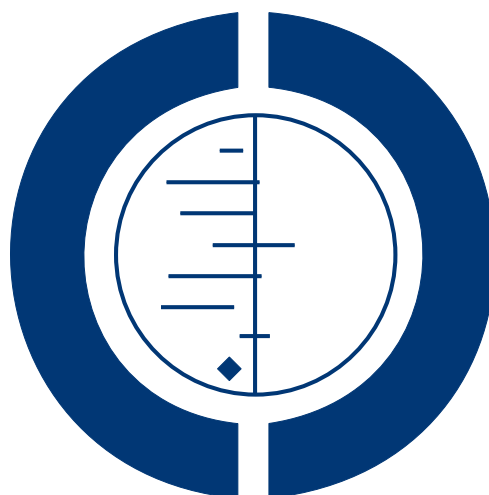# Nebulised surfactant in preterm infants with or at risk of respiratory distress syndrome (Review)

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Nebulised surfactant in preterm infants with or at risk of respiratory distress syndrome

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A B S T R A C T

Background

Nebulised surfactant has the potential to deliver surfactant to the infant lung with the goal of avoiding endotracheal intubation and ventilation, ventilator-induced lung injury and bronchopulmonary dysplasia (BPD).

Objectives

To determine the effect of nebulised surfactant administration either as prophylaxis or treatment compared to placebo, no treatment or intratracheal surfactant administration on morbidity and mortality in preterm infants with, or at risk of, respiratory distress syndrome (RDS).

Search methods

Searches were performed of CENTRAL (*The Cochrane Library*, January 2012), MEDLINE and PREMEDLINE (1950 to January 2012), EMBASE (1980 to January 2012) and CINAHL (1982 to January 2012), as well as proceedings of scientific meetings, clinical trial registries, Google Scholar and reference lists of identified studies. Expert informants and surfactant manufacturers were contacted.

Selection criteria

Randomised, cluster-randomised or quasi-randomised controlled trials of nebulised surfactant administration compared to placebo, no treatment, or other routes of administration (laryngeal, pharyngeal instillation of surfactant before the first breath, thin endotracheal catheter surfactant administration or intratracheal surfactant instillation) on morbidity and mortality in preterm infants at risk of RDS. We considered published, unpublished and ongoing trials.

Data collection and analysis

Two review authors independently assessed studies for eligibility and quality, and extracted data.

Main results

No studies of prophylactic or early nebulised surfactant administration were found. A single small study of late rescue nebulised surfactant was included. The study is of moderate risk of bias. The study enrolled 32 preterm infants born < 36 weeks' gestation with RDS on nasal continuous positive airway pressure (nCPAP). The study reported no significant difference between nebulised surfactant

administration compared to no treatment groups in chronic lung disease (risk ratio (RR) 5.00; 95% confidence interval (CI) 0.26 to 96.59) or other outcomes (oxygenation 1 to 12 hours after randomisation, need for mechanical ventilation, days of mechanical ventilation or continuous positive airways pressure (CPAP) or days of supplemental oxygen). No side effects of the nebulised surfactant therapy or aerosol inhalation were reported.

Authors' conclusions

There are insufficient data to support or refute the use of nebulised surfactant in clinical practice. Adequately powered trials are required to determine the effect of nebulised surfactant administration for prevention or early treatment of RDS in preterm infants. Nebulised surfactant administration should be limited to clinical trials.

PLAIN LANGUAGE SUMMARY

Nebulised surfactant in preterm infants with or at risk of respiratory distress syndrome

There is insufficient evidence from randomised controlled trials to guide the use of nebulised surfactant in preterm infants at risk of respiratory distress syndrome.

Respiratory distress syndrome is caused by a deficiency of the naturally occurring lining chemicals of the lung (surfactant) and occurs mainly in infants born before term (37 weeks' gestation). Usual treatment includes instilling artificial surfactant directly into the newborn infant's trachea followed by mechanical ventilation. However, this process can lead to lung injury, which can affect the infant's long-term health. A potential alternative strategy is to use nebulised surfactant. This procedure has the potential to reduce the need for tracheal intubation after birth and subsequent lung damage caused by mechanical ventilation. This review found one small randomised controlled trial of nebulised surfactant administration in preterm infants with respiratory distress syndrome that reported no beneficial effect of nebulised surfactant. This study is too small and has a moderate risk of bias making conclusions uncertain. In view of the encouraging results from other observational studies, high-quality trials of nebulised surfactant in preterm infants with or at risk of respiratory distress syndrome are justified.

BACKGROUND

Description of the condition

Respiratory distress syndrome (RDS) results from pulmonary surfactant deficiency and is an important cause of morbidity and mortality in preterm infants. Randomised controlled trials (RCTs) and meta-analyses have demonstrated the efficacy of surfactant therapy in both prevention and treatment of infants with or at risk for RDS. A wide variety of surfactant preparations have been studied. These include synthetic surfactants (Soll 2000; Soll 2010) and surfactants derived from animal sources (natural surfactants) (Soll 1997; Seger 2009). Although both synthetic and animal-derived surfactant preparations are effective, clinical trials suggest that animal-derived surfactant preparations (Soll 2001) may be more effective than protein-free synthetic surfactant (Tooley 1987). Furthermore, clinical trials have shown earlier treatment may be superior to selective use of surfactant in preventing morbidity and mortality in preterm infants (Yost 2000; Stevens 2007; Rojas-Reyes 2012), and a multiple-dose is superior to a single-dose strategy (Soll 2009). New protein-containing synthetic surfactants have been successfully tested (Pfister 2007; Pfister 2009) although these preparations are not currently available for clinical use.

Despite the benefits of surfactant, many infants develop bronchopulmonary dysplasia (BPD) and chronic lung disease (CLD). Although the aetiology of CLD in preterm infants is multifactorial (Allen 2003), ventilator-induced lung injury (VILI) remains one of the main implicated risk factors (Coalson 1999; Clark 2000). VILI has been shown to start with only a few resuscitative positive pressure ventilation (PPV) breaths (Grossmann 1986; Björklund 1997; Flecknoe 2008; O'Reilly 2008).

Both surfactant prophylaxis and therapy necessitate endotracheal intubation to facilitate surfactant administration. Although surfactant by itself is an established effective intervention for either prevention or treatment of RDS, the endotracheal intubation and PPV that follow are not without side effects.

Endotracheal intubation is a potentially traumatic procedure often performed without optimal pain management (Sarkar 2006).

It may be accompanied by significant haemodynamic instability including hypoxia, bradycardia, blood pressure fluctuation and intracranial pressure increase (Marshall 1984; Ghanta 2007). Intubation is inevitably associated with colonisation of the trachea, retained secretions resulting in collapse, differential aeration and high resistance to air flow resulting in increased work of breathing, potentially leading to nosocomial pneumonia and sepsis (Young 2005; Aly 2008). Intubation is associated with an inflammatory process that can lead to lung injury and BPD (Young 2005). Current evidence suggests PPV of an immature, surfactant-deficient lung is harmful and may exacerbate the development of BPD (Björklund 1997; Van Marter 2000). Björklund 1997 reported resuscitation of surfactant-deficient immature lambs with as few as six breaths damages the lung and blunts the therapeutic effect of subsequent surfactant replacement. Grossmann 1986 reported similar results. Flecknoe 2008 reported that just six hours of ventilation is enough to cause marked airway epithelial injury in very preterm and near-term foetal sheep. O'Reilly 2008 reported that ventilator-induced injury extends to involve the conducting airways as well.

One approach for surfactant administration is the InSurE (INtubation-SURfactant-Extubation) technique pioneered by Victorin and Verder (Verder 1994; Victorin 1990). Review of trials found early surfactant replacement therapy with prompt extubation to nasal continuous positive airway pressure (nCPAP), as in the InSurE technique, is associated with less need for mechanical ventilation, lower incidence of BPD and fewer air leak syndromes when compared with later selective surfactant replacement and continued mechanical ventilation with extubation from low ventilator support (Stevens 2007). However, the limited data available show the InSurE procedure to be associated with a trend for decreased cerebral oxygenation, higher cerebral oxygen extraction and decreased electric brain activity (Hellstrom-Westas 1992; van de Berg 2009). Furthermore, the InSurE procedure may need to be repeated if the first dose of surfactant was not sufficiently effective (Bohlin 2007), leading to additional risk of brain damage.

The main strategy used to avoid endotracheal intubation and PPV in premature infants is application of nCPAP or continuous distending pressure (CDP) immediately following birth (Kamper 1999; Ho 2002a; Ho 2002b). Some studies suggest CDP may lead to less CLD compared to elective intubation, surfactant and PPV (Aly 2001; DeKlerk 2001; SUPPORT Study Group 2010; Dunn 2011). Similarly, nasal intermittent positive pressure ventilation (NIPPV) has been shown to increase the likelihood of avoiding intubation and mechanical ventilation, reduce frequency of apnoea and a trend for less CLD without an increase in adverse effects (Lemyre 2002; Davis 2008). Although CDP and NIPPV strategies avoid endotracheal intubation and PPV, it precludes surfactant administration, which is a standard and confirmed treatment for RDS. Furthermore, CDP, NIPPV and InSurE may fail in 25% to 50% of preterm infants (Reininger 2005; Kugelman 2007; Morley 2008).

Description of the intervention

Non-invasive methods of surfactant administration have the potential to reduce the need for intubation and endotracheal surfactant administration. Potential strategies include:

1. intra-amniotic instillation (Petrikovsky 1995);
2. pharyngeal instillation (Kattwinkel 2004);
3. administration via laryngeal mask airway surfactant (Trevisanuto 2005);
4. administration via thin endotracheal catheter without intermittent positive pressure ventilation (IPPV) (Kribs 2007; Kribs 2010; Dargaville 2011);
5. nebulised surfactant administration in spontaneously breathing infants (Jorch 1997).

This review will focus on nebulised surfactant administration. The typical protocol for nebulised surfactant administration (Finer 2006) involves using an aerosol generator with nebulised surfactant administered via a nCPAP system, tight face-mask system or nasopharyngeal tube. Aerosol generators include jet nebulisers, ultrasonic nebulisers and vibrating membrane nebulisers. There is an aerosolised form of peptide-containing surfactant available but other forms of surfactant have also been tried.

In preterm animal models and animal models of induced lung injury, nebulised surfactant improved ventilation and lung mechanics, even with minimal deposition in the lungs (Lewis 1991; Lewis 1993a; Lewis 1993b; Lewis 1993c; Wolfson 2008). Johnson 2006 and Johnson 2007 measured surface activity of aerosolised lucinactant in vitro (using a pulsating bubble surfactometer) and in vivo (using a foetal rabbit bioassay). In both models, lucinactant retained its activity after capillary aerosol generation. Similar findings have been described for bovine surfactant (Jorch 1994). On average 0.08% to 15% of total administered aerosolised surfactant could be recovered in animal models (Lewis 1993c; Fok 1998; Bahlmann 2000). Multiple factors are reported to influence aerosol surfactant dose delivery, including patient weight or size; minute ventilation (Cole 2000), aerosol flow and patient peak inspiratory flow; aerosol particle size (as large as possible to avoid potential exhalation yet small enough to bypass the oropharynx) (Mazela 2007); aerosol generator used and type of surfactant (Fok 1998). An ultrasonic nebuliser and colfosceril palmitate (Exosurf) have been shown to have higher deposition than a jet nebuliser and beractant (Survanta) (Fok 1998).

Small human neonatal pilot and case series studies demonstrate conflicting results. Reports include studies showing that nebulised surfactant may reduce the need for endotracheal intubation and is well tolerated (Jorch 1997; Finer 2006), with no adverse effects reported apart from transient oxygen desaturation during dosing, and another report that nebulised surfactant had no beneficial effects (Arroe 1998).

How the intervention might work

The nebulised surfactant administration technique is designed to emit a continuous dense surfactant microaerosol of diameter less than 2 μm ideal for deep lung deposition. The technique is designed to avoid endotracheal intubation yet offer the benefits of surfactant administration. Combining this surfactant administration strategy with antenatal corticosteroid administration and CDP may offer potential synergy to treat RDS, avoiding both endotracheal intubation and PPV, and reducing lung injury that may lead to BPD. In a variety of animal models of induced lung injury, nebulised surfactant improved pulmonary mechanics, lung structure integrity, and reduced lung inflammation, even with minimal deposition in the lungs (Lewis 1991; Lewis 1993a; Wolfson 2008). However, other studies have showed that nebulised surfactant did not improve pulmonary parameters (Fok 1998).

Why it is important to do this review

Despite significant advances in neonatal intensive care, CLD results in a significant health burden to preterm infants born at less than 32 weeks' gestation who received mechanical ventilation. CLD results in substantial neonatal and infant morbidity and health resource utilisation (Allen 2003). CLD is associated with chronic respiratory difficulties (Kilbride 2003; Doyle 2006), prolonged and recurrent hospitalisation (Chye 1995), neurodevelopmental disability including cerebral palsy, neurosensory and motor disability (Skidmore 1990; Hughes 1999; Majnemer 2000) and poor cognitive outcome (Hughes 1999). CLD has a major impact on the daily life of families that persists beyond the neonatal period (Korhonen 1999). Nebulised surfactant is a physiological and logical technique with the potential benefit of avoiding ventilation, VILI and BPD.

OBJECTIVES

To determine the effect of nebulised surfactant administration compared to placebo, no treatment or intratracheal surfactant instillation on morbidity or mortality, or both, in preterm infants at risk for or having RDS.

METHODS

Criteria for considering studies for this review

Types of studies

Published, unpublished and ongoing RCTs; quasi-randomised trials regardless of unit of allocation (individual or cluster) were considered to be eligible for inclusion in this review.

Types of participants

Preterm infants (less than 37 weeks' gestation) at risk for or having RDS of any severity and at any postnatal age as included in the trials.

We defined prophylactic surfactant therapy as all treatment strategies in which the intent was to treat a preterm infant based on the risk of RDS within the first hour of life. We defined risk of RDS as gestational age of less than 32 weeks or birthweight less than 1250 g.

We defined treatment of established disease ('rescue therapy') as treatment of a preterm infant less than 37 weeks' gestational age requiring respiratory support and having signs and symptoms of RDS.

Types of interventions

Nebulised surfactant administration at any dose, using any type of surfactant (synthetic, animal derived or protein-containing synthetic), any route of conduit (nasopharyngeal tube, laryngeal airway, nasal prong or face mask), and using any aerosol generator compared with either placebo, no treatment or intratracheal instilled surfactant. We planned to perform separate comparisons for all above comparative groups if trial data were available.

Types of outcome measures

We planned to study the following primary and secondary outcome measures.

Primary outcomes

1. CLD defined as need for oxygen or respiratory support at 36 weeks' postmenstrual age (PMA) (Shennan 1988).
2. Mortality prior to hospital discharge.
3. Neurodevelopmental disability assessed at 18 months' postnatal age or later defined as neurological abnormality including cerebral palsy on clinical examination, developmental delay more than two standard deviations below population mean on a standardised test of development, blindness (visual acuity less than 6/60) or deafness (any hearing impairment requiring amplification) at any time after term corrected.

Secondary outcomes

1. Intratracheal surfactant received post-intervention.
2. Mechanical ventilation.
3. Days on mechanical ventilation.
4. Days on CPAP.
5. Days of high-flow nasal cannula.
6. Days of low-flow nasal cannula.
7. Days of supplemental oxygen administration.
8. Pulmonary interstitial emphysema.

9. Pneumothorax.

10. Use of high-frequency oscillatory ventilation (HFOV) as a rescue treatment for respiratory distress.

11. Use of jet ventilation as a rescue treatment for respiratory distress.

12. Use of extracorporeal membrane oxygenation (ECMO) as a rescue treatment for respiratory distress.

13. Use of postnatal corticosteroids as rescue treatment for respiratory distress.

14. CLD defined as need for oxygen or respiratory support at 28 days of age.

15. Use of diuretic as a prophylaxis or rescue treatment for CLD.

16. Use of postnatal corticosteroid as a prophylaxis or rescue treatment for CLD.

17. Use of home oxygen.

18. Asthma diagnosed by physician or challenge test.

19. Rehospitalisation for asthma.

20. Rehospitalisation for hyperactive airway disease.

21. Rehospitalisation for pneumonia.

22. Neonatal mortality (mortality at less than 28 days of age).

23. Intraventricular haemorrhage (any and severe - Papile grade 3 or 4) (Papile 1978).

24. Cystic periventricular leukomalacia.

25. Patent ductus arteriosus (PDA) - symptomatic or treated with cyclo-oxygenase inhibitors or surgical ligation.

26. Necrotising enterocolitis (confirmed = Bell stage 2 or greater) (Bell 1978).

27. Retinopathy of prematurity (any and severe = stage 3 or higher) (International Committee 2005).

28. Apnoea treated with methylxanthines or respiratory support.

29. Time to regain birth weight (days).

30. Systemic infection in first 48 hours of life.

31. Postnatal growth failure (weight less than 10th percentile at discharge).

32. Duration of hospitalisation (days).

33. Adverse effect of the intervention including hypoxia and bradycardia during administration.

34. Discontinuation of intervention because of side effects (e.g. bradycardia).

Search methods for identification of studies

See: Cochrane Neonatal Group methods used in reviews.
We used the standard search strategy of the Cochrane Neonatal Review Group (CNRG) as outlined in *The Cochrane Library*. We considered unpublished studies to be eligible for review. The search of MEDLINE and PREMEDLINE (via OVID interface) included the following MeSH terms and free text words: "infant, premature, preterm, newborn, neonate", "surfactant", "laryngeal", "mask", "airway". We limited searches to "randomised and quasi-

randomised clinical trials" (Appendix 1). We adapted this search strategy to suit other electronic sources like the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and CINAHL. We did not apply any language restrictions.

Electronic searches

We searched the following electronic databases:
1. the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, January 2012);
2. MEDLINE and PREMEDLINE (1950 to January 2012) via OVID interphase;
3. EMBASE (1980 to January 2012) via OVID interphase;
4. CINAHL (1982 to January 2012) via EBSCO interphase;
5. GoogleScholar.

Searching other resources

We conducted additional searches of the following:
1. Ongoing trials in the following trial registries (searched January 2012):
    ○ ClinicalTrials.gov (U.S. National Institutes of Health);
    ○ Current Controlled Trials;
    ○ Australian New Zealand Clinical Trials Registry;
    ○ International Clinical Trials Registry Platform (ICTRP).
2. Abstract of conferences from:
    ○ Proceedings of the Pediatric Academic Societies (American Pediatric Society, Society for Pediatric Research and European Society for Pediatric Research) from 1990 to 2011 from the journal *Pediatric Research* and Abstracts Online;
    ○ Proceedings of the European Academy of Paediatric Societies (EAPS) (The European Society for Paediatric Research (ESPR), the European Academy of Paediatrics (EAP) and the European Society of Paediatric and Neonatal Intensive Care (ESPNIC)) from 2003 to 2011 from Abstracts Online;
    ○ Proceedings of the Perinatal Society of Australia and New Zealand (PSANZ) from 1996 to 2011 (handsearch).
3. Reference lists: after reading the identified individual studies that examined the effect of laryngeal surfactant installation on the morbidity mortality, or both, in preterm infants at risk of RDS, we screened the reference lists of these papers to identify further relevant studies;
4. Personal communications with expert informants and authors of included studies;
5. Pharmaceutical companies: we contacted the companies that developed different types of surfactant for possible unpublished studies using their product.

Data collection and analysis

We used the standardised review method of the CNRG for conducting a systematic review (http://neonatal.cochrane.org/en/index.html). We entered and cross-checked data using Review Manager 5.1 software (RevMan 2011).

Selection of studies

Both review authors independently reviewed the titles and abstracts of potentially relevant studies against the inclusion and exclusion criteria. The two review authors independently assessed titles and the abstracts of studies identified by the search strategy for eligibility for inclusion in this review. We retrieved full-text versions for closer examination for eligible studies or when inadequate information was provided in the abstract.

Data extraction and management

Both review authors independently extracted data from the full-text articles using a specifically designed spreadsheet matrix to manage the information. These forms were used to decide trial inclusion or exclusion, extract data from eligible trials and for requesting additional published information from authors of the original report. We entered and cross-checked data using RevMan 5.1 software (RevMan 2011). We then compared the extracted data for any differences. If noted, we planned to resolve differences by mutual discussion and consensus.

Assessment of risk of bias in included studies

We used the standardised review methods of the CNRG (http://neonatal.cochrane.org/en/index.html) to assess the methodological quality of included studies. Review authors independently assessed study quality and risk of bias (see: Characteristics of included studies) using the following criteria documented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

  1. Sequence generation: was the allocation sequence adequately generated?

  2. Allocation concealment: was allocation adequately concealed?

  3. Blinding of participants, personnel and outcome assessors for each main outcome or class of outcomes: was knowledge of the allocated intervention adequately prevented during the study?

  4. Incomplete outcome data for each main outcome or class of outcomes: were incomplete outcome data adequately addressed?

  5. Selective outcome reporting: are reports of the study free of suggestion of selective outcome reporting?

  6. Other sources of bias: was the study apparently free of other problems that could put it at a high risk of bias? We gave particular attention to completeness of follow-up of all randomised infants and to the length of follow-up studies to identify whether any benefits claimed are robust.

When necessary, we requested additional information and clarification of published data from the authors of individual trials. We assessed each trial for risk of bias based on the criteria listed above and marked as:

- low risk of bias;
- unclear risk of bias;
- high risk of bias.

We resolved discrepancies by mutual discussion and consensus. We planned to provide levels of agreement among review authors and details of resolution of any differences.

Measures of treatment effect

We analysed treatment effects in the individual trials using RevMan 5.1 (RevMan 2011).

Dichotomous data

We reported dichotomous data using risk ratio (RR) and risk difference (RD), each with 95% confidence interval (CI). If there was a statistically significant reduction in RD we then calculated the number needed to treat for a beneficial outcome (NNTB) or number needed to treat for a harmful outcome (NNTH) and associated 95% CI.

Continuous data

We reported continuous data using mean difference (MD) with 95% CI.

Unit of analysis issues

The unit of randomisation was the intended unit of analysis and we expected this to be individual infants. Cluster RCTs were planned to be included.

Cluster randomised trials

We planned to include cluster-randomised trials in the analyses, along with individually randomised trials, using methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using an estimate of the intra-cluster correlation coefficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources were used, we planned to report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we had identifies both cluster randomised trials and individually randomised trials, we planned to synthesise the relevant information. We considered it reasonable to combine the results from both if there was little heterogeneity between study designs, and the interaction between the effect of intervention and the choice of randomisation unit was considered to be unlikely.

Dealing with missing data

We planned to obtain missing data from the study authors when possible. If this was not possible, then we planned to conduct analyses on available data (i.e. ignoring the missing data). In addition, we planned to conduct another analysis by using an imputation method (both best- and worst-case scenarios) and last observation carried forward to the final assessment (LOCF) method for dichotomous and continuous outcome data, respectively.

For dichotomous outcomes we planned to conduct both best- and worst-case scenarios and intention-to-treat (ITT) analysis with imputation. We planned to compare results obtained from two analysis options to have a better understanding of the robustness of results relative to the different analytic approaches. We planned to consider an imputation approach of best-case scenarios (i.e. all missing participants in the intervention group did not experience poor outcomes (e.g. death, BPD) and all missing participants in the control group experienced poor outcomes) and worst-case scenarios (i.e. all missing participants in the intervention group experienced the event and all missing participants in the control condition did not). We planned to conduct sensitivity analysis to compare results based on different imputation assumptions (i.e. best- versus worst-case scenarios).

We planned to analyse missing continuous data on an end point basis, including only participants with a final assessment, or using LOCF if the trial authors report any LOCF data.

Assessment of heterogeneity

We used RevMan 5.1 (RevMan 2011) to assess the heterogeneity of treatment effects between trials. We used the two formal statistics described below.

1. The Chi^2 test, to assess whether observed variability in effect sizes between studies was greater than would be expected by chance. Since this test has low power when the number of studies included in the meta-analysis is small, we planned to set the probability at the 10% level of significance.

2. The I^2 statistic to ensure that pooling of data was valid. We planned to grade the degree of heterogeneity as: 0% to 30%: might not be important; 31% to 50%: moderate heterogeneity; 51% to 75%: substantial heterogeneity; 76% to 100%: considerable heterogeneity.

Where there was evidence of apparent or statistical heterogeneity, we planned to assess the source of the heterogeneity using sensitivity and subgroup analysis looking for evidence of bias or methodological differences between trials.

Assessment of reporting biases

We planned to investigate reporting and publication bias by examining the degree of asymmetry of a funnel plot. RevMan 5.1 (RevMan 2011) has the capability to produce this graph, which plots the effect size estimated from each individual study against some measure of study sample size. A symmetrical appearance of the funnel plot will indicate absence of publication bias. Otherwise, existence of bias is related to the degree of asymmetry.

Data synthesis

We planned to perform statistical analyses according to the recommendations of CNRG (http://neonatal.cochrane.org/en/index.html). We planned to analyse all infants randomised on an ITT basis. We planned to analyse treatment effects in the individual trials. We planned to use a fixed-effect model in the first instance to combine the data. For any meta-analyses, for categorical outcomes we planned to calculate typical estimates of RR and RD, each with 95% CI; for continuous outcomes we planned to calculate the MD if outcomes were measured in the same way between trials, and standardised mean difference (SMD) to combine trials that measured the same outcome, but use different scales. When we judged meta-analysis to be inappropriate, we planned to analyse and interpret individual trials separately.

Subgroup analysis and investigation of heterogeneity

Providing sufficient data were available, we planned to explore potential sources of clinical heterogeneity through the following a priori subgroup analyses:

1. timing of nebulised surfactant administration: prophylactic, early rescue (within the first two hours of life), late rescue (within the first week of life), or very late rescue (after the first week of life);

2. type of surfactant aerosol generator used (jet, ultrasonic or vibrating membrane nebuliser);

3. aerosol particle diameter regardless of aerosol generator and type of surfactant used (2 μm or less, greater than 2 μm in diameter);

4. type of surfactant used (specialised surfactant made for inhalation, other non-specialised surfactant) regardless of being synthetic or natural;

5. route of administration (nasopharyngeal tube, laryngeal airway, nasal prong or face mask);

6. type of surfactant used (synthetic, animal derived or protein-containing synthetic);

7. gestational age at delivery (less than 28, 28 to 31, 32 to 34 and 35 or greater completed weeks' gestation).

Sensitivity analysis

Where sufficient data were available, we planned to explore methodological heterogeneity through the use of sensitivity analyses, which will serve to test the degree of robustness of the results obtained by the meta-analysis. We planned to perform sensitivity analyses through excluding trials of lower quality, based on a lack of any of the following: allocation concealment, adequate

randomisation, blinding of treatment, less than 10% loss to fol-low-up. Sensitivity analysis for effect of losses would include an analysis using LOCF and imputation analysis (as above).

R E S U L T S

Description of studies

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

Results of the search

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

A total of five reports were considered for this review. Four were eliminated because they did not involve random allocation, a control group, or both (Jorch 1997; Arroe 1998; Finer 2010) or did involve infant-simulator only (Pearson 2005). One study (Berggren 2000) was included in the present review. Details of this study are provided in the Characteristics of included studies table. No ongoing trials were identified.

Included studies

Types of participants

Berggren 2000 enrolled 34 preterm infants, with 32 infants reported who met inclusion criteria including clinically and radiologically diagnosed RDS, corrected gestational age < 36 weeks, age two to 36 hours, arterio/alveolar oxygen tension ratio (a/A pO$_2$) 0.15 to 0.22, fraction inspired oxygen (FiO$_2$) needed to maintain arterial oxygen saturation (SaO$_2$) 85% to 95%; transcutaneous partial pressure oxygen (tcpO$_2$) 6 to 8 kPa tcpO$_2$ 6 to 8 kPa, partial pressure oxygen (PaO$_2$) 7.5 to 9 kPa > 0.4, and no evidence of lung or cardiovascular malformation. Two infants were later excluded because they did not fulfil the inclusion criteria.

Types of interventions

Berggren 2000 compared 480 mg of nebulised surfactant (Curosurf) generated via jet aerosol generator (Aiolos®, Karlstad, Sweden) and given via nCPAP equipment versus no treatment. There was no standard 'failure criteria', but in most cases a/A pO$_2$ < 0.15 was considered as an indication for intubation and ventilation.

Types of outcomes measures

Berggren 2000 reported the following:
- a/A pO$_2$ at 0, 2, 4, 6 and 12 hours post-randomisation;
- air leak;
- requirement of mechanical ventilation;
- duration of mechanical ventilation;
- duration of CPAP;
- duration of oxygen supplement;
- PDA;
- pathological cerebral ultrasound at one week;
- CLD.

Neurodevelopmental disability and some of the pre-specified secondary outcome measures of the review were not reported by Berggren 2000.

Excluded studies

No other randomised, cluster-randomised or quasi-RCTs were identified for exclusion from the review. Four observational non-randomised and non-controlled studies were identified and excluded from this review (Jorch 1997; Arroe 1998; Pearson 2005; Finer 2010).

Risk of bias in included studies

The single included study (Berggren 2000) was at moderate risk of bias. Although the study reported an ITT analysis, the study had unclear sequence generation and methods for maintaining allocation concealment, lacked blinding and standardised failure criteria, and had analyses of multiple respiratory end points. Ratings of methodological quality are given in the Characteristics of included studies table.

Allocation

Berggren 2000 randomised infants using a centralised scheme. Method of sequence generation was not reported. Allocation was concealed by using sealed envelopes.

Blinding

Berggren 2000 did not mask investigators, outcome assessors or families to study group.

Incomplete outcome data

Berggren 2000 reported 2/34 (6%) infants excluded (one in each group) post allocation as not meeting enrolment criteria.

Selective reporting

Primary outcomes were not specific - described as 'safety and need for mechanical ventilation' (Berggren 2000).

Other potential sources of bias

Indication for intubation and ventilation (failure of intervention) was not standardised, but in most cases a/A pO_2 < 0.15 was considered as an indication for intubation and ventilation. pH was lower in the treatment group compared to controls at randomisation (7.29 versus 7.32; P < 0.019).

Effects of interventions

Prophylactic treatment of preterm infants with nebulised surfactant versus no treatment

No studies were found that enrolled infants at risk of RDS irrespective of the need for respiratory support or diagnosis of RDS.

Treatment of RDS with nebulised surfactant versus no treatment (Comparison 1)

One study compared treatment of RDS with nebulised surfactant versus no treatment (Berggren 2000).

Primary outcome measures

Chronic lung disease at 36 weeks' postmenstrual age

Berggren 2000 reported no significant difference in CLD (32 infants; RR 5.00; 95% CI 0.26 to 96.59) (Analysis 1.1). Test for heterogeneity not applicable.
Mortality and neurodevelopmental outcome were not reported.

Secondary outcome measures

Berggren 2000 reported no significant difference in mechanical ventilation (RR 1.20; 95% CI 0.46 to 3.15) (Analysis 1.2), air leak (RR 1.00; 95% CI 0.30 to 3.32) (Analysis 1.3), PDA (RR 1.50; 95% CI 0.29 to 7.81) (Analysis 1.4) or pathological cerebral ultrasound at one week (RR 0.29; 95% CI 0.01 to 6.50) (Analysis 1.5). Berggren 2000 reported no significant difference in median days of IPPV (intervention six days versus control five days), CPAP (intervention seven days versus control six days) and oxygen (intervention 15 days versus control seven days). Test for heterogeneity not applicable.
Other secondary outcome measures were not reported.

Subgroup analyses

The following subgroup analyses were pre-specified. As only one study reported data, the outcomes are as reported above.

1. Timing of nebulised surfactant administration: prophylactic, early rescue (within the first two hours of life), late rescue (within the first week of life), or very late rescue (after the first week of life): Berggren 2000 reported late rescue treatment (mean age at treatment 19 hours).

2. Type of surfactant aerosol generator used (jet, ultrasonic or vibrating membrane nebuliser): Berggren 2000 reported use of jet aerosol generator (Aiolos®, Karlstad, Sweden).

3. Aerosol particle diameter regardless of aerosol generator and type of surfactant used (2 μm or less, greater than 2 μm in diameter): Berggren 2000 reported 99% of the particles in the aerosol had a diameter < 2 μm.

4. Type of surfactant used (specialised surfactant made for inhalation, other non-specialised surfactant) regardless of being synthetic or natural: Berggren 2000 reported use of non-specialised surfactant (Curosurf1, Chiesi Farmaceutici, Parma, Italy).

5. Type of surfactant used (synthetic, animal derived or protein-containing synthetic): Berggren 2000 reported use of animal derived surfactant (Curosurf1, Chiesi Farmaceutici, Parma, Italy).

6. Route of administration (nasopharyngeal tube, laryngeal airway, nasal prong or face mask): Berggren 2000 reported administration via nasal prongs using nasal CPAP circuit (Infant Flow System1, Dansjo Medical AB, Bromma, Sweden).

7. Gestational age at delivery (less than 28, 28 to 31, 32 to 34 and 35 or greater completed weeks' gestation): Berggren 2000 enrolled infants with median gestational age 31 weeks (range 28 to 34 weeks) and median birth weight 1603 to 1620 g (range 755 to 2855 g).

Sensitivity analysis

We planned to perform a sensitivity analysis based on the following: inadequate randomisation, allocation concealment or blinding of treatment, or greater than 10% loss to follow-up. Berggren 2000 reported unclear randomisation and allocation concealment, and 6% losses post randomisation. Berggren 2000 reported no masking of investigators, outcome assessors or families to study group.

DISCUSSION

Summary of main results

Only one small study was identified and found to be eligible for inclusion. This study enrolled preterm infants with RDS on nCPAP

and reported no significant differences between nebulised surfactant and control group in CLD, a/A pO$_2$ 1 to 12 hours after randomisation, number of infants needing mechanical ventilation, time on ventilator or CPAP, or duration of oxygen supplement. No side effects of the nebulised surfactant therapy or aerosol inhalation were noted.

Overall completeness and applicability of evidence

The single small study included in the review reported outcomes for 32 preterm infants with RDS on nCPAP and used nebulised surfactant as treatment of established RDS. The data are largely applicable to late treatment of established RDS in relatively mature preterm infants. However, the study was underpowered to detect important clinical benefits and harms of nebulised surfactant for treatment of RDS. Furthermore, the study is of moderate risk of bias.

No study was found that examined the effect of nebulised surfactant administration for prevention of RDS (e.g. at resuscitation) or early treatment of RDS in keeping with the known benefits of prophylactic (Rojas-Reyes 2012) and early surfactant treatment (Stevens 2007) in very preterm infants.

Quality of the evidence

The single included study (Berggren 2000) was of moderate risk of bias. The study was unblinded, had unclear sequence generation, lacked standard definition for failure criteria (intubation and ventilation) and had analysis of multiple respiratory end points.

Potential biases in the review process

An extensive search for published and unpublished literature was performed including searches of trial registries for ongoing studies. Two review authors independently assessed eligibility, study quality and extracted data. Agreement was reached through consensus.

Agreements and disagreements with other studies or reviews

Berggren 2000 and Arroe 1998; demonstrated no beneficial effects of nebulised surfactant, either during the period of nebulisation or after the nebulisation. The discrepancy between these negative results and other pilot observations (Jorch 1997; Pearson 2005; Finer 2010) might be attributed to multiple factors:

• excessive loss of aerosolised surfactant in the nCPAP device: Jorch 1997 reported successful treatment of RDS by aerosolised surfactant using a jet nebuliser and delivery of the aerosol via a

nasopharyngeal tube. This is may raise the issue of excessive loss when using nCPAP;

• size of the particles in the generated aerosol: however a diameter < 2 μm as used by Berggren 2000 should be ideal for deposition in peripheral airspaces;

• the effectiveness of delivery of aerosolised surfactant: the effectiveness of delivery of aerosolised surfactant depends on the type of aerosol generator (jet, ultrasonic or vibrating membrane nebuliser). Arzhavitina 2010 hypothesise that a vibrating membrane nebuliser is the best device for substances with surface activity such as surfactant, as the residual volume in the device is minimal and the substance output maximal. These results still need confirmation by in vivo studies;

• timing of nebulised surfactant administration: for endotracheal administration prophylactic (Soll 1998) and early surfactant treatment (Soll 1999) have been demonstrated to be more beneficial.

A non-systematic review of literature by Mazela 2007 concluded that nebulised surfactant is a potentially beneficial strategy for non-invasive surfactant delivery and further studies are needed.

AUTHORS' CONCLUSIONS

Implications for practice

A single underpowered study of jet-nebulised animal-derived surfactant in preterm infants did not detect any benefits or harms in preterm infants with established RDS on CPAP. There are insufficient data to support or refute its use in clinical practice. Nebulised surfactant administration should be limited to clinical trials.

Implications for research

Adequately powered trials with appropriately designed delivery systems are required to determine the effect of nebulised surfactant administration for prevention or treatment of RDS in preterm infants. Studies should measure short- and long-term outcomes pre-specified in this review. Given the evidence for prophylactic and early surfactant administration, trials should enrol infants early in the course of respiratory illness.

Currently there are no ongoing registered trials for nebulised surfactant with ClinicalTrials.gov (searched 27 January 2012).

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Berggren 2000

Methods	Multicentre RCT
Participants	Preterm infants who fulfilled the following enrolment criteria: • corrected gestational age < 36 weeks • age 2 to 36 hours • clinically and radiologically diagnosed progressive RDS • a/A pO_2 0.15 to 0.22 • FiO_2 needed to maintain SaO_2 85% to 95%; $tcpO_2$ 6 to 8 kPa and PaO_2 7.5 to 9 kPa • No evidence lung or cardiovascular malformation Infants were excluded if they did not fulfil the above criteria
Interventions	Nebulised surfactant group (N = 17): received nCPAP according to normal clinical routines. In addition, total of 480 mg of nebulised surfactant (Curosurf) was generated via jet aerosol generator (Aiolos®, Karlstad, Sweden) and given via nCPAP equipment. Surfactant was diluted to 20 mg/mL before nebulisation, and 5-mL portions of the diluted material were aerosolised alternating with 2-mL portions of saline. The procedure took around 3 hours Standard protocol (N = 17): received nCPAP alone, without nebulised surfactant. Placebo treatment with, for instance, saline, was considered unethical and therefore not applied Indication for intubation and ventilation was not standardised, but in most cases a/A pO_2 < 0.15 was considered as indication for intubation and ventilation
Outcomes	Outcomes included: • a/A pO_2 at 0, 1, 2, 4, 6 and 12 hours post-randomisation • air leak • requirement of mechanical ventilation • duration of mechanical ventilation • duration of CPAP • duration of oxygen supplement • PDA • pathological cerebral ultrasound at 1 week • chronic lung disease
Notes	Study sponsorship not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Centralised randomisation. Method of sequence generation not reported

Berggren 2000   (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Allocation using sealed envelopes kept on neonatal ward. Numbering and opaqueness not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo used
Blinding of outcome assessment (detection bias) All outcomes	High risk	No placebo used, blinding of outcome assessment not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/34 (6%) infants excluded (1 in each group) post allocation as not meeting enrolment criteria
Selective reporting (reporting bias)	Unclear risk	Primary outcomes not specific - 'safety and need for mechanical ventilation'
Other bias	High risk	Indication for intubation and ventilation was not standardised, but in most cases a/A pO_2 < 0.15 was considered as indication for intubation and ventilation. pH was lower in the treatment group compared to controls at randomisation (7.29 versus 7.32; P < 0.019)

a/A pO_2: arterio/alveolar oxygen tension ratio; CLD: chronic lung disease; nCPAP: nasal continuous positive airway pressure; PDA: patent ductus arteriosus; RCT: randomised controlled trial; RDS: respiratory distress syndrome

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

Study	Reason for exclusion
Arroe 1998	Observational non-randomised and non-controlled study
Finer 2010	Observational non-randomised and non-controlled study
Jorch 1997	Observational non-randomised and non-controlled study
Pearson 2005	Observational non-randomised and non-controlled study involving infant-simulator

DATA AND ANALYSES

Comparison 1. Treatment of RDS with nebulised surfactant versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Chronic lung disease	1	32	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.26, 96.59]
2 Mechanical ventilation	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.46, 3.15]
3 Air leak	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.30, 3.32]
4 Patent ductus arteriosus	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.29, 7.81]
5 Pathological cerebral ultrasound at 1 week	1	26	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.01, 6.50]

Analysis 1.1. Comparison 1 Treatment of RDS with nebulised surfactant versus no treatment, Outcome 1 Chronic lung disease.

Review: Nebulised surfactant in preterm infants with or at risk of respiratory distress syndrome

Comparison: 1 Treatment of RDS with nebulised surfactant versus no treatment

Outcome: 1 Chronic lung disease

Study or subgroup	Nebulised surfactant n/N	No treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Berggren 2000	2/16	0/16		100.0 %	5.00 [0.26, 96.59]
Total (95% CI)	**16**	**16**		**100.0 %**	**5.00 [0.26, 96.59]**

Total events: 2 (Nebulised surfactant), 0 (No treatment)
Heterogeneity: not applicable
Test for overall effect: Z = 1.07 (P = 0.29)
Test for subgroup differences: Not applicable

0.2   0.5   1   2   5
Favours experimental   Favours control
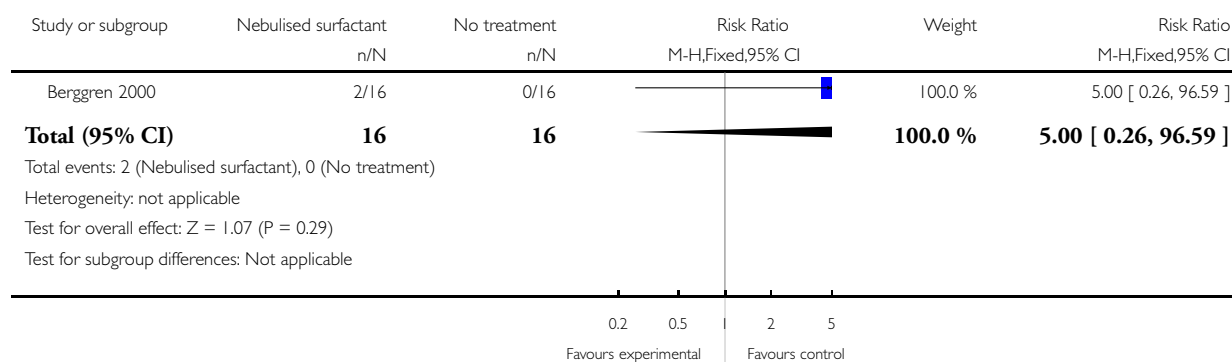
Analysis 1.2. Comparison 1 Treatment of RDS with nebulised surfactant versus no treatment, Outcome 2 Mechanical ventilation.

Review: Nebulised surfactant in preterm infants with or at risk of respiratory distress syndrome

Comparison: 1 Treatment of RDS with nebulised surfactant versus no treatment

Outcome: 2 Mechanical ventilation
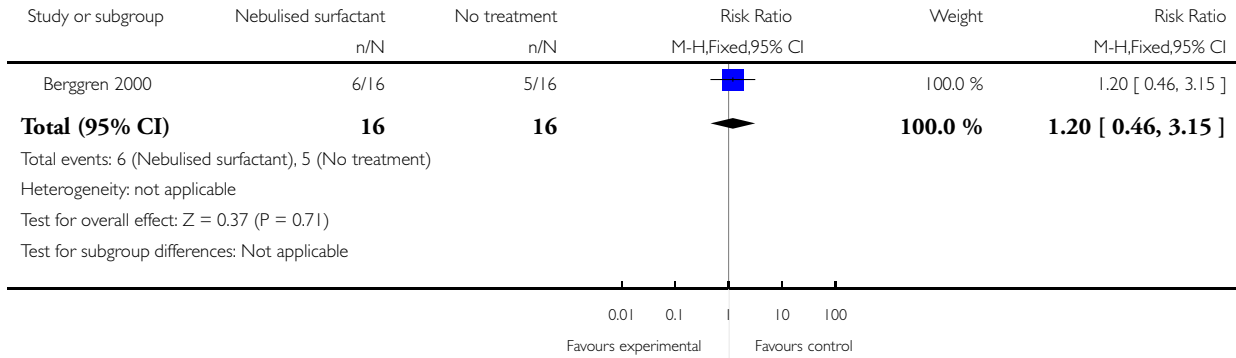
Study or subgroup	Nebulised surfactant n/N	No treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Berggren 2000	6/16	5/16		100.0 %	1.20 [0.46, 3.15]
Total (95% CI)	**16**	**16**		**100.0 %**	**1.20 [0.46, 3.15]**

Total events: 6 (Nebulised surfactant), 5 (No treatment)

Heterogeneity: not applicable

Test for overall effect: Z = 0.37 (P = 0.71)

Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10    100
     Favours experimental   Favours control
```
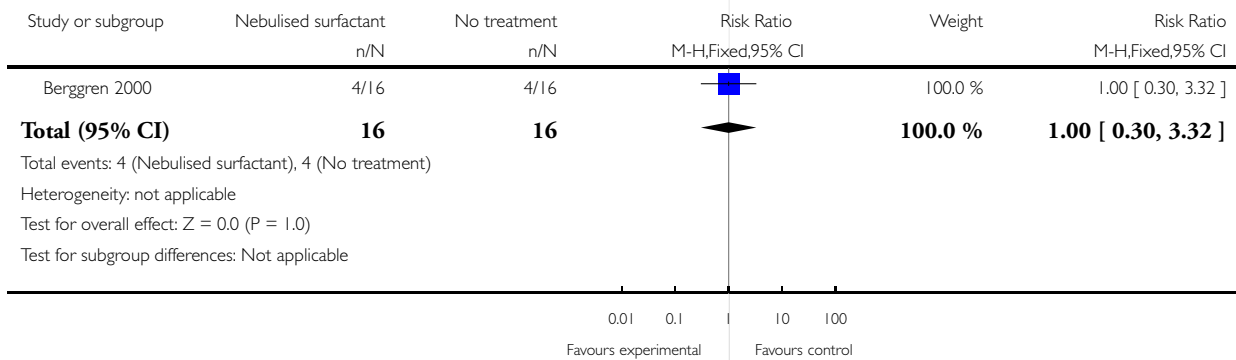
Analysis 1.3. Comparison 1 Treatment of RDS with nebulised surfactant versus no treatment, Outcome 3 Air leak.

Review: Nebulised surfactant in preterm infants with or at risk of respiratory distress syndrome

Comparison: 1 Treatment of RDS with nebulised surfactant versus no treatment

Outcome: 3 Air leak

Study or subgroup	Nebulised surfactant n/N	No treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Berggren 2000	4/16	4/16		100.0 %	1.00 [0.30, 3.32]
Total (95% CI)	**16**	**16**		**100.0 %**	**1.00 [0.30, 3.32]**

Total events: 4 (Nebulised surfactant), 4 (No treatment)

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)

Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10    100
     Favours experimental   Favours control
```
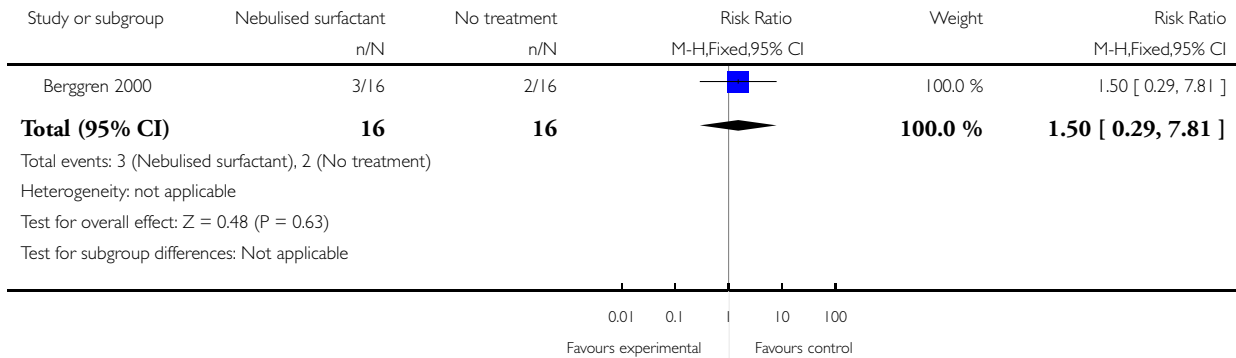
Analysis 1.4.   Comparison I Treatment of RDS with nebulised surfactant versus no treatment, Outcome 4 Patent ductus arteriosus.

Review: Nebulised surfactant in preterm infants with or at risk of respiratory distress syndrome

Comparison: I Treatment of RDS with nebulised surfactant versus no treatment

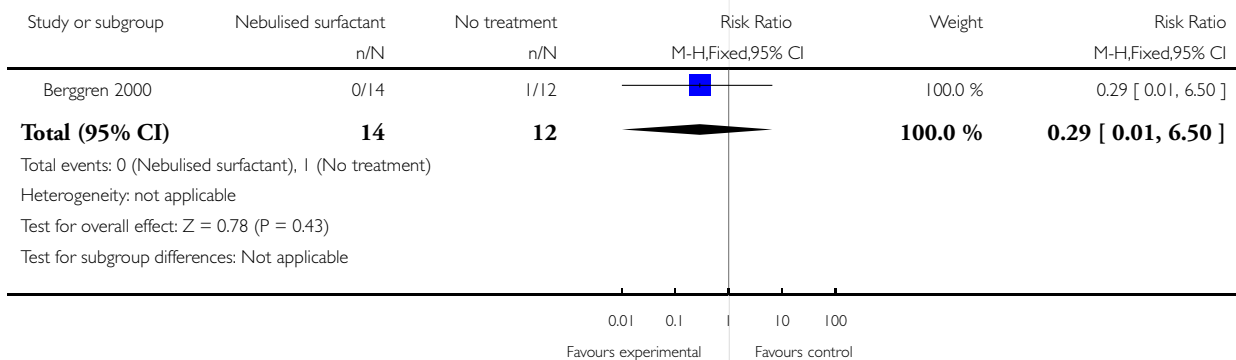Outcome: 4 Patent ductus arteriosus

Study or subgroup	Nebulised surfactant n/N	No treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Berggren 2000	3/16	2/16		100.0 %	1.50 [0.29, 7.81]
Total (95% CI)	**16**	**16**		**100.0 %**	**1.50 [0.29, 7.81]**

Total events: 3 (Nebulised surfactant), 2 (No treatment)

Heterogeneity: not applicable

Test for overall effect: Z = 0.48 (P = 0.63)

Test for subgroup differences: Not applicable

```
        0.01    0.1     I    10   100
        Favours experimental   Favours control
```

Analysis 1.5.   Comparison I Treatment of RDS with nebulised surfactant versus no treatment, Outcome 5 Pathological cerebral ultrasound at I week.

Review: Nebulised surfactant in preterm infants with or at risk of respiratory distress syndrome

Comparison: I Treatment of RDS with nebulised surfactant versus no treatment

Outcome: 5 Pathological cerebral ultrasound at I week

Study or subgroup	Nebulised surfactant n/N	No treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Berggren 2000	0/14	1/12		100.0 %	0.29 [0.01, 6.50]
Total (95% CI)	**14**	**12**		**100.0 %**	**0.29 [0.01, 6.50]**

Total events: 0 (Nebulised surfactant), I (No treatment)

Heterogeneity: not applicable

Test for overall effect: Z = 0.78 (P = 0.43)

Test for subgroup differences: Not applicable

```
        0.01    0.1     I    10   100
        Favours experimental   Favours control
```

APPENDICES

Appendix 1. MEDLINE search strategy

#1 exp pregnancy
#2 exp infant premature
#3 exp infant newborn
#4 exp obstetric labor premature
#5 exp premature birth
#6 pregnan*.mp OR prematur*.mp OR preterm.mp OR neonat*.mp OR infant*.mp OR newborn.mp
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
#8 aerosoli*.mp
#9 nebuli*.mp
#10 #8 OR #9
#11 exp pulmonary surfactants
#12 surfactant*.mp OR Beractant.mp OR Poractant.mp OR Curosurf.mp OR Survanta.mp OR Exosurf.mp OR Lucinactant.mp OR Aerosurf.mp
#13 #11 OR #12
#14 #7 AND #10 AND #13

HISTORY

Protocol first published: Issue 1, 2010

Review first published: Issue 10, 2012

CONTRIBUTIONS OF AUTHORS

Mohamed E Abdel-Latif wrote the first draft of the review and revised subsequent drafts; assessed study eligibility, carried out data extraction, and entered data.

David A Osborn assessed study eligibility, entered data, carried out data extraction, checked data, commented and revised subsequent drafts of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Biological Agents [*administration & dosage]; Infant, Newborn; Infant, Premature; Nebulizers and Vaporizers; Phospholipids [*administration & dosage]; Pulmonary Surfactants [*administration & dosage]; Respiratory Distress Syndrome, Newborn [*drug therapy]

MeSH check words

Humans