significant. After combining the data from two studies (Luchetti 1998; Luchetti 2002), the PO₂/FiO₂ ratio at 12 and 24 hours of surfactant administration was significantly higher in the surfactant group (MD 99.08, 95% CI 57.43 to 140.72) (Analysis 2.2) and (MD 109.64, 95% CI 63.29 to 155.99) (Analysis 2.3; Figure 6), respectively. There was significant heterogeneity for the combined PO₂/FiO₂ ratio and we performed a random-effects meta-analysis.

Figure 6. Forest plot of comparison: 2 Secondary outcome: 2.3 Po₂/Fio₂ ratio at 24 hrs.

The effect on CO₂ elimination was measured as PCO₂ (partial pressure of arterial CO₂) values in two studies (Luchetti 1998; Luchetti 2002) and as ventilation index (VI = respiratory rate x peak-inspiratory pressure (cm H₂O) x arterial PCO₂ (mm Hg)/1000) in the third study (Tibby 2000). A significant reduction of PCO₂ in the surfactant group as compared to control group was observed in Luchetti 1998 and Luchetti 2002 at 12 and 24 hours and at 1,

3, 6, 12, 24 and 48 hours, respectively. The ventilation index did not significantly change in the Tibby 2000 study after surfactant administration. The pooled PCO₂ values from two studies (Luchetti 1998; Luchetti 2002) were significantly less in the surfactant group at 12 and 24 hours (MD -7.63 mmHg, 95% CI -8.99 to -6.28) (Analysis 2.4) and (MD -7.90 mmHg, 95% CI -9.42 to -6.38) (Analysis 2.5; Figure 7), respectively; there was no heterogeneity (Figure 7).

Figure 7. Forest plot of comparison: 2 Secondary outcome: 2.5 pCO₂ at 24 hrs (mmHg).

4. Respiratory mechanics (effects on pulmonary compliance and airways resistance)

Data regarding compliance after surfactant administration were available from two studies (Luchetti 2002; Tibby 2000). The static compliance was significantly higher in the surfactant group at 1, 3, 6, 12, 24 and 48 hours in Luchetti 2002. In the Tibby 2000 study, compliance fell (0.36 to 0.27 mL/cm H₂O/kg; P < 0.01) in the placebo group only at 30 hours post-surfactant administration. Only the Tibby 2000 study provided data regarding airway resistance, where it increased (229 cm H₂O/L/s to 391 cm H₂O/L/s; P < 0.001) significantly in the placebo group only at 30 hours post-surfactant administration.

5. Recurrent lower respiratory tract disease

No data were available regarding recurrent lower respiratory tract disease in follow-up for enrolled participants.

Assessment of reporting bias

There were not a sufficient number of included studies to assess publication bias by funnel plot.

Subgroup analysis

There were insufficient data to perform subgroup analyses for different age groups (< 1 month, 1 to < 12 months and 12 to < 60 months) and participants with or without risk factors for severe bronchiolitis.

Sensitivity analysis

We repeated the analysis after excluding studies with unclear risk of biases. The duration of mechanical ventilation was not statistically different as a whole, but became significant after excluding the Luchetti 1998 study where no blinding was mentioned. For duration of ICU stay, the difference among the groups was still significant after excluding the Luchetti 1998 study from the analysis. We performed a random-effects meta-analysis for the duration of mechanical ventilation and duration of ICU stay while combining all three studies' data because of significant heterogeneity. Results were not much different in the meta-analysis when using the fixed-effect or random-effects models. There were no incomplete outcome data to perform sensitivity analysis with best and worst possible outcomes.

Investigation of heterogeneity

There was statistically significant heterogeneity for outcomes of duration of mechanical ventilation, duration of ICU stay and PO_2/FiO_2 ratios. The heterogeneity was attributed to the [Luchetti 1998](#) study (no blinding and higher values of different parameters in the control group) as there was no heterogeneity after excluding this study from analysis. We performed a random-effects meta-analysis for PO_2/FiO_2 ratios as only two studies ([Luchetti 1998](#); [Luchetti 2002](#)) were included for analysis.

Level of evidence as per GRADE

The level of evidence for duration of mechanical ventilation, duration of intensive care unit stay, oxygenation parameters, and carbon dioxide parameters was of moderate quality ([Summary of findings for the main comparison](#)).

DISCUSSION

Summary of main results

The review evaluated the effects of surfactant therapy for bronchiolitis in critically ill infants. The results of the review are summarised in [Summary of findings for the main comparison](#). There was no mortality reported in two included studies. The duration of mechanical ventilation was significantly less in the surfactant group as compared to the control group in children with severe bronchiolitis. No adverse effects and no complications were reported with surfactant treatment. The results regarding duration of ICU stay, PO_2/FiO_2 ratio and PCO_2 favoured surfactant treatment. The compliance was higher in the surfactant group in individual studies. Data were available from only one study for duration of hospital stay and airway resistance.

Overall completeness and applicability of evidence

The limited available evidence suggests usefulness of surfactant therapy for bronchiolitis in critically ill infants. Overall, the total number of participants (79) in the identified studies was small. One of the included studies did not mention mortality. Data were not available from any of the three studies for most of the secondary outcomes, except for duration of ICU stay. Two included studies ([Luchetti 2002](#); [Tibby 2000](#)) excluded participants with congenital heart disease and the other study ([Luchetti 2002](#)) excluded infants with chronic lung diseases, where bronchiolitis may be more severe. Currently there is a lack of evidence for effective therapy, except for nebulised adrenaline, in infants with bronchiolitis. The present review suggests that there is insufficient evidence of benefit of surfactant in children with bronchiolitis who require mechanical ventilation.

Quality of the evidence

The quality of evidence for each outcome is described in [Summary of findings for the main comparison](#). The three included studies in the review enrolled a total of 79 participants. There was no high risk of bias but there was significant unclear risk, as shown in [Figure 2](#). The duration of mechanical ventilation and duration of ICU stay were significantly lower in two studies ([Luchetti 1998](#); [Luchetti 2002](#)), but these were not significantly different in the third study ([Tibby 2000](#)) where air placebo was used. Similarly, results for oxygenation and CO_2 elimination were significantly better for two studies ([Luchetti 1998](#); [Luchetti 2002](#)), but not for

the third one ([Tibby 2000](#)). The quality of evidence was moderate for all the objectives, as shown in [Summary of findings for the main comparison](#). We downgraded the quality of the body of evidence for all the outcomes because of the small number of total participants in the included studies ([Summary of findings for the main comparison](#)). Patients were younger in [Tibby 2000](#) compared to [Luchetti 1998](#). Data regarding blinding of outcome assessors were not available from two studies: [Luchetti 1998](#) had predefined criteria for discontinuation of ventilation, whereas [Tibby 2000](#) did not. The ventilation strategy was also different between studies: [Luchetti 1998](#) used tidal volume of 10 mL/kg, whereas [Luchetti 2002](#) and [Tibby 2000](#) allowed permissive hypercapnia.

Potential biases in the review process

The search strategy for this review was broad and it was performed by the Trials Search Co-ordinator of the Cochrane Acute Respiratory Infections (ARI) Group, thus it is unlikely that any relevant study was missed. Study selection, data extraction and analysis were carried out independently by two review authors. The quality of included trials varied with many unclear risks of bias ([Figure 2](#)). Not all data related to assessment of bias were available from the published studies and there was no reply from study authors regarding these. There were other limitations in this review. For most of the secondary outcome measures, data were available from two of three included studies. The standard deviations (SDs) for [Tibby 2000](#) were not available and we calculated them from P values or standard error of mean (SEM). Similarly, SD for PO_2/FiO_2 ratio and PCO_2 were not available for [Luchetti 2002](#) and we imported them from another study ([Luchetti 1998](#)).

Agreements and disagreements with other studies or reviews

We did not identify any additional relevant studies since the previous version of this review ([Jat 2012](#)). The results were similar for both reviews. In one of the excluded trials with 153 participants with acute respiratory failure from acute lung injury (nine were of RSV pneumonia but none with bronchiolitis), participants were randomised to receive surfactant or air placebo; the surfactant acutely improved oxygenation and significantly reduced mortality, although no significant reduction in duration of ventilator therapy, ICU or hospital stay was observed ([Willson 2005](#)). In a pilot study, part of the second excluded study ([Moller 2003](#)), where 19 children (two with RSV bronchiolitis) with acute respiratory distress syndrome (ARDS) received surfactant, there was a significant increase in PaO_2/FiO_2 at four hours and 48 hours after surfactant administration. In a RCT (part of [Moller 2003](#)) (there were no children with bronchiolitis), surfactant therapy in severe ARDS improved oxygenation immediately after administration. In a third excluded study, administration of surfactant in children with acute hypoxaemic respiratory failure (six children had RSV pneumonia but none had bronchiolitis) was safe and was associated with rapid improvement in oxygenation, earlier extubation and reduced requirement for intensive care ([Willson 1999](#)). There was variability in type, timing and dose of surfactant in included studies. Two studies ([Luchetti 1998](#); [Luchetti 2002](#)) used porcine-derived surfactant (Curosurf) and the third study ([Tibby 2000](#)) used bovine surfactant (Survanta). Similarly, out of three excluded studies, calfactant was used in two ([Willson 1999](#); [Willson 2005](#)) and bovine surfactant (Alveofact) in the third ([Moller 2003](#)). There are different compositions of different types of surfactants ([Appendix](#)

1) and effects of different surfactants may differ. The surfactant was administered after 12 and 24 hours of ventilation in the [Luchetti 2002](#) and [Luchetti 1998](#) studies, respectively, and it was administered within 24 hours of ventilation in [Tibby 2000](#) (children with > 24 hours of ventilation were excluded). The surfactant was administered in two doses and two to three doses over about five minutes in [Luchetti 1998](#) and [Luchetti 2002](#), respectively, but it was administered in two doses at 24 hours apart in the third study ([Tibby 2000](#)). [Luchetti 2002](#) and [Tibby 2000](#) included only RSV bronchiolitis, whereas only 4 out of 20 participants had RSV bronchiolitis in the [Luchetti 1998](#) study. The most surfactant protein deficiency had been demonstrated in RSV-induced respiratory failure as compared to controlled ventilated children ([Kerr 1999](#)). It may be possible that surfactant may produce different effects in respiratory failure due to different aetiologies.

AUTHORS' CONCLUSIONS

Implications for practice

In infants, the administration of surfactant did not reduce the duration of mechanical ventilation significantly compared with placebo or no treatment, irrespective of timing, although duration of intensive care unit (ICU) stay was shorter in the surfactant group and there was a better effect of surfactant on gas exchange. After excluding a study which produced significant heterogeneity, the duration of mechanical ventilation was also less in the surfactant group. However, it is difficult to suggest the usefulness of surfactant therapy for bronchiolitis in critically ill infants because of the small number of methodologically flawed included trials.

Cost-effectiveness is another concern. The use of surfactant for bronchiolitis in critically ill infants did not appear to have any adverse effects in the included studies. Thus, it is difficult to recommend for or against the use of surfactant in infants with bronchiolitis who require mechanical ventilation.

Implications for research

The level of evidence for duration of mechanical ventilation, duration of intensive care unit stay, oxygenation parameters, and carbon dioxide parameters was of moderate quality. There is a need for larger trials with adequate power to evaluate the effectiveness of exogenous surfactant administration in infants with bronchiolitis who require mechanical ventilation. The type (animal-derived or synthetic), dose (dose per aliquot and total number of aliquots) and timing (at the time of ventilation, after 12 hours of ventilation or after 24 hours of ventilation) of surfactant administration also need to be addressed in future trials. Finally, a cost-effective analysis is worth considering regarding the cost of surfactant and cost of intensive care for critically ill infants with bronchiolitis.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

[Luchetti 1998](#)

Methods	RCT
Participants	20 children; 20 days to 2.5 years of age at an ICU in Italy with diagnosis of severe bronchiolitis requiring mechanical ventilation with continuous positive pressure ventilation (CPPV) > 24 hrs without improvement; and PaO ₂ /FiO ₂ < 21 kPa, FiO ₂ ≥ 0.6, PaCO ₂ > 5.6 kPa and PIP (peak inspiratory pressure) > 35 cm H ₂ O at 24 hrs of ventilation. All received β ₂ agonist and antibiotics
Interventions	CPPV plus surfactant (porcine-derived, Curosurf, 50 mg/kg, in 2 to 3 doses) versus CPPV only. No placebo was used in control group
Outcomes	Gas exchange, PIP (at 1, 3, 12, 24 hours) duration of mechanical ventilation and ICU stay

Surfactant therapy for bronchiolitis in critically ill infants (Review)

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Luchetti 1998 (Continued)

Notes The study was conducted in 2 winter seasons over 2 consecutive years

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors stated that participants were randomly assigned to one of the groups
Allocation concealment (selection bias)	Low risk	Sealed envelope method was used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no incomplete outcome data
Selective reporting (reporting bias)	Low risk	No selective reporting
Other bias	Unclear risk	Information regarding funding and conflict of interest was not provided

Luchetti 2002

Methods	Multicentre (6 sites), RCT
Participants	40 children; 1 week to 2 years of age at an ICU in Italy with diagnosis of respiratory failure ($\text{PaO}_2/\text{FiO}_2$ ratio ≤ 150 mm Hg and $\text{PaCO}_2 \geq 40$ mm Hg) due to respiratory syncytial virus (RSV) bronchiolitis; conventional mechanical ventilation (CMV) for at least 12 hours without significant improvement
Interventions	Conventional mechanical ventilation (CMV) plus surfactant (50 mg/kg of porcine-derived natural surfactant, Curosurf, in 2 aliquots over about 5 mins) versus CMV only. No placebo was used in control group
Outcomes	Primary: days on mechanical ventilation and length of ICU stay Secondary: gas exchange, respiratory mechanics, haemodynamic stability, re-treatment needed, incidence of complications and mortality
Notes	Patients with severe head injury with Glasgow Coma Score < 8 , brain death, chronic lung disease, pre-existing airways disease, congenital heart diseases (CHD) and neuromuscular diseases were considered as exclusion criteria

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

Luchetti 2002 (Continued)

Random sequence generation (selection bias)	Unclear risk	Authors stated that patients were randomly assigned
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding was attempted in controls by performing similar manoeuvres on them as per experimental group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data collector and outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data
Selective reporting (reporting bias)	Low risk	No selective reporting
Other bias	Unclear risk	Information regarding funding and conflict of interest was not provided

Tibby 2000

Methods	Randomised controlled pilot study
Participants	19 children with median corrected age of 4 weeks in paediatric ICU in UK requiring mechanical ventilation due to RSV-induced respiratory failure
Interventions	Bovine surfactant (Survanta, 2 doses, 100 mg/kg, 24 hours apart) versus air placebo. No steroids or bronchodilators were used
Outcomes	Indices of gas exchange - oxygenation index (OI), ventilation index (VI), alveolar arterial gradient (Aa); lung compliance and resistance at 1, 2, 6, 24, 30, 60 hours; and phospholipid molecular species composition in bronchoalveolar lavage fluid (BALF)
Notes	Patients with neuromuscular disease, uncorrected CHD, pre-existing pneumothorax, ventilation for > 24 hours, oxygenation index (OI) < 5 and a ventilation index (VI) < 20 at enrolment were excluded from study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors stated that infants were randomised to receive one of the interventions
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias)	Low risk	Participants and health care providers were blinded

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Tibby 2000 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data regarding mortality were not mentioned
Selective reporting (reporting bias)	Low risk	No selective reporting
Other bias	Unclear risk	Information regarding funding and conflict of interest was not provided

Aa: alveolar arterial gradient

BALF: bronchoalveolar lavage fluid

CHD: congenital heart diseases

CMV: conventional mechanical ventilation

CPPV: continuous positive pressure ventilation

ICU: intensive care unit

FiO₂: fractional inspired oxygen

H₂O: water

kPa: unit of pressure

mmHg: mm of mercury

OI: oxygenation index

PaCO₂: partial pressure of arterial carbon dioxide

PIP: peak inspiratory pressure

RCT: randomised controlled trial

RSV: respiratory syncytial virus

VI: ventilation index

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Moller 2003	Included children with acute respiratory distress syndrome (ARDS) secondary to pneumonia and sepsis, but not bronchiolitis
Willson 1999	Participants were children with acute hypoxaemic respiratory failure requiring mechanical ventilation with clinical and radiographic evidence of diffuse, bilateral parenchymal lung injury; not due to bronchiolitis
Willson 2005	Included children with acute lung injury (respiratory failure due to radiographically evident bilateral parenchymal lung disease), not with bronchiolitis

ARDS: acute respiratory distress syndrome

DATA AND ANALYSES

Comparison 1. Primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	2	60	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Duration of mechanical ventilation (hours)	3	79	Mean Difference (IV, Random, 95% CI)	-63.04 [-130.43, 4.35]

Analysis 1.1. Comparison 1 Primary outcomes, Outcome 1 Mortality.

Study or subgroup	Surfactant n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Luchetti 1998	0/10	0/10			Not estimable
Luchetti 2002	0/20	0/20			Not estimable
Total (95% CI)	30	30			Not estimable
Total events: 0 (Surfactant), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours surfactant 0.02 0.1 1 10 50 Favours control

Analysis 1.2. Comparison 1 Primary outcomes, Outcome 2 Duration of mechanical ventilation (hours).

Study or subgroup	Surfactant		Control		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Luchetti 1998	10	105.6 (9.6)	10	213.6 (24)		39.16%	-108 [-124.02, -91.98]
Luchetti 2002	20	110.4 (19.2)	20	139.2 (16.8)		39.61%	-28.8 [-39.98, -17.62]
Tibby 2000	9	126 (111.3)	10	170 (111.3)		21.23%	-44 [-144.25, 56.25]
Total ***	39		40			100%	-63.04 [-130.43, 4.35]
Heterogeneity: Tau ² =2952.42; Chi ² =63.17, df=2(P<0.0001); I ² =96.83%							
Test for overall effect: Z=1.83(P=0.07)							

Favours surfactant -500 -250 0 250 500 Favours control

Comparison 2. Secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of ICU stay (days)	3	79	Mean Difference (IV, Random, 95% CI)	-3.31 [-6.38, -0.25]
2 Gas exchange (Po ₂ /Fio ₂ ratio at 12 hrs)	2	60	Mean Difference (IV, Random, 95% CI)	99.08 [57.43, 140.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Gas exchange (PO_2/F_{IO_2} ratio at 24 hrs)	2	60	Mean Difference (IV, Random, 95% CI)	109.64 [63.29, 155.99]
4 Gas exchange (pCO_2 at 12 hrs (mmHg))	2	60	Mean Difference (IV, Fixed, 95% CI)	-7.63 [-8.99, -6.28]
5 Gas exchange (pCO_2 at 24 hrs (mmHg))	2	60	Mean Difference (IV, Fixed, 95% CI)	-7.9 [-9.42, -6.38]

Analysis 2.1. Comparison 2 Secondary outcomes, Outcome 1 Duration of ICU stay (days).

Study or subgroup	Surfactant		Control		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Luchetti 1998	10	10.1 (1.2)	10	15.7 (1.5)		37.35%	-5.6[-6.79,-4.41]
Luchetti 2002	20	6.4 (0.9)	20	8.2 (1.1)		38.94%	-1.8[-2.42,-1.18]
Tibby 2000	9	6.7 (4.4)	10	8.9 (4.4)		23.71%	-2.2[-6.19,1.79]
Total ***	39		40			100%	-3.31[-6.38,-0.25]
Heterogeneity: $\tau^2=6.19$; $Chi^2=30.76$, $df=2$ ($P<0.0001$); $I^2=93.5\%$							
Test for overall effect: $Z=2.12$ ($P=0.03$)							
					Favours surfactant	-20 -10 0 10 20	Favours control

Analysis 2.2. Comparison 2 Secondary outcomes, Outcome 2 Gas exchange (PO_2/F_{IO_2} ratio at 12 hrs).

Study or subgroup	Surfactant		Control		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Luchetti 1998	10	225.6 (18.8)	10	148.1 (14.3)		49.23%	77.5[62.86,92.14]
Luchetti 2002	20	260 (18.8)	20	140 (14.3)		50.77%	120[109.65,130.35]
Total ***	30		30			100%	99.08[57.43,140.72]
Heterogeneity: $\tau^2=861.28$; $Chi^2=21.58$, $df=1$ ($P<0.0001$); $I^2=95.37\%$							
Test for overall effect: $Z=4.66$ ($P<0.0001$)							
					Favours control	-200 -100 0 100 200	Favours surfactant

Analysis 2.3. Comparison 2 Secondary outcomes, Outcome 3 Gas exchange (PO_2/F_{IO_2} ratio at 24 hrs).

Study or subgroup	Surfactant		Control		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Luchetti 1998	10	231.6 (20.3)	10	145.9 (12)		49.38%	85.7[71.08,100.32]
Luchetti 2002	20	269 (20.3)	20	136 (12)		50.62%	133[122.67,143.33]
Total ***	30		30			100%	109.64[63.29,155.99]
					Favours control	-200 -100 0 100 200	Favours surfactant

Analysis 2.4. Comparison 2 Secondary outcomes, Outcome 4 Gas exchange (pCO₂ at 12 hrs (mmHg)).

Analysis 2.5. Comparison 2 Secondary outcomes, Outcome 5 Gas exchange (pCO₂ at 24 hrs (mmHg)).

APPENDICES

Appendix 1. Details of surfactants available for clinical use

Animal-derived	Preparation/composition	Phospho-lipids conc. mg/ ml (%)	SP-B (µg per µmol)	SP-C (µg per µmol)
Beractant (Survanta)	Minced bovine lung extract + DPPC + palmitic acid + tripalmitin	25 (84)	0 to 1.3	1 to 20
Calfactant (Infasurf)	Bovine lung lavage + DPPC + cholesterol	35 (95)	5.4	8.1

(Continued)

Poractant alfa (Curosurf)	Minced porcine lung extract (liquid gel chromatography)	80 (99)	2 to 3.7	5 to 11.6
Synthetic				
Colfosceril palmitate (Exosurf)	DPPC, hexadecanol, tyloxapol	13.5	none	none
Pumactant (ALEC)	DPPC, PG	40	none	none
Lucinactant (Surfaxin)	DPPC, PG	30	KL-4 19.8	none
DPPC: dipalmitoylphosphatidylcholine PG: phosphatidylglycerol				

Appendix 2. MEDLINE and CENTRAL search strategy

1 exp Bronchiolitis/
2 bronchiolit*.tw.
3 respiratory syncytial viruses/ or respiratory syncytial virus, human/
4 Respiratory Syncytial Virus Infections/
5 (respiratory syncytial virus* or rsv).tw.
6 or/1-5
7 exp Surface-Active Agents/
8 exp Pulmonary Surfactants/
9 surfactant*.tw,nm.
10 tensides.tw.
11 amphiphilic agent*.tw.
12 poractant*.tw,nm.
13 beractant*.tw,nm.
14 calfactant*.tw,nm.
15 infasurf.tw,nm.
16 venticute*.tw,nm.
17 survanta.tw,nm.
18 curosurf.tw,nm.
19 exosurf.tw,nm.
20 alec.tw,nm.
21 or/7-20
22 6 and 21

Appendix 3. EMBASE.com search strategy

#17. #13 AND #16 21 25 May 2011
#16. #14 OR #15 864,776 25 May 2011
#15. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEAR/1 blind*):ab,ti AND [embase]/lim 824,994 25 May 2011
#14. 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp AND [embase]/lim 242,572 25 May 2011
#13. #5 AND #12 296 25 May 2011
#12. #6 OR #7 OR #8 OR #9 OR #10 OR #11 125,238 25 May 2011
#11. poractant*:ab,ti OR beractant*:ab,ti OR calfactant*:ab,ti OR infasurf:ab,ti OR venticute*:ab,ti OR survanta:ab,ti OR curosurf:ab,ti OR exosurf:ab,ti OR alec:ab,ti AND [embase]/lim 675 25 May 2011
#10. 'amphiphilic agent':ab,ti OR 'amphiphilic agents':ab,ti AND [embase]/lim 35 25 May 2011
#9. tensides:ab,ti AND [embase]/lim 126 25 May 2011
#8. surfactant*:ab,ti AND [embase]/lim 33,345 25 May 2011
#7. 'surface-active agents':ab,ti OR 'surface-active agent':ab,ti AND [embase]/lim 529 25 May 2011
#6. 'surfactant'/exp OR 'lung surfactant'/de AND [embase]/lim 116,054 25 May 2011
#5. #1 OR #2 OR #3 OR #4 20,018 25 May 2011
#4. 'respiratory syncytial virus':ab,ti OR 'respiratory syncytial viruses':ab,ti OR rsv:ab,ti AND [embase]/lim 9,335 25 May 2011
#3. 'respiratory syncytial pneumovirus'/de OR 'respiratory syncytial virus infection'/exp AND [embase]/lim 9,088 25 May 2011

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#2. bronchiolit*:ab,ti AND [embase]/lim 6,772 25 May 2011
#1. 'bronchiolitis'/exp AND [embase]/lim 9,220 25 May 2011

Appendix 4. CINAHL (Ebsco) search strategy

S14 S6 and S13 15
S13 S7 or S8 or S9 or S10 or S11 or S12 1860
S12 TI (poractant* or beractant* or calfactant* or infasurf or venticute* or survanta or curosurf or exosurf or alec) or AB (poractant* or beractant* or calfactant* or infasurf or venticute* or survanta or curosurf or exosurf or alec) 61
S11 TI amphiphilic agent* or AB amphiphilic agent* 1
S10 TI tensides or AB tensides 1
S9 TI surfactant* or AB surfactant* 773
S8 (MH "Pulmonary Surfactants") 556
S7 (MH "Surface-Active Agents+") 998
S6 S1 or S2 or S3 or S4 or S5 1583
S5 TI (respiratory syncytial virus* or rsv) or AB (respiratory syncytial virus* or rsv) 734
S4 (MH "Respiratory Syncytial Viruses") 236
S3 (MH "Respiratory Syncytial Virus Infections") 695
S2 TI bronchiolit* or AB bronchiolit* 616
S1 (MH "Bronchiolitis+") 549

Appendix 5. LILACS (BIREME) search strategy

VHL > Search > (MH:Bronchiolitis OR bronchiolit\$ OR Bronquirolitis OR Bronquirolite OR MH:C08.127.446.435\$ OR MH:C08.381.495.146.135\$ OR MH:C08.730.099.135\$ OR MH:"Respiratory Syncytial Viruses" OR "Virus Sincitiales Respiratorios" OR "Virus Sinciciais Respiratórios" OR "respiratory syncytial virus" OR "respiratory syncytial viruses" OR MH:"Respiratory Syncytial Virus, Human" OR "Virus Sincitial Respiratorio Humano" OR "Virus Sincicial Respiratório Humano" OR "Virus Humano Respiratorio Sincitial" OR MH:"Respiratory Syncytial Virus Infections" OR "Infecciones por Virus Sincitial Respiratorio" OR "Infecções por Vírus Respiratório Sincicial") AND (MH:"Surface-Active Agents" OR Tensoactivos OR Tensoativos OR surfactant\$ OR MH:D27.720.877\$ OR MH:SP4.011.097.039.724\$ OR MH:"Pulmonary Surfactants" OR "pulmonary surfactants" OR "pulmonary surfactant" OR "Surfactantes Pulmonares" OR surfactant\$ OR tenside\$ OR "amphiphilic agent" OR "amphillic agents" OR poractant OR beractant OR calfactant OR infasurf OR venticute OR survanta OR curosurf OR exosurf OR alec)

Appendix 6. Web of Science (ISI Thomson) search strategy

Topic=(bronchiolitis or respiratory syncytial virus* or rsv) AND Topic=(surfactant* or tensides or amphiphillic agent* or poractant or beractant or calfactant or infasurf or venticute or survanta or curosurf or exosurf or alec)

Refined by: Topic=(random* or placebo* or clinical trial* or singl* blind* or doubl* blind*)

Timespan = 1985-2011. Databases = SCI-EXPANDED, CPCI-S.

Appendix 7. Data extraction from included studies

Study and group→ Parameters↓	Luchetti 1998		Luchetti 2002		Tibby 2000	
	Surfac- tant group	Control group	Surfactant group	Control group	Surfac- tant group	Control group
Number of participants	10	10	20	20	09	10
Age	10.4 ± 1.8 months*	11.2 ± 2.0 months*	8.7 ± 8.1 months*	7.4 ± 6.5 months*	9 (7 to 14) weeks#	6.5 (4.5 to 9.5) weeks#
Male:female	6:4	5:5	8:12	11:9	6:3	4:6
Mortality	0	0	0	0	NA	NA

(Continued)

Duration of mechanical ventilation (hrs); mean $\pm$ SD	105.6 $\pm$ 9.6	213.6 $\pm$ 24	110.4 $\pm$ 19.2	139.2 $\pm$ 16.8	126 $\pm$ 111.32 ^{\$}	170 $\pm$ 111.32 ^{\$}
Duration of ICU stay (days); mean $\pm$ SD	10.1 $\pm$ 1.2	15.7 $\pm$ 1.5	6.4 $\pm$ 0.9	8.2 $\pm$ 1.1	6.7 $\pm$ 4.43 ^{\$}	8.9 $\pm$ 4.43 ^{\$}
Duration of hospital stay (days)	NA	NA	NA	NA	13	17
PO ₂ /FiO ₂ ratio at 12 hrs (mmHg); mean $\pm$ SD	225.6 $\pm$ 18.8	148.1 $\pm$ 14.3	260 $\pm$ 18.8 [£]	140 $\pm$ 14.3 [£]	NA	NA
PO ₂ /FiO ₂ ratio at 24 hrs (mmHg); mean $\pm$ SD	231.6 $\pm$ 20.3	145.9 $\pm$ 12.0	269 $\pm$ 20.3 [£]	136 $\pm$ 12.0 [£]	NA	NA
PCO ₂ at 12 hrs (mmHg); mean $\pm$ SD	37.5 $\pm$ 3.0	45.0 $\pm$ 2.3	34.5 $\pm$ 3.0 [£]	42.2 $\pm$ 2.3 [£]	NA	NA
PCO ₂ at 24 hrs (mmHg); mean $\pm$ SD	37.5 $\pm$ 3.0	45.0 $\pm$ 3.0	34.5 $\pm$ 3.0 [£]	42.6 $\pm$ 3.0 [£]	NA	NA
Compliance at 12 hrs (ml/cm H ₂ O/kg); mean $\pm$ SD	NA	NA	0.79 $\pm$ NA	0.59 $\pm$ NA	NA	NA
Compliance at 24 hrs (ml/cm H ₂ O/kg); mean $\pm$ SD	NA	NA	0.83 $\pm$ NA	0.62 $\pm$ NA	NA	NA
Resistance at 12 hrs	NA	NA	NA	NA	NA	NA
Resistance at 24 hrs (cm H ₂ O/L/sec); mean $\pm$ SD	NA	NA	NA	NA	NA	NA

*mean $\pm$ SD; #median (IQR); NA: data not available; SD: standard deviation; ^{\$}SD calculated from P value; [£] SD imported from another study (Luchetti 1998); **SD calculated from SEM (standard error of mean); ^{##} SD imported from another study (Tibby 2000).

WHAT'S NEW

Date	Event	Description
25 June 2015	New search has been performed	We did not identify any new studies for inclusion.
25 June 2015	New citation required but conclusions have not changed	Our conclusions remain unchanged.

CONTRIBUTIONS OF AUTHORS

Dr Jat (KRJ) designed and co-ordinated the review.

KRJ and Dr Chawla (DC) collected and analysed data for the review. Both review authors approved the final version of the review.

DECLARATIONS OF INTEREST

Kana R Jat: none known.

Deepak Chawla: none known.

NOTES

This review was previously published in 2006 and later withdrawn in 2010 as the authors were not able to update it (Venture 2006).

INDEX TERMS

Medical Subject Headings (MeSH)

Bronchiolitis [*drug therapy]; Critical Illness; Length of Stay; Pulmonary Surfactants [*therapeutic use]; Randomized Controlled Trials as Topic; Respiration, Artificial [statistics & numerical data]; Time Factors

MeSH check words

Child, Preschool; Humans; Infant; Infant, Newborn