Cochrane Library

Cochrane Database of Systematic Reviews

Protein-free synthetic surfactant for the prevention and treatment of respiratory distress syndrome in neonates (Protocol)

Lasalvia P, Buitrago Lopez A, Rojas-Reyes MX, Özek E, Soll R

Lasalvia P, Buitrago Lopez A, Rojas-Reyes MX, Özek E, Soll R.
Protein-free synthetic surfactant for the prevention and treatment of respiratory distress syndrome in neonates.
Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD012821.
DOI: 10.1002/14651858.CD012821.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Protein-free synthetic surfactant for the prevention and treatment of respiratory distress syndrome in neonates

Pieralessandro Lasalvia[1], Adriana Buitrago Lopez[1], Maria Ximena Rojas-Reyes[2], Eren Özek[3], Roger Soll[4]

[1]Department of Clinical Epidemiology and Biostatistics, Pontificia Universidad Javeriana, Bogota, Colombia. [2]Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Pontificia Universidad Javeriana, Bogotá, Colombia. [3]Pediatrics / Division of Neonatology, Maramara University Medical Center, Istanbul, Turkey. [4]Division of Neonatal-Perinatal Medicine, University of Vermont Medical Center, Burlington, Vermont, USA

Contact address: Maria Ximena Rojas-Reyes, Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Pontificia Universidad Javeriana, Cr. 7 #40-62, 2nd floor, Bogotá, DC, Colombia. mxrojas@gmail.com, mxrojas@javeriana.edu.co.

Editorial group: Cochrane Neonatal Group.
Publication status and date: New, published in Issue 10, 2017.

Citation: Lasalvia P, Buitrago Lopez A, Rojas-Reyes MX, Özek E, Soll R. Protein-free synthetic surfactant for the prevention and treatment of respiratory distress syndrome in neonates. *Cochrane Database of Systematic Reviews* 2017, Issue 10. Art. No.: CD012821. DOI: 10.1002/14651858.CD012821.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the effectiveness of intratracheal administration of synthetic protein-free pulmonary surfactant in neonates at risk of developing RDS or with established RDS.

Comparison 1: Does intratracheal administration of synthetic protein-free pulmonary surfactant compared to air placebo or normal saline or no treatment reduce mortality and other complications of preterm birth in preterm infants at risk of developing RDS?

Comparison 2: Does intratracheal administration of synthetic protein-free pulmonary surfactant compared to air placebo or normal saline or no treatment reduce mortality and other complications of preterm birth in preterm infants with clinical and/or radiologic evidence of respiratory distress syndrome requiring assisted ventilation?

BACKGROUND

Description of the condition

Pulmonary surfactant is an aggregate of lipid and proteins present on the alveolar surface. Pulmonary surfactant is predominantly dipalmitoylphosphatidylcholine (DPPC) with lesser amounts of other phospholipids including phosphatidylglycerol (PG), phosphatidylethanolamine, and phosphatidylinositol. Pulmonary surfactant also contains neutral lipids and distinct surfactant proteins (Jobe 1993).

The physiologic function of surfactant includes the ability to lower surface tension, as well as the ability to rapidly absorb, spread, and reform a monolayer in the dynamic conditions associated with the respiratory cycle (Jobe 1993). Surfactant lines the alveolar surface and prevents atelectasis at end-expiration by minimizing surface tension on air-water surfaces (Jobe 2006).

Respiratory distress syndrome (RDS) is caused by a deficiency

or dysfunction of pulmonary surfactant resulting in inadequate pulmonary function and respiratory failure.

Description of the intervention

The first attempts to utilize synthetic surfactants occurred in the 1960s. Investigators attempted to aerosolize DPPC to infants with established respiratory distress syndrome (Robillard 1964; Chu 1967). These investigators could not demonstrate any beneficial effect of surfactant replacement. The poor results were due to an incomplete understanding of what constitutes pulmonary surfactant. The first successful animal model of surfactant replacement therapy was conducted by Enhorning and coworkers (Enhorning 1972). Enhorning administered a crude, natural surfactant extract obtained from lavage of the lungs of mature rabbits directly into the trachea of immature rabbits, and noted improvement in lung compliance and alveolar expansion. Success in animal models led to widespread clinical trials of surfactant therapy in the newborn. A wide variety of surfactant products has been formulated and studied in clinical trials. These include protein-free synthetic surfactants and animal-derived or 'natural' surfactant extracts. Animal-derived surfactant extracts are derived from animal or human sources. Protein-free synthetic surfactants are complex combinations of DPPC and other phospholipids, neutral lipids, lipoprotein, or alcohols. Components of synthetic surfactants are not directly obtained from the extraction of surfactant from animal lung.

How the intervention might work

The therapeutic action of surfactant can be classified in three phases: acute effects; subacute effects; and chronic effects (Jobe 2006). The first phase is a consequence of surfactant distribution in the lungs. If a sufficiently homogeneous distribution is obtained, fetal lungs will expand with lower volumes, will achieve higher lung volumes and will avoid airway collapse during respiration. This immediately results in increased oxygenation. The subacute and chronic effects depend on the long half-life of surfactant in the airway and the relatively high amount of surfactant that is administered. Catabolism may take several days and the preterm lung efficiently recycles exogenous surfactant. The same may not happen when lungs suffer some kind of injury. In this case, physiologic pathways may be compromised and a second dose of surfactant may be warranted.

Why it is important to do this review

Cochrane Reviews have extensively evaluated pulmonary surfactant use for preventing and treating respiratory disease in neonates. Most of these reviews focus on infants with or at risk of RDS. These reviews include reviews of surfactant in the prevention (Soll 2000; Soll 2010) and treatment (Soll 1998; Seger 2009) of RDS, reviews that compare different animal-derived products (Singh 2015) or animal derived vs synthetic products (Soll 2001), and reviews that evaluate newer protein-containing synthetic surfactants (Pfister 2007; Pfister 2009).

Reviews also compare timing of surfactant treatment (Stevens 2007;Abdel-Latif 2011c, Bahadue 2012; Rojas-Reyes 2012), surfactant dosing (Soll 2009), and methods of surfactant instillation (Abdel-Latif 2011a: Abdel-Latif 2011b; Abdel-Latif 2012).

Several reviews evaluate surfactant in conditions other than RDS, including surfactant for pulmonary hemorrhage in neonates (Aziz 2012), surfactant for bacterial pneumonia in late preterm and term infants (Tan 2012), and surfactant treatment in meconium aspiration syndrome (El Shahed 2007; Hahn 2013).

This review will merge and update the two previously separate reviews regarding protein-free synthetic surfactant for therapeutic (Soll 1998) and prophylactic (Soll 2010) use in neonates with or at risk of RDS. In addition, this review will incorporate newer methodological standards for systematic reviews including 'Summary of findings' tables and GRADE recommendations.

OBJECTIVES

To evaluate the effectiveness of intratracheal administration of synthetic protein-free pulmonary surfactant in neonates at risk of developing RDS or with established RDS.

Comparison 1: Does intratracheal administration of synthetic protein-free pulmonary surfactant compared to air placebo or normal saline or no treatment reduce mortality and other complications of preterm birth in preterm infants at risk of developing RDS?

Comparison 2: Does intratracheal administration of synthetic protein-free pulmonary surfactant compared to air placebo or normal saline or no treatment reduce mortality and other complications of preterm birth in preterm infants with clinical and/or radiologic evidence of respiratory distress syndrome requiring assisted ventilation?

METHODS

Criteria for considering studies for this review

Types of studies

Inclusion criteria.

1. Randomized or quasi-randomized controlled trials comparing intratracheal synthetic protein-free surfactant with air placebo or normal saline or no treatment in infants at risk for or having respiratory distress syndrome.

2. No language restriction.

Exclusion criteria.

1. Studies carried out on non-humans.
2. Letters, abstracts, systematic reviews, meta-analysis, ecological studies and conference presentations.
3. Cross-over trials and cluster trials.

Types of participants

For the prophylactic use: Preterm infants at risk for respiratory distress syndrome (with or without evidence of surfactant deficiency).

For the therapeutic use: Preterm infants with clinical and/or radiologic evidence of respiratory distress syndrome requiring assisted ventilation.

Types of interventions

Infants randomized to receive protein-free synthetic surfactant as treatment or prophylaxis versus control treatment (intratracheal administration of air placebo or normal saline or no treatment). Protein-free surfactant preparations include Exosurf Neonatal (dipalmitoylphosphatidylcholine (DPPC), hexadecanol, and tyloxapol), dry powdered DPPC and phosphatidylglycerol (PG), or any other protein-free synthetic surfactants.

Types of outcome measures

Outcomes presented in previous reviews will be considered for inclusion in this updated review (Soll 1998; Soll 2010). In order to better synthesize results, outcomes will be ranked by a clinical expert as critical, important or not important following the GRADE working group recommendation (Guyatt 2011).

Primary outcomes

For both comparisons (prophylactic indication and treatment) the primary outcomes identified were:

1. mortality from any cause (including neonatal mortality < 28 days of age and mortality prior to hospital discharge);
2. bronchopulmonary dysplasia defined as supplemental oxygen at 28 to 30 days of age;
3. chronic lung disease defined as supplemental oxygen at 36 weeks' postmenstrual age;
4. bronchopulmonary dysplasia or death at 28 days of age;
5. chronic lung disease or death at 36 weeks' postmenstrual age.

Secondary outcomes

The secondary outcomes identified were:

1. respiratory distress syndrome (for prophylactic studies only);
2. pneumothorax;
3. pulmonary interstitial emphysema;
4. air leak syndromes (including pulmonary interstitial emphysema, pneumothorax, pneumomediastinum);
5. pulmonary haemorrhage;
6. patent ductus arteriosus (PDA) (PDA that has been treated with cyclo-oxygenase inhibitor or surgery);
7. culture-proven bacterial sepsis;
8. culture-proven fungal sepsis;
9. necrotizing enterocolitis (NEC) (defined as Bell stage II or greater);
10. intraventricular haemorrhage (IVH) (any grade and severe (grade 3 to 4));
11. periventricular leukomalacia (PVL);
12. retinopathy of prematurity (ROP) (all stages and severe (stage 3 or greater));
13. rehospitalization;
14. cerebral palsy (any and moderate/severe cerebral palsy);
15. neurodevelopmental outcome at approximately two years' corrected age (acceptable range 18 months to 28 months) including: cerebral palsy, mental delay (Bayley Scales of Infant Development Mental Developmental Index < 70), legal blindness (< 20/200 visual acuity), and hearing deficit (aided or < 60 dB on audiometric testing). The composite outcome 'neurodevelopmental impairment' was defined as having any one of the aforementioned deficits.

Search methods for identification of studies

We will use the standard search methods of the Cochrane Neonatal Review Group.

Electronic searches

We will bring the search from the previous review up to date.

We will search the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE Ovid, Embase and CINAHL. We will include trials in all languages.

Search terms: {surfactant OR pulmonary surfactant}, limited to humans and further limited to the age group of newborn infants (infant, newborn) and type of publication (clinical trial). We will perform similar search using the following text words: exosurf, colfoseril, DPPC with similar limits noted above. From the resulting studies, we will select randomized or quasi-randomized controlled studies that fulfill the inclusion criteria.

To identify long-term neurodevelopmental sequelae, we will perform a search using the following keywords: (outcome OR sequelae OR follow-up OR mental retardation OR cerebral palsy OR hearing OR visual OR motor OR mental OR psychological) AND (surfactant OR pulmonary surfactant) not limited to any age group or language. We will search the bibliography cited in

each publication obtained in order to identify additional relevant articles.

Searching other resources

Published abstracts: We will handsearch the abstracts of the Society for Pediatric Research (USA) (published in *Pediatric Research*) from 1985 to 1999 using the following key words: {surfactant OR pulmonary surfactant} AND {respiratory distress syndrome}. We will search abstracts from 2000 to 2013 electronically through the Pediatric Academic Societies (PAS) website (abstracts online).
We will also search clinical trials' registries for ongoing or recently completed trials (ClinicalTrials.gov; Controlled-Trials.com; and who.int/ictrp/search/en/).

Data collection and analysis

For each included study, we will collect information regarding the method of randomization, blinding, surfactant use as intervention, treatment use as control, stratification and whether the trial was single or multicenter. We will note information regarding trial participants including birth weight criteria, gestational age and other inclusion or exclusion criteria.

Selection of studies

We will include all randomized and quasi-randomized controlled trials fulfilling the selection criteria described in the previous section. Lasalvia P and Buitrago A will review the results of the search and will separately select the studies for inclusion. They will try to resolve any disagreement by discussion. If consensus cannot be reached, Rojas MX will resolve the disagreement.

Data extraction and management

The review authors will separately extract, assess and code all data for each study using a form that was designed specifically for this review. We will resolve disagreements by discussion. Lasalvia P will enter data into Review Manager 5 (Review Manager 2014); Rojas MX will then check the entries.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2011) for the following domains.

- Sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Any other bias.

The two authors will resolve any disagreements by discussion or, in the event of deadlock, by calling on a third author to act as arbitrator. See Appendix 2 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

Statistical analyses will be performed using Review Manager 5 software (Review Manager 2014). Categorical data will be analyzed using risk ratio (RR), risk difference (RD), the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH). Continuous data will be analyzed using mean difference (MD). We will report the 95% confidence interval (CI) on all estimates.

Unit of analysis issues

We will assess dichotomous data using participants (rather than events) as the unit of analysis to avoid counting the same participant more than once.

Dealing with missing data

We will perform all outcomes analyses on an intention-to-treat basis (i.e. we will include in these analyses all participants randomly assigned to each group). The denominator for each outcome in each trial will be the number randomly assigned minus the number of participants whose outcomes were known to be missing.
We will request additional data from authors of studies in cases of lack of information on critical and important outcomes.
We will address the potential impact of missing data on the findings of the review in the 'Discussion' section.

Assessment of heterogeneity

We will estimate treatment effects of individual trials and will evaluate the presence of heterogeneity among trials' results by inspecting forest plots and quantifying the impact of heterogeneity using the I^2 statistic.
We will consider the degree of heterogeneity based on the I^2 as follows: less than 25% indicates no heterogeneity; 25% to 49% indicates low heterogeneity; 50% to 75% indicates moderate heterogeneity; and more than 75% indicates substantial heterogeneity. If we note statistical heterogeneity ($I^2 > 50\%$), we will explore possible causes (e.g. differences in study quality, participants, intervention regimens or outcome assessments) using post hoc subgroup analyses.

Assessment of reporting biases

We will assess possible reporting biases on two levels: within-study and between-studies.
We will examine within-study selective outcome reporting as a part of the overall 'Risk of bias' assessment.
We will attempt to find protocols for included studies and compare the outcomes stated in the protocols with those reported in the publications. We will compare the outcomes listed in the 'Methods' section of a publication with those for which results are reported if protocols are not found.
We will contact study authors for clarification if we identify indications of reporting bias.
If there are at least 10 studies included in the review (independently for prophylactic and for therapeutic use), we will create a funnel plot of effect estimates against their standard errors (SE) to assess possible reporting bias between studies. We will consider possible explanations if we find asymmetry of the funnel plot.

Data synthesis

We will perform meta-analysis using Review Manager 5 software (RevMan 2011). For estimates of typical RR and RD, we will use the Mantel-Haenszel method. For measured quantities, we will use the inverse variance method. We will use a fixed-effect model for all meta-analyses.

Quality of evidence

We will use the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes.
Six clinical experts in neonatology evaluated and ranked outcomes. For prophylactic use they defined the following outcomes as critical.

1. Respiratory distress syndrome of the newborn.
2. Pneumothorax.
3. Neonatal mortality.
4. Mortality at hospital discharge.
5. Bronchopulmonary dysplasia defined as supplemental oxygen at 28 to 30 days of age.
6. Chronic lung disease defined as supplemental oxygen at 36 weeks' postmenstrual age.
7. Bronchopulmonary dysplasia or death at 28 days of age.
8. Chronic lung disease or death at 36 weeks' postmenstrual age.

Neurodevelopment outcome at two years was categorized as important but not critical.
Pulmonary hemorrhage was categorized as an important safety outcome.
For therapeutic use they considered the following outcomes as critical.

1. Pneumothorax.
2. Neonatal mortality.
3. Mortality at hospital discharge.
4. Bronchopulmonary dysplasia defined as supplemental oxygen at 28 to 30 days of age.
5. Chronic lung disease defined as supplemental oxygen at 36 weeks' postmenstrual age.
6. Bronchopulmonary dysplasia or death at 28 days of age.
7. Chronic lung disease or death at 36 weeks' postmenstrual age.

Neurodevelopment outcome at two years was categorized as important but not critical.
Pulmonary haemorrhage was categorized as an important safety outcome.
Other outcomes were considered as not critical or not important.
Two authors will independently assess the quality of the evidence for each of the outcomes above. We will consider evidence from randomized controlled trials as high quality but downgrade the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We will use the GRADEpro GDT Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence.
The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades:

1. High: We are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

The following 'a priori' subgroup analyses are planned.
For the prophylactic use of surfactant we will evaluate the impact of the intervention by the following subgroups.

- Surfactant product: DPPC/high-density lipoprotein (HDL), DPPC/PG, DPPC/hexadecanol/tyloxapol.
- Gestational age (infants born at < 28 weeks' gestation).
- Birth weight (< 1000 grams).

For the use of surfactant as treatment of established RDS we will evaluate the impact of the intervention by the following subgroups' surfactant product.

- Surfactant product: DPPC/high-density lipoprotein (HDL), DPPC/PG, DPPC/hexadecanol/tyloxapol.
- Gestational age (infants born at < 28 weeks' gestation).

- Birth weight (< 1000 grams).

Sensitivity analysis

We plan to carry out the following sensitivity analyses.

- A comparison based on our 'Risk of bias' assessments.
- A sensitivity analysis to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect.
- A comparison of results from fixed-effect models versus results from random-effects models should non-explained heterogeneity be found.

ACKNOWLEDGEMENTS

This review-update protocol was supported by the Faculty of Medicine of Pontificia Universidad Javeriana, Bogotá, Colombia that is a Cochrane Associated Center - Cochrane Colombia.

Pier Lasavia is a medical student participant from the Systematic Reviews Seed Research Program of the "Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine of the Pontificia Universidad Javeriana, Bogotá, Colombia".

Authors thanks Dr. Eren Özek for his work in the previous version of this review. For this updating review protocol, many aspects of the previous review have been kept.

REFERENCES

Additional references

Abdel-Latif 2011a
Abdel-Latif ME, Osborn DA. Pharyngeal instillation of surfactant before the first breath for prevention of morbidity and mortality in preterm infants at risk of respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2011, Issue 3. [DOI: 10.1002/14651858.CD008311.pub2

Abdel-Latif 2011b
Abdel-Latif ME, Osborn DA. Laryngeal mask airway surfactant administration for prevention of morbidity and mortality in preterm infants with or at risk of respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2011, Issue 7. [DOI: 10.1002/14651858.CD008309.pub2

Abdel-Latif 2011c
Abdel-Latif ME, Osborn DA. Pharyngeal instillation of surfactant before the first breath for prevention of morbidity and mortality in preterm infants at risk of respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2011, Issue 3. [DOI: 10.1002/14651858.CD008311.pub2

Abdel-Latif 2012
Abdel-Latif ME, Osborn DA. Nebulised surfactant in preterm infants with or at risk of respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2012, Issue 10. [DOI: 10.1002/14651858.CD008310.pub2

Aziz 2012
Aziz A, Ohlsson A. Surfactant for pulmonary haemorrhage in neonates. *Cochrane Database of Systematic Reviews* 2012, Issue 7. [DOI: 10.1002/14651858.CD005254.pub3

Bahadue 2012
Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2012, Issue 11. [DOI: 10.1002/14651858.CD001456.pub2

Chu 1967
Chu J, Clements JA, Cotten EK, Klaus MH, Sweet AY, Tooley WH, et al. Neonatal pulmonary Ischemia. *Pediatrics* October 1967;**40 Suppl**(4):709–82.

El Shahed 2007
El Shahed AI, Dargaville P, Ohlsson A, Soll RF. Surfactant for meconium aspiration syndrome in full term/near term infants. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD002054.pub2

Enhorning 1972
Enhorning G, Robertson B. Lung expansion in the premature rabbit fetus after tracheal deposition of surfactant. *Pediatrics* 1972;**50**:58–66.

GRADEpro GDT [Computer program]
GRADE Working Group, McMaster University. GRADEpro GDT. Version accessed 09 March 2017. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Guyatt 2011
Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, Alderson P, Glasziou P, Falck-Ytter Y, Schünemann HJ. GRADE guidelines: 2. Framing the question and deciding on important outcomes [GRADE guidelines: 2. Framing the question and deciding on important outcomes]. *Journal of Clinical Epidemiology* 2011;**64**(4):395–400.

Hahn 2013
Hahn S, Choi HJ, Soll R, Dargaville PA. Lung lavage for meconium aspiration syndrome in newborn infants. *Cochrane Database of Systematic Reviews* 2013, Issue 4. [DOI: 10.1002/14651858.CD003486.pub2

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

Jobe 1993
Jobe AH. Pulmonary surfactant therapy. *New England Journal of Medicine* 1993;**328**(12):861–8.

Jobe 2006
Jobe AH. Mechanisms to explain surfactant responses. [Mechanisms to explain surfactant responses.]. *Biology of the neonate* 2006;**89**(4):298–302.

Pfister 2007
Pfister RH, Soll RF, Wiswell T. Protein containing synthetic surfactant versus animal derived surfactant extract for the prevention and treatment of respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: 10.1002/14651858.CD006069.pub3

Pfister 2009
Pfister RH, Soll R, Wiswell TE. Protein-containing synthetic surfactant versus protein-free synthetic surfactant for the prevention and treatment of respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD006180.pub2

Review Manager 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Robillard 1964
Robillard E, Alarie Y, Dagenais-Perusse P, Baril E, Guilbeault A. Micro-aerosol administration of synthetic dipalmitoyl lecithin in the respiratory distress syndrome: a preliminary report. *Canadian Medical Association Journal* 1964;**90**: 55–7.

Rojas-Reyes 2012
Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews* 2012, Issue 3. [DOI: 10.1002/14651858.CD000510.pub2

Schünemann 2013
Schünemann H, Broż ek J, Guyatt G, Oxman A, editors. GRADE Working Group. GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations. Available from www.guidelinedevelopment.org/handbook Updated October 2013.

Seger 2009
Seger N, Soll R. Animal derived surfactant extract for treatment of respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD007836

Singh 2015
Singh N, Halliday HL, Stevens TP, Suresh G, Rojas-Reyes MX, Soll R. Comparison of animal-derived surfactants for the prevention and treatment of respiratory distress syndrome in preterm infants. *Cochrane Database of Systematic Reviews* 2015, Issue 12. [DOI: 10.1002/14651858.CD010249.pub2

Soll 2000
Soll RF. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews* 2000, Issue 2. [DOI: 10.1002/14651858.CD000511

Soll 2001
Soll RF, Blanco F. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2001, Issue 2. [DOI: 10.1002/14651858.CD000144

Soll 2009
Soll R, Ozek E. Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD000141.pub2

Soll 2010
Soll R, Ozek E. Prophylactic protein free synthetic surfactant for preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD001079.pub2

Stevens 2007
Stevens TP, Harrington EW, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: 10.1002/14651858.CD003063.pub3

Tan 2012
Tan K, Lai NM, Sharma A. Surfactant for bacterial pneumonia in late preterm and term infants. *Cochrane Database of Systematic Reviews* 2012, Issue 2. [DOI: 10.1002/14651858.CD008155.pub2

References to other published versions of this review

Soll 1992
Soll RF, McQueen MC. Respiratory distress syndrome. In: Sinclair JC, Bracken MB editor(s). *Effective Care of the Newborn Infant*. Oxford: Oxford University Press, 1992: 325–58.

Soll 1998
Soll RF. Synthetic surfactant for respiratory distress syndrome in preterm infants. *Cochrane Database of Systematic Reviews* 1998, Issue 3. [DOI: 10.1002/14651858.CD001149

Soll 2000c
Soll RF. Prophylactic synthetic surfactant for preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews* 2000, Issue 2. [DOI: 10.1002/14651858.CD001079

Soll 2010a
Soll R, Ozek E. Prophylactic protein free synthetic surfactant for preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD001079.pub2

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Risk of bias tool

We will use the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality (to meet the validity criteria) of the trials. For each trial, we will seek information regarding the method of randomisation, and the blinding and reporting of all outcomes of all the infants enrolled in the trial. We will assess each criterion as low, high, or unclear risk. Two review authors will separately assess each study. We will resolve any disagreement by discussion. We will add this information to the table Characteristics of included studies. We will evaluate the following issues and enter the findings into the 'Risk of bias' table.

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

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

a. low risk (any truly random process e.g. random number table; computer random number generator);

b. high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number);

c. unclear risk.

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

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

a. low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);

b. high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);

c. unclear risk.

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

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

a. low risk, high risk or unclear risk for participants;

b. low risk, high risk or unclear risk for personnel;

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

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

a. low risk for outcome assessors;

b. high risk for outcome assessors;

c. unclear risk for outcome assessors.

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

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

a. low risk (< 20% missing data);

b. high risk ($\geq$ 20% missing data);

c. unclear risk.

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

For each included study, we will describe how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

a. low risk (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);

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

c. unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?
For each included study, we will describe any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We will assess whether each study was free of other problems that could put it at risk of bias as:
a. low risk;
b. high risk;
c. unclear risk.
If needed, we plan to explore the impact of the level of bias through undertaking sensitivity analyses.

CONTRIBUTIONS OF AUTHORS

Pier Lasavia and Adriana Buitrago wrote the first draft of the protocol. María Ximena Rojas and Roger Soll commented and contributed to the protocol and approved it before its publication.

DECLARATIONS OF INTEREST

MXR-R has no conflict of interest in the proposed review.

ABL has no conflict of interest in the proposed review.

PL has no conflict of interest in the proposed review.

EO has no conflict of interest to declare.

RS has previously consulted with a variety of companies that have manufactured surfactant products but has not done so for over 10 years.

SOURCES OF SUPPORT

Internal sources

- Faculty of Medicine of Pontificia Universidad Javeriana, Cochrane COLOMBIA-Associated Center, Colombia.

Supported the time dedicated by María Ximena Rojas and Adriana Buitrago.

External sources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, USA.

Editorial support of the Cochrane Neonatal Review Group has been funded with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201600005C