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Surfactant for meconium aspiration syndrome in term and late preterm infants

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Amr I El Shahed | Peter A Dargaville | Arne Ohlsson | Roger Soll

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Abstract

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Background

Surfactant replacement therapy has been proven beneficial in the prevention and treatment of neonatal respiratory distress syndrome (RDS). The deficiency of surfactant or surfactant dysfunction may contribute to respiratory failure in a broader group of disorders, including meconium aspiration syndrome (MAS).

Objectives

To evaluate the effect of surfactant administration in the treatment of late preterm and term infants with meconium aspiration syndrome.

Search methods

We searched *The Cochrane Library* (Issue 4, 2006), MEDLINE and EMBASE (1985 to December 2006), previous reviews including cross-references, abstracts, conference and symposia proceedings, expert informants, and journal handsearching, without language restrictions. We contacted study authors for additional data.

We ran an updated search in November 2014 and searched the following sites for ongoing or recently completed trials: www.clinicaltrials.gov; www.controlled-trials.com; and www.who.int/ictrp.

Selection criteria

Randomised controlled trials which evaluated the effect of surfactant administration in late preterm and term infants with meconium aspiration syndrome are included in the analyses.

Data collection and analysis

We extracted data on clinical outcomes including mortality, treatment with extracorporeal membrane oxygenation (ECMO), pneumothorax, duration of assisted ventilation, duration of supplemental oxygen, intraventricular haemorrhage (any grade and severe IVH), and chronic lung disease. We conducted data analyses in accordance with the standards of the Cochrane Neonatal Review Group.

Main results

Four randomised controlled trials met our inclusion criteria. The meta-analysis of four trials (326 infants) showed no statistically significant effect on mortality [typical risk ratio (RR) 0.98, 95% confidence interval (CI) 0.41 to 2.39; typical risk difference (RD) -0.00, 95% CI -0.05 to 0.05]. There was no heterogeneity for this outcome (I^2 = 0% for both RR and RD). The risk of requiring extracorporeal membrane oxygenation was significantly reduced in a meta-analysis of two trials (n = 208); [typical RR 0.64, 95% CI 0.46 to 0.91; typical RD -0.17, 95% CI -0.30 to -0.04; number needed to treat for an additional beneficial outcome (NNTB) 6, 95% CI 3 to 25]. There was no heterogeneity for RR (1^2 = 0%) but moderate heterogeneity for RD (I^2 = 50%). One trial (n = 40) reported a statistically significant reduction in the length of hospital stay (mean difference -8 days, 95% CI -14 to -3 days; test for heterogeneity not applicable). There were no statistically significant reductions in any other outcomes studied (duration of assisted ventilation, duration of supplemental oxygen, pneumothorax, pulmonary interstitial emphysema, air leaks, chronic lung disease, need for oxygen at discharge or intraventricular haemorrhage).

Authors' conclusions

In infants with MAS, surfactant administration may reduce the severity of respiratory illness and decrease the number of infants with progressive respiratory failure requiring support with ECMO. The relative efficacy of surfactant therapy compared to, or in conjunction with, other approaches to treatment including inhaled nitric oxide, liquid ventilation, surfactant lavage and high frequency ventilation remains to be tested.

Plain language summary

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Surfactant for meconium aspiration syndrome in term and late preterm infants

Lay title: Surfactant treatment for infants who have inhaled meconium into the lungs in or around the time of birth

Review question: Does the administration of surfactant improve lung function and lead to better clinical outcomes in infants born at or near term who have inhaled meconium in or around the time of birth?

Background: The lungs of newborn babies can be damaged by meconium aspiration syndrome. Meconium aspiration syndrome is caused when a stressed baby passes a bowel movement while still in the womb and then breathes some of this material into the lungs. Pulmonary surfactant, the complex combination of chemicals that line the surface of the lung, may be altered or inactivated in babies who have meconium aspiration. It is thought that treatment with additional surfactant might help overcome this damage.

Study characteristics: Four randomised controlled trials enrolling 326 infants met our inclusion criteria.

Results: This review of trials found that surfactant can prevent worsening of breathing difficulties and reduce the need for heart-lung bypass therapy in some babies suffering from meconium aspiration syndrome .

Authors' conclusions

Available in **English** | Español

Implications for practice

The results of this systematic review provide some support for the use of surfactant treatment in meconium aspiration syndrome (MAS). In infants with MAS leading to moderate to severe respiratory failure, surfactant administration will decrease the number of infants treated with extracorporeal membrane oxygenation (ECMO). This may have implications especially in resource-poor settings where ECMO is not available. In the only study reporting on the duration of hospital stay, this outcomes was significantly reduced.

Implications for research

Although surfactant therapy may be of use in severe MAS, the efficacy of surfactant therapy compared to other approaches including inhaled nitric oxide, liquid ventilation, and high frequency ventilation remains to be tested. Other approaches to surfactant therapy, including the use of surfactant lavage, may prove to be effective in the treatment of MAS. Trials that compare surfactant treatment to surfactant lavage and air (control) would be appropriate. The findings of this review need to be confirmed in randomised controlled trials of appropriate size.

Background

Description of the condition

The deficiency of surfactant or surfactant dysfunction may contribute to respiratory failure in a broad group of disorders, including meconium aspiration syndrome (MAS). Meconium inhibits the surface tension-lowering properties of surfactant (Chen 1985; Moses 1991). Instillation of meconium into the airways of term animals leads to acute mechanical obstruction and worsening pulmonary mechanics and gas exchange (Chen 1985; Tran 1980; Tyler 1978). A significant reduction in lung compliance, an increase in expiratory lung resistance and increased functional residual capacity can be demonstrated (Tran 1980). Investigators have postulated that the changes in compliance associated with meconium aspiration result from displacement of surfactant by free fatty acids (Clark 1987). In animals with experimentally induced meconium aspiration, treatment with large doses of animal-derived surfactant extract improves compliance and ventilation (Sun 1993).

Description of the intervention

Surfactant replacement therapy has been proven beneficial in the prevention and treatment of neonatal respiratory distress syndrome (RDS) (Soll 1992). Respiratory distress syndrome is due to a primary deficiency in the production and release of pulmonary surfactant. Surfactant therapy has been shown to improve oxygenation, decrease the need for ventilatory support, and improve clinical outcome in infants with RDS. Surfactant-treated infants have a reduced mortality and a decreased incidence of pneumothorax.

Uncontrolled studies of surfactant treatment in infants with MAS suggest that surfactant may be of benefit in MAS. In a pilot study of seven infants with MAS treated with surfactant, all seven demonstrated an improvement in respiratory failure (Auten 1991). Khammash 1993 treated 20 infants with severe MAS. Infants received an intratracheal dose of bovine surfactant extract (100 mg phospholipid/kg). Improvement in oxygenation index (OI) and arterial/alveolar ratio (a/A pO_2) were noted in 75% of the treated infants in the six hours following surfactant instillation. None of the treated infants required further experimental therapy, including extracorporeal membrane oxygenation (ECMO).

Other approaches to prevent or treat MAS include amnioinfusion (infusion of saline into the amniotic cavity), oronasopharyngeal suctioning of meconium-stained neonates before delivery and the use of surfactant lavage in infants with the diagnosis of MAS.

In a systematic review of amnioinfusion in women with meconium-stained fluid, Hofmeyr 2010 found no significant reduction in the primary outcomes of MAS, perinatal death or severe morbidity, and maternal death or severe morbidity. However, some benefits were reported in a subgroup analysis including studies performed at facilities where perinatal surveillance was limited.

Vain 2004 assessed the effectiveness of intrapartum suctioning for the prevention of MAS in a large multicentre randomised controlled trial. The primary outcome was the incidence of MAS. No significant difference between treatment groups was seen in the incidence of MAS, in mortality, or in the duration of ventilation, oxygen treatment, and hospital care. The authors concluded that routine intrapartum oropharyngeal and nasopharyngeal suctioning of

term-gestation infants born through meconium-stained amniotic fluid does not prevent MAS. These findings led to changes in clinical practice, with routine suctioning of the oropharynx and the nasopharynx currently not recommended (AAP 2006).

Why it is important to do this review

This systematic review evaluates randomised controlled trials that studied the effect of bolus surfactant administration for the treatment of term and late preterm infants with MAS. This updates the previous review *Surfactant for meconium aspiration syndrome in full term/near term infants* (El Shahed 2007).

Studies that utilised dilute surfactant solutions to lavage meconium from the airways are not included in this review (Hahn 2013).

Several other Cochrane reviews evaluate surfactant in the treatment of respiratory disorders in neonates. Most of these reviews focus on infants with or at risk of RDS. Systematic reviews include reviews of surfactant in the prevention (Soll 1998; Soll 2010) and treatment (Seger 2009; Soll 1998) of RDS, reviews that compare animal-derived products to synthetic products (Soll 2001), and reviews that evaluate newer protein-containing synthetic surfactants (Pfister 2007; Pfister 2009).

Other reviews compare timing of treatment (Bahadue 2012; Rojas-Reyes 2012; Stevens 2007), surfactant dosing (Soll 2009), methods of surfactant instillation (Abdel-Latif 2011a; Abdel-Latif 2011b: Abdel-Latif 2012) or the use of surfactant in conditions other than RDS including surfactant for pulmonary haemorrhage in neonates (Aziz 2012) and surfactant for bacterial pneumonia in late preterm and term infants (Tan 2012).

Objectives

To evaluate the effect of surfactant administration in the treatment of late preterm and term infants with meconium aspiration syndrome (MAS).

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials comparing surfactant treatment to routine management of late preterm and term infants with MAS.

Types of participants

Late preterm and term infants with MAS (modified from the previous review, which planned to include only term infants).

Types of interventions

Intratracheal administration of surfactant versus placebo or no therapy. We have not included studies that utilised dilute surfactant solutions to lavage meconium from the airways.

Types of outcome measures

For the update of this review, the following primary and secondary outcomes were selected:

Primary outcomes

1. Mortality

Secondary outcomes

1. Treatment with extracorporeal membrane oxygenation (ECMO);
2. Pneumothorax;
3. Pulmonary interstitial emphysema;
4. Air leaks (pneumothorax, pneumomediastinum, pulmonary interstitial emphysema);
5. Duration of assisted mechanical ventilation (days);
6. Duration of supplemental oxygen (days);
7. Need for supplemental oxygen at discharge;
8. Chronic lung disease (defined as need for oxygen therapy at 28 days or 36 weeks postmenstrual age);
9. Intraventricular haemorrhage (any grade);
10. Severe IVH (grade III - IV);
11. Duration of hospital stay (days).

Additional outcomes for the update in 2014:

1. Death or chronic lung disease at 28 days;
2. Death or chronic lung disease at 36 weeks postmenstrual age;
3. Neurodevelopmental follow-up.

Search methods for identification of studies

For the previous review in 2007, we searched *The Cochrane Library* (Issue 4, 2006) in December 2006. We searched MEDLINE (OVID, 1966 to December 2006) using the following strategy: (exp Pulmonary Surfactants/ or surfactan:.mp. or Surface-Active Agents/ or (surfactan: adj2 lavage:).mp.) and (Meconium Aspiration Syndrome/ or Meconium/). We searched EMBASE (OVID, 1980 to 2006 Week 06), using the following strategy: (Lung Surfactant/ or exp Surfactant/ or (surfactan: adj2 lavage:).mp. or surfactan:.mp.) and (Meconium or Aspiration/ or meconium/).

We searched previous reviews and cross-references, and abstracts published in Pediatric Research or electronically from Pediatric Academic Societies meetings from 2000 to December 2006, without any language restrictions.

In November 2014 we updated the electronic searches. See: Appendix 1. In addition, we searched for ongoing or recently completed trials in the following clinical trials registries (www.clinicaltrials.gov; www.controlled-trials.com; and www.who.int/ictrp).

Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group, as documented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

Review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion.

Data extraction and management

For each included study, we collected information regarding the method of randomisation, blinding, drug intervention, stratification, and whether the trial was single- or multicentre. We noted information regarding trial participants, including gestational age criteria, birth weight criteria, cause of respiratory failure, severity of respiratory failure, and postnatal age at the time of treatment. We extracted information on clinical outcomes, including mortality, treatment with ECMO, pneumothorax, pulmonary interstitial emphysema, chronic lung disease, duration of assisted ventilation, duration of supplemental oxygen, need for supplemental oxygen at discharge, duration of hospital stay, and intraventricular haemorrhage (any grade and grades III and IV). We contacted investigators or study sponsors for clarification or provision of data not specifically noted in the original report. For the update in 2007, two review authors (AS, AO) independently evaluated all studies, abstracted the data onto extraction forms and compared and agreed the abstracted data. One review author (AS) entered the data into RevMan 4.2.9 and the other review author (AO) checked the data for accuracy. Unpublished information on the subgroup of infants with MAS obtained from Lotze at al (Lotze 1998) included in the original review were entered unchanged. Unpublished information regarding the multicentre trial conducted in Chile and previously published in abstract form was obtained from the authors (Maturana 2005) and the data from the unpublished report were entered into RevMan 5.3.

Assessment of risk of bias in included studies

We have used the standard review methods of the CNRG (About the CNRG) to assess the methodological quality of included studies.

For the 2014 update of the review, two review authors (AO, AS) assessed the following areas and completed a 'Risk of bias' table for each included study; see Characteristics of included studies.

Selection bias (random sequence generation and allocation concealment).

For each included study, we categorised the risk of selection bias as:

Random sequence generation:

Low risk - adequate (any truly random process, e.g. random number table; computer random number generator); High risk - inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); Unclear risk - no or unclear information provided.

Allocation concealment:

Low risk - adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); High risk - inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); Unclear risk - no or unclear information provided.

Performance bias

For each included study, we categorised the methods used to blind study personnel to knowledge of which intervention a participant received. (As our study population consisted of neonates they would all be blinded to the study intervention).

Low risk - adequate for personnel (a placebo that could not be distinguished from the active drug was used in the control group); High risk - inadequate - personnel aware of group assignment; Unclear risk - no or unclear information provided.

Detection bias

For each included study, we categorised the methods used to blind outcome assessors to knowledge of which intervention a participant received. (As our study population consisted of neonates they would all be blinded to the study intervention). Blinding was assessed separately for different outcomes or classes of outcomes. We categorised the methods used with regards to detection bias as:

Low risk - adequate; follow-up was performed with assessors blinded to group; High risk - inadequate; assessors at follow-up were aware of group assignment; Unclear risk - no or unclear information provided.

Attrition bias

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised the methods with respect to the risk of attrition bias as: Low risk - adequate (fewer than 10% missing data); High risk - inadequate (more than 10% missing data); Unclear risk - no or unclear information provided.

Reporting bias

For each included study, we described how we investigated the risk of selective outcome reporting bias and what we found. We assessed the methods as: Low risk - adequate (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported); High risk - inadequate (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest 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); Unclear risk - no or unclear information provided (e.g. the study protocol was not available).

Other bias

For each included study, we described any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as: Low risk - no concerns of other bias raised; High risk - concerns raised about multiple checking of the data with the results made known to the investigators, difference in number of participants enrolled in abstract and final publications of the paper; Unclear - concerns raised about potential sources of bias that could not be verified by contacting the study authors.

Where necessary, we planned to explore the impact of the level of bias through undertaking sensitivity analyses (Higgins 2011).

Measures of treatment effect

The statistical methods included (typical) risk ratio (RR), (typical) risk difference (RD), number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) for dichotomous outcomes, and mean difference (MD), all reported with 95% confidence intervals (CI). We used a fixed-effect model for meta-analysis.

Unit of analysis issues

The unit of randomisation and the unit of analysis was in all cases the individual infant.

Dealing with missing data

We intended to contact the authors of all published studies if clarification was required, or to provide additional information. In the case of missing data, we intended to describe the number of participants with missing data in the Main results section. We present results only for the available participants. We intended to discuss the implications of missing data in the Discussion section of the review.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis (Higgins 2003). If we had identified substantial heterogeneity, we would have explored it by prespecified subgroup analysis and sensitivity analysis. We used the following cut-offs for the degree of heterogeneity; < 25%, no heterogeneity; 25 to 49%, low heterogeneity; 50 to 74%, moderate heterogeneity and ≥ 75% high heterogeneity (Higgins 2011).

Assessment of reporting biases

If available, we planned to obtain the study protocols of all included studies so that we could compare outcomes reported in the protocol to those reported in the findings for each of the included studies. We would have investigated reporting and publication bias by examining the degree of asymmetry of a funnel plot (if at least 10 trials were available for a given outcome). Where we suspected reporting bias (see selective reporting in Assessment of risk of bias in included studies), we would have attempted to contact study authors to provide missing outcome data. Where this was not possible, and the missing data were thought to introduce serious bias, we would have explored the impact of including such studies in the overall assessment of results by conducting a sensitivity analysis.

Data synthesis

We analysed the data using Review Manager 5 software (RevMan 2014). We conducted a fixed-effect Mantel-Haenszel meta-analysis for combining data where trials examined the same intervention and we judged the trial populations and methods to be sufficiently similar.

Subgroup analysis and investigation of heterogeneity

If sufficient data were available, we had planned to explore potential sources of clinical heterogeneity through the following a priori subgroup analyses: (i) studies done with and without availability of inhaled nitric oxide; (ii) studies done with and without availability of extracorporeal membrane oxygenation (ECMO).

Sensitivity analysis

If sufficient data were available, we had planned to explore methodological heterogeneity through the use of sensitivity analyses. We planned to perform these through including trials of higher quality, based on the presence of any of the following: adequate sequence generation, allocation concealment, and fewer than 10% lost to follow-up.

Results

Description of studies

Results of the search

Seventeen potential studies were identified, of which four are included in the review.

Included studies

For details, see the table Characteristics of included studies.

We include four studies in this review:

Findlay 1996 is a single-centre study performed in the USA:

- Objective: To determine whether high-dose surfactant therapy improves the pulmonary morbidity of term infants ventilated for meconium aspiration syndrome (MAS).
- Population: Term newborn infants with MAS, diagnosed by the presence of meconium below the vocal cords at birth with or without characteristic chest radiographic findings, who needed ventilator support before six hours of age with a fractional inspired oxygen ($Fi0_2$) level of 0.5 or more, mean airway pressure of 7 cm of H_2O or more and arterial/alveolar (a/A) pO_2 ratio of 0.22 or less.
- Intervention: Infants in the study group received up to four doses of 150 mg (6ml)/kg beractant (Survanta), installed every six hours by continuous infusion for 20 minutes via a side hole endotracheal tube adapter. Infants in the control group received 6 ml/kg air placebo.
- Outcomes: Primary outcomes included decrease in Oxygen Index (OI), increase in a/A pO_2 ratio and decrease in the need for respiratory support (mean airway pressure (MAP), ventilation days). Secondary outcomes included the need for ECMO, incidence of air leaks, duration of oxygen therapy, discharge with supplemental oxygen, and mortality at less than 28 days of life.

Lotze 1998 is a multicentre study performed in the USA:

- Objective: To determine whether surfactant (beractant) administration to term newborns in respiratory failure and at risk of requiring extracorporeal membrane oxygenation (ECMO) treatment would significantly reduce the incidence of severe complications through 28 days of age and the need for ECMO.
- Population: Infants weighing 2000 gm or more with gestational ages of 36 weeks or greater with respiratory failure secondary to MAS, sepsis or idiopathic persistent pulmonary hypertension of newborn (requiring FiO_2 1.00 with OI of 15 to 39).
- Intervention: Infants were randomly assigned to receive either four doses of beractant 100 mg/kg or air placebo before ECMO treatment and four additional doses during ECMO, if ECMO was required (only infants with MAS are included in this analysis and the data were provided by the authors).
- Outcomes: Need for ECMO and incidence of severe complications (haemorraghic, neurologic, pulmonary, renal, cardiovascular, infectious, metabolic and technical) during the first 28 days of age or at discharge.

The Chinese Collaborative Study (Chinese Study Group 2005) is a multicentre study performed in China:

- Objective: To evaluate the safety and efficacy of exogenous surfactant replacement therapy for MAS in term and late preterm neonates.
- Population: Term and late preterm neonates with MAS (diagnosis based on the presence of meconium in the airways with or without meconium-stained amniotic fluid at delivery, typical chest x-ray findings, onset of respiratory distress, and abnormal blood gas findings indicating respiratory failure and acidosis), birth weight greater than 2500 gm, postnatal age less than 36 hours, a/A pO_2 ratio less than 0.22, OI greater than 15 and need for mechanical ventilation for one to two hours without improvement.
- Intervention: The infants in the surfactant group received an initial dose of porcine lung-derived surfactant (Curosurf) at 200 mg/kg, with repeated doses of 200, 100 and 100 mg/kg given at 6 to 12 hourly intervals to a maximum of four doses if OI increased by more than two from baseline. The control group received the standard

care without a placebo.

- Outcomes: The primary outcomes were a reduction of OI to less than 10 and an increase of the pretreatment a/A pO_2 ratio of 100% over baseline 24 hours after surfactant treatment. The secondary outcomes were duration of mechanical ventilation, incidence of complications and survival to discharge from hospital.

Maturana 2005 is a multicentre study performed in Chile:

- Objective: To evaluate the use of up to three doses of surfactant administered as a bolus (150 mg/kg) versus placebo to reduce the number of days on mechanical ventilation in term infants with moderate to severe MAS.
- Population: Term newborns more than 37 weeks of gestation with moderate to severe MAS (defined as the presence of meconium-stained amniotic fluid with or without evidence of meconium in the lower airway, abnormal x-ray consistent with MAS and respiratory insufficiency defined as an oxygen requirement of 50% or more in an oxyhood to achieve saturation of greater than 90% or PaO_2 more than 50 mmHg if the infant was not ventilated, or an OI more than eight if the infant was on mechanical ventilation.
- Intervention: Infants were randomly assigned to receive either 150 mg /kg/dose (6ml) of Survanta or an equivalent amount of air as placebo every six hours for total of three doses if they remained intubated.
- Outcomes: The primary outcome was days on mechanical ventilation. Secondary outcomes included days requiring oxygen therapy with a target arterial oxygen saturation of more than 90%, air leaks (pneumothorax, pneumomediastinum, interstitial emphysema), persistent pulmonary hypertension (PPHN), OI after two hours following the first treatment dose, and mortality before discharge.
- Notes: We obtained from the first author an unpublished manuscript of the study that included an additional four randomised infants (three infants in the surfactant group and one in the control group) compared to the published abstract. In the analyses we report on 28 infants in the surfactant group and 29 in the air-placebo group as per the additional information we received from the authors.

Excluded studies

We excluded 14 studies from the analysis. These are detailed in the table Characteristics of excluded studies, with reasons for their exclusion.

Risk of bias in included studies

Randomised controlled trials that evaluate the effect of bolus surfactant administration in term or late preterm infants with MAS are included in the analysis. We discuss specific methodologic issues below:

Randomisation: The four included studies allocated treatments by randomisation. In Maturana 2005 the randomisation scheme was computer-generated. The Collaborative Chinese Study (Chinese Study Group 2005) and Maturana 2005 used sealed randomisation envelopes. Findlay 1996 did not report on the method of randomisation, but stated that physicians and nurses caring for the infants were unaware of the infants' assignment groups. Lotze 1998 used a central randomisation service and stratified infants by primary diagnosis and disease severity.

Blinding of treatment: In Findlay 1996 the attending staff were unaware of treatment assignment. In Lotze 1998, the dosing investigator was prohibited from participating in any other aspects of infants' care and from revealing the treatment assignment. In the Chinese Collaborative Study (Chinese Study Group 2005), staff were not blinded to treatment groups. In Maturana 2005, the assigned treatment was administered by a person not involved in the direct infant care and was given behind a screen. The number of infants enrolled in the trial differed between the published abstract (Maturana 2005) and the information obtained from the first author (three additional infants in the surfactant group and one additional infant in the control group). Differences noted between abstracts and full reports may indicate elements of bias/poor data quality control, possibly including any of the following methodological issues: multiple examination of the data; changes in the definitions of outcomes; no prespecified sample size; closure of participant recruitment when statistical significance has been reached for the outcome under study, and other sources of bias (Walia 1999).

Blinding of outcome assessment: Outcomes were assessed by staff members unaware of treatment assignment in three of the four studies (Findlay 1996; Lotze 1998; Maturana 2005).

Exclusion after randomisation: In Chinese Study Group 2005, 66 infants were enrolled and five infants (four in the surfactant group and one in the control group) were excluded from the final analysis because of violation of the entry criteria. In Lotze 1998 all 330 randomised infants were accounted for (168 of these infants were enrolled on the basis of MAS, and the remaining infants on the basis of PPHN or sepsis). Two infants were later withdrawn from the study when parental consent was withdrawn. Their limited data were subsequently excluded from analysis. The diagnosis on which their enrolment was based and whether or not they had MAS was not reported.

Effects of interventions

SURFACTANT THERAPY versus PLACEBO OR NO TREATMENT (COMPARISON 1):

PRIMARY OUTCOME:

Mortality (Outcome 1.1):

All four studies enrolling 326 infants reported on mortality. Surfactant had no statistically significant effect on mortality [typical risk ratio (RR) 0.98, 95% confidence interval (CI) 0.41 to 2.39; typical risk difference (RD) -0.00, 95% CI -0.05 to 0.05] (Analysis 1.1). Heterogeneity of treatment effect for this outcome was low (I^2 = 0%) for both RR and RD.

SECONDARY OUTCOMES:

Treatment with extracorporeal membrane oxygenation (ECMO) (Outcome 1.2):

Two studies enrolling 208 infants reported on treatment with ECMO. Surfactant statistically significantly reduced treatment with ECMO [typical RR 0.64, 95% CI 0.46 to 0.91; typical RD -0.17, 95% CI -0.30 to -0.04; Number needed to treat for an additional beneficial outcome (NNTB) 6, 95% CI 3 to 25]. (Analysis 1.2) Heterogeneity of treatment effect for this outcome was moderate for RR (I^2 = 50%) and low for RD (I^2 = 0%).

Pneumothorax (Outcome 1.3):

Three studies enrolling 269 infants reported on the occurrence of pneumothorax. Surfactant did not statistically significantly reduce the occurrence of pneumothorax (typical RR 0.82, 95% CI 0.39 to 1.73; typical RD -0.02, 95% CI -0.08 to 0.05) (Analysis 1.3). Heterogeneity of treatment effect for this outcome was moderate for RR (I^2 = 50%) and high for RD (I^2 = 75%).

Pulmonary interstitial emphysema (Outcome 1.4):

One study enrolling 61 infants reported on the occurrence of interstitial emphysema. Surfactant had no statistically significant effect on pulmonary interstitial emphysema (RR 0.55, 95% CI 0.18 to 1.70; RD -0.10, 95% CI -0.30 to 0.09) (Analysis 1.4). Tests for heterogeneity were not applicable.

Air leaks (pneumothorax, pneumomediastinum, interstitial emphysema) (Outcome 1.5):

One study enrolling 57 infants reported on a combination of air leaks. Surfactant did not have a statistically significant effect on air leaks (RR 1.04, 95% CI 0.23 to 4.71; RD 0.00, 95% CI -0.16 to 0.16) (Analysis 1.5). Tests for heterogeneity were not applicable.

Duration of assisted mechanical ventilation (days) (Outcome 1.6):

Three studies enrolling 158 infants reported on duration of assisted mechanical ventilation. Mechanical ventilated was stated as the outcome in all three studies, but whether or not this included continuous positive airway pressure was not indicated. Surfactant had no statistically significant effect on the duration of assisted ventilation (MD 0.60 days, 95% CI -0.41 to 1.62) (Analysis 1.6). Heterogeneity of treatment effect for this outcome was moderate to high (I^2 = 73%).

Duration of supplemental oxygen (days) (Outcome 1.7):

Two studies enrolling 97 infants reported on duration of supplemental oxygen. Surfactant did not statistically significantly reduce the duration of supplemental oxygen (MD 0.40, 95% CI -2.83 to 3.64) (Analysis 1.7). Heterogeneity of treatment effect for this outcome was high (I^2 = 88%).

Need for supplemental oxygen at discharge (Outcome 1.8):

One study enrolling 40 infants reported on the need for oxygen at discharge. Surfactant had no statistically significant effect on need for supplemental oxygen at discharge (RR 0.75, 95% CI 0.32 to 1.77; RD -0.10, 95% CI -0.39 to 0.19) (Analysis 1.8). Tests for heterogeneity were not applicable.

Chronic lung disease (age at diagnosis not stated) (Outcome 1.9):

One study enrolling 168 infants reported on chronic lung disease. Surfactant had no statistically significant effect on chronic lung disease (RR 0.47, 95% CI 0.12 to 1.80; RD -0.04, 95% CI -0.11 to 0.03) (Analysis 1.9). Tests for heterogeneity were not applicable.

Intraventricular haemorrhage (any grade) (Outcome 1.10):

Two studies enrolling 229 infants reported on the incidence of intraventricular haemorrhage (any grade). Surfactant had no statistically significant effect on intraventricular haemorrhage (any grade) (typical RR 0.67, 95% CI 0.31 to 1.46; typical RD -0.04, 95% CI -0.12 to 0.04) (Analysis 1.10). Heterogeneity of treatment effect for this outcome was low to moderate (RR, I^2 = 47%) and moderate (RD, I^2 = 51%).

Severe intraventricular haemorrhage (grades III and IV) (Outcome 1.11):

One study enrolling 168 infants reported on the incidence of severe intraventricular haemorrhage (grades III and IV). Surfactant had no statistically significant effect on severe intraventricular haemorrhage (grades III and IV) (RR 2.79, 95% CI 0.30 to 26.31; RD 0.02, 95% CI -0.02 to 0.07) (Analysis 1.11).Tests for heterogeneity were not applicable.

Duration of hospital stay (days) (Outcome 1.12):

One study enrolling 40 infants reported on the duration of hospital stay. Surfactant statistically significantly reduced the duration of hospital stay (MD -8 days, 95% CI -14 to -3) (Analysis 1.12). Tests for heterogeneity were not applicable.

Additional outcomes for the update in 2014:

Death or chronic lung disease at 28 days: outcome not reported.

Death or chronic lung disease at 36 weeks postmenstrual age: outcome not reported.

Neurodevelopmental follow-up: outcome not reported.

Discussion

Deficiency or dysfunction, or both, of pulmonary surfactant may contribute to respiratory failure in a broad group of disorders including pneumonia, meconium aspiration syndrome (MAS), and adult respiratory distress syndrome. We identified four randomised controlled trials that studied the effect of surfactant therapy in term and late preterm infants with MAS. Three of the studies were placebo-controlled using air as the placebo, and in these three studies the outcomes were assessed blinded to group of allocation (Findlay 1996; Lotze 1998; Maturana 2005). In the fourth study, the clinical staff were not blinded to group allocation (Chinese Study Group 2005). The sample sizes of the studies were small with 40, 57, 61, and 168 infants enrolled (Findlay 1996; Maturana 2005; Chinese Study Group 2005; Lotze 1998) respectively. The number of infants enrolled in Maturana 2005 differed between the published abstract and the information obtained from the author. There were four more infants included in the report that we obtained from the authors.

Surfactant treatment did not have a statistically significant effect on the primary outcome of mortality. In the meta-analysis of the results from two studies (Findlay 1996; Lotze 1998), surfactant treatment resulted in a statistically and clinically important reduction in the need for extracorporeal membrane oxygenation (ECMO) treatment, with a number needed to treat for an additional beneficial outcome (NNTB) of 6 (95% CI 3 to 25). ECMO treatment was not

available for the units in the Chinese Collaborative study (Chinese Study Group 2005), nor in the study from Chile (Maturana 2005). The one study (Findlay 1996) that reported on duration of hospital stay demonstrated a reduction in hospital days. There were no other statistically significant reductions in any of the other important clinical outcomes (duration of assisted ventilation, duration of supplemental oxygen, air leaks, chronic lung disease, duration of assisted ventilation, need for supplemental oxygen at discharge and intraventricular haemorrhage). The trends for all respiratory tract-associated outcomes favoured the use of surfactant.

A number of investigators have attempted to treat MAS with dilute surfactant solutions used as a lavage to wash residual meconium from the airway (Dargaville 2011; Ibara 1995; Lam 1999; Ogawa 1996). Wiswell 2002 enrolled 22 infants [15 surfactant (Surfaxin) and 7 control]. There were non-significant trends for surfactant-lavaged infants to be weaned from mechanical ventilation earlier (mean of 6.3 vs. 9.9 days, respectively), as well as to have a more rapid decline in their oxygenation index (OI) compared with control infants. Since the last update of this review, Dargaville 2011 has published a randomised controlled trial of lavage with two dilute bovine surfactants in the treatment of MAS. Sixty-six infants were randomised, with one ineligible infant excluded from the analysis. In this study, fewer infants who underwent lavage died or required ECMO (10% compared with 31% in the control group). However, surfactant lavage did not alter the duration of respiratory support (median duration in the lavage group 5.5. days and in the control group 6.0 days). Randomised comparisons are warranted of surfactant bolus versus surfactant lavage therapy in MAS.

Current evidence indicates that amnioinfusion prior to birth or suctioning of the oropharynx/nasopharynx prior to the delivery of the shoulders do not prevent MAS from occurring. At the present time, the two most promising interventions appear to be treatment with surfactant or surfactant lavage. As few infants have been studied to date, further research is warranted, possibly using a three-armed trial with 1) surfactant administration, 2) surfactant lavage and 3) a control group receiving air.

Clinical experience indicates that persistent pulmonary hypertension of the newborn (PPHN) is one of the major causes of death in infants with MAS (Hsieh 2004). There is evidence that meconium injury may directly trigger postnatal release of vasoconstrictors such as ET-1, TXA2, and prostaglandin E2 (PGE2), which play a role in the development of pulmonary hypertension (Soukka 1998).

Infants with MAS and PPHN are usually treated with oxygen, conventional or high frequency mechanical ventilation or both, inotropic support, induction of alkalosis, and sedation. When these measures fail, ECMO has been shown to improve the outcome (UK Collab 1996). Inhaled nitric oxide (iNO) is frequently used for the treatment of newborns with severe pulmonary hypertension and respiratory failure. Consequently, increasing clinical and experimental evidence suggest that exogenous NO, given by inhalation, selectively reduces pulmonary vasoconstriction and improves oxygenation in a variety of pathological conditions of the newborn lungs, including meconium aspiration (Neonatal iNO 1997; Van Meurs 2003). In recent experimental data, Aaltonen 2007 demonstrated that iNO in MAS is associated with diminished pulmonary hypertensive response as well as decreased DNA oxidation and neuronal damage in hippocampal tissue that may potentially have significant adverse long-term effects on the developmental status of the affected newborns.

ECMO procedures are complex because they require systemic anticoagulation and major vessel cannulation. Studies of iNO therapy for PPHN have shown rapid improvement in oxygenation, reducing the need for ECMO therapy without affecting the mortality (Christou 2000; Clark 2000). Finer 2000 showed that iNO treatment improves oxygenation in approximately 50% of term or late preterm neonates with hypoxaemic respiratory failure, and

reduces the combined end point of death or the need for ECMO therapy (risk ratio 0.73) as compared with control subjects. However, lack of an early response to iNO treatment within a few hours in infants who are referred for ECMO therapy and younger age at the time of presentation may indicate the need for ECMO therapy in at least 50% of those with hypoxic respiratory failure (Fakioglu 2005).