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TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
BACKGROUND 3
OBJECTIVES 3
METHODS 3
RESULTS 4
DISCUSSION 6
AUTHORS' CONCLUSIONS 6
ACKNOWLEDGEMENTS 7
REFERENCES 8
CHARACTERISTICS OF STUDIES 9
DATA AND ANALYSES 14
Analysis 1.1. Comparison 1 Synthetic surfactant vs control, Outcome 1 Pneumothorax. 15
Analysis 1.2. Comparison 1 Synthetic surfactant vs control, Outcome 2 Pulmonary interstitial emphysema. 15
Analysis 1.3. Comparison 1 Synthetic surfactant vs control, Outcome 3 Pulmonary hemorrhage. 15
Analysis 1.4. Comparison 1 Synthetic surfactant vs control, Outcome 4 Patent ductus arteriosus. 16
Analysis 1.5. Comparison 1 Synthetic surfactant vs control, Outcome 5 Necrotizing enterocolitis. 16
Analysis 1.6. Comparison 1 Synthetic surfactant vs control, Outcome 6 Apnea of prematurity. 16
Analysis 1.7. Comparison 1 Synthetic surfactant vs control, Outcome 7 Intraventricular hemorrhage. 17
Analysis 1.8. Comparison 1 Synthetic surfactant vs control, Outcome 8 Severe IVH. 17
Analysis 1.9. Comparison 1 Synthetic surfactant vs control, Outcome 9 Bronchopulmonary dysplasia. 18
Analysis 1.10. Comparison 1 Synthetic surfactant vs control, Outcome 10 Neonatal mortality. 18
Analysis 1.11. Comparison 1 Synthetic surfactant vs control, Outcome 11 BPD or death at 28 days. 18
Analysis 1.12. Comparison 1 Synthetic surfactant vs control, Outcome 12 Retinopathy of prematurity in survivors examined. 19
Analysis 1.13. Comparison 1 Synthetic surfactant vs control, Outcome 13 Severe retinopathy of prematurity in survivors examined. 19
Analysis 1.14. Comparison 1 Synthetic surfactant vs control, Outcome 14 Mortality prior to hospital discharge. 19
Analysis 1.15. Comparison 1 Synthetic surfactant vs control, Outcome 15 Mortality at 1 year. 20
Analysis 1.16. Comparison 1 Synthetic surfactant vs control, Outcome 16 Lost to follow-up. 20
Analysis 1.17. Comparison 1 Synthetic surfactant vs control, Outcome 17 Cerebral palsy in survivors examined. 20
Analysis 1.18. Comparison 1 Synthetic surfactant vs control, Outcome 18 Moderate - severe cerebral palsy in survivors examined. 21
WHAT'S NEW 21
HISTORY 21
DECLARATIONS OF INTEREST 21
SOURCES OF SUPPORT 21
INDEX TERMS 21

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[Intervention Review]

Synthetic surfactant for respiratory distress syndrome in preterm infants

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ABSTRACT

Background

This section is under preparation and will be included in the next issue.

Objectives

To assess the effect of intratracheal administration of synthetic surfactant in premature newborns with established respiratory distress syndrome (RDS).

Search methods

Searches were made of the Oxford Database of Perinatal Trials, Medline (MeSH terms: pulmonary surfactants; limits: age groups, newborn infant; publication types, clinical trial), previous reviews including cross references, abstracts, conference and symposia proceedings, expert informants, and journal handsearching in the English language.

Selection criteria

Randomized controlled trials which compared the effect of synthetic surfactant treatment to routine management in the treatment of preterm infants with respiratory distress syndrome.

Data collection and analysis

Data regarding clinical outcome including the incidence of pneumothorax, pulmonary interstitial emphysema, pulmonary hemorrhage, patent ductus arteriosus, necrotizing enterocolitis, apnea of prematurity, intraventricular hemorrhage (any grade, and severe intraventricular hemorrhage), bronchopulmonary dysplasia, neonatal mortality, bronchopulmonary dysplasia or death, retinopathy of prematurity (any retinopathy, and retinopathy greater than Stage 3), mortality at hospital discharge, mortality to one year of age, and cerebral palsy (any, and moderate/severe cerebral palsy) was excerpted from the report of the clinical trials by the reviewer. Data were analyzed according to the standards of the Cochrane Neonatal Review Group.

Main results

Six randomized controlled trials of synthetic surfactant treatment of established respiratory distress syndrome were identified. Five of the studies used Exosurf Neonatal (a synthetic surfactant composed of dipalmitoylphosphatidylcholine, hexadecanol and tyloxapol); one small study utilized a mixture of dipalmitoylphosphatidylcholine (DPPC) and phosphatidylglycerol (PG). Treatment with intratracheal Exosurf Neonatal in premature infants with established respiratory distress syndrome improves pulmonary gas exchange and decreases the requirement for ventilatory support. In individual trials, the use of Exosurf Neonatal resulted in a statistically significant reduction in pneumothorax, patent ductus arteriosus, bronchopulmonary dysplasia (BPD), BPD or death at 28 days, and mortality. Similar results

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are seen when these large trials of Exosurf Neonatal are analyzed in conjunction with the smaller trial of dry powdered DPPC and phosphatidylglycerol (PG). The meta-analysis supports a decrease in the risk of pneumothorax (typical relative risk 0.64, 95% CI 0.55, 0.76, typical risk difference -0.09, 95% CI -0.12,-0.06), a decrease in the risk of pulmonary interstitial emphysema (typical relative risk 0.62, 95% CI 0.54, 0.71, typical risk difference -0.12, 95% CI -0.16, -0.09), a decrease in the risk of patent ductus arteriosus (typical relative risk 0.90, 95% CI 0.84, 0.97; typical risk difference -0.06 95% CI -0.10, -0.02), a decrease in the risk of intraventricular hemorrhage (typical relative risk 0.88, 95% CI 0.77, 0.99; typical risk difference -0.04, 95% CI -0.08, -0.00), a decrease in the risk of bronchopulmonary dysplasia (typical relative risk 0.75, 95% CI 0.61, 0.92; typical risk difference -0.04, 95% CI -0.06, -0.01), a decrease in the risk of neonatal mortality (typical relative risk 0.73, 95% CI 0.61, 0.88; typical risk difference -0.05, 95% CI -0.07, -0.02), a decrease in the risk of bronchopulmonary dysplasia or death at 28 days (typical relative risk 0.73, 95% CI 0.65, 0.83; typical risk difference -0.06, 95% CI -0.11, -0.05), a decrease in the risk of mortality prior to hospital discharge (typical relative risk 0.79, 95% CI 0.68, 0.92; typical risk difference -0.05, 95% CI -0.07, -0.02) and a decrease in the risk of mortality during the first year of life (typical relative risk 0.80, 95% CI 0.69, 0.94; typical risk difference -0.04, 95% CI -0.07, -0.01). Treatment with synthetic surfactant increases the risk of apnea of prematurity (typical relative risk 1.20, 95% CI 1.09, 1.31; typical risk difference 0.08, 95% CI 0.04, 0.12).

Authors' conclusions

Intratracheal administration of synthetic surfactant to infants with established respiratory distress syndrome has been demonstrated to improve clinical outcome. Infants who are treated with synthetic surfactant have a decreased risk of pneumothorax, a decreased risk of pulmonary interstitial emphysema, a decreased risk of intraventricular hemorrhage, a decreased risk of bronchopulmonary dysplasia, a decreased risk of neonatal mortality, a decreased risk of mortality prior to hospital discharge and at 1 year of age. Infants who receive synthetic surfactant treatment for established RDS have an increased risk of apnea of prematurity.

PLAIN LANGUAGE SUMMARY

Synthetic surfactant for respiratory distress syndrome in preterm infants

Synthetic surfactant is effective in reducing respiratory distress syndrome in preterm babies. Pulmonary surfactant is a substance that prevents the air sacs of the lungs from collapsing by reducing surface tension. Sometimes it is absent in immature lungs and respiratory distress syndrome (RDS) can develop. Synthetic surfactants have been developed and can be used for babies born prematurely (before 34 weeks) who have RDS. The review of trials found evidence that synthetic surfactant for babies with RDS is effective. Synthetic surfactant reduced the risk of pneumothorax (air in the lung cavity) and death. The only adverse effect is the increased risk of pulmonary hemorrhage (bleeding in the lungs), seen with the use of either synthetic or natural surfactant.

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BACKGROUND

Respiratory Distress Syndrome (RDS) is caused by a deficiency or dysfunction of pulmonary surfactant. Surfactant lines the alveolar surface and prevents atelectasis at end expiration. Pulmonary surfactant is predominantly dipalmitoylphosphatidylcholine with lesser amounts of other phospholipids including phosphatidylglycerol (PG), phosphatydylethanolamine, and phosphatidylinositol. Pulmonary surfactant also contains neutral lipids and distinct surfactant proteins. The physiologic function of surfactant includes the ability to lower surface tension, as well as the ability to rapidly adsorb, spread, and reform a monolayer in the dynamic conditions associated with the respiratory cycle (Jobe 1993).

The first attempts to utilize synthetic surfactants occurred in the 1960s. Investigators attempted to aerosolize dipalmitoylphosphatidylcholine (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 (1972). Enhorning administered a crude, natural surfactant extract obtained from lavage of the lungs of mature rabbits directly into the trachea of immature rabbits. Improvement in lung compliance and alveolar expansion was noted. 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 synthetic surfactants and natural surfactant extracts. Natural surfactant extracts are derived from animal or human sources. Currently used synthetic surfactants are complex combinations of dipalmitoylphosphatidylcholine and other phospholipids, neutral lipids, lipoprotein, or alcohols. Components of synthetic surfactants are not directly obtained from the extraction of surfactant from animal lung.

The original trials of DPPC alone are not included in this review, since neither the surfactant nor the route of administration are considered adequate. Included trials all used complex synthetic surfactants in an attempt to treat infants with established respiratory distress syndrome. In these studies, infants requiring assisted ventilation with clinical and radiographic evidence of respiratory distress syndrome were randomized to receive intratracheal synthetic surfactant or control treatment. Investigators hoped to decrease the need for cardiorespiratory support and the incidence of complications associated with prematurity.

The following analysis is a systematic review of six randomized controlled trials which compare synthetic surfactant administration in infants with established respiratory distress syndrome to control treatment. Results of some of these analyses were previously published in 'Effective Care of the Newborn Infant' (Soll 1992).

OBJECTIVES

To assess the effect of intratracheal synthetic surfactant treatment in infants with established respiratory distress syndrome (RDS).

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials comparing intratracheal synthetic surfactant treatment of established respiratory distress syndrome to control treatment.

Types of participants

Neonates with clinical and radiologic evidence of respiratory distress syndrome requiring assisted ventilation.

Types of interventions

Infants randomized to receive synthetic surfactant treatment versus control treatment (intratracheal administration of air placebo). Five studies utilized Exosurf Neonatal (dipalmitoylphosphatidylcholine, hexadecanol, and tyloxapol) (Phibbs 1991, Long 1991, US Exosurf 1991, Smyth 1995, McMillan 1995). Wilkinson (1985) used dry powdered DPPC and phosphatidylglycerol.

Types of outcome measures

Data for the following clinical outcomes are included in the meta-analysis: 1) pneumothorax, 2) pulmonary interstitial emphysema, 3) pulmonary hemorrhage, 4) patent ductus arteriosus, 5) necrotizing enterocolitis, 6) apnea of prematurity, 7) intraventricular hemorrhage, 8) severe intraventricular hemorrhage (Grade III or PVED), 9) bronchopulmonary dysplasia, 10) retinopathy of prematurity, 11) severe retinopathy of prematurity (greater than stage 3), 12) neonatal mortality, 13) mortality prior to hospital discharge, 14) bronchopulmonary dysplasia or death, 15) mortality at 1 year of age, 16) not assessed at follow-up, 17) cerebral palsy, 18) moderate/severe cerebral palsy.

Search methods for identification of studies

Searches were made of the Oxford Database of Perinatal Trials, Medline (MeSH terms: pulmonary surfactants; limits: age groups, newborn infant; publication types, clinical trial), previous reviews including cross references, abstracts, conference and symposia proceedings, expert informants, and journal handsearching in the English language.

Data collection and analysis

For each included study, information was collected regarding the method of randomization, blinding, drug intervention, stratification, and whether the trial was single or multicenter. Information regarding trial participants including birthweight criteria, and other inclusion or exclusion criteria was noted. Information on clinical outcome was analyzed including pneumothorax, pulmonary interstitial emphysema, pulmonary hemorrhage, patent ductus arteriosus, necrotizing enterocolitis, apnea of prematurity, intraventricular hemorrhage (any intraventricular hemorrhage and severe intraventricular hemorrhage), bronchopulmonary dysplasia, retinopathy of prematurity (any retinopathy and severe retinopathy greater than Stage 3), neonatal mortality, mortality prior to hospital discharge, bronchopulmonary dysplasia or death, mortality at 1 year of age, assessment at follow-up, and cerebral palsy (any cerebral palsy and moderate/severe cerebral palsy).

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RESULTS

Description of studies

Studies included in this review: Wilkinson 1985; Phibbs 1991; Long 1991; US Exosurf 1991; Smyth 1995; McMillan 1995. Details of each study are given in the "Characteristics of Included Studies" table and references.

Wilkinson (1985) evaluated the use of dry DPPC/PG in a small, randomized controlled trial. Infants of 31 weeks' gestation or less who did not require intubation in the delivery room (and therefore were not enrolled in the prevention study) were enrolled if they subsequently developed respiratory distress syndrome requiring assisted ventilation and demonstrated an immature lecithin/sphingomyelin ratio. Neither immediate nor long-term benefit could be demonstrated with treatment.

With the exception of Wilkinson (1985), all other trials of synthetic surfactant treatment utilized Exosurf Neonatal. Phibbs (1991) studied the effect of a single dose of Exosurf Neonatal in infants weighing 650 grams or more who had RDS requiring assisted ventilation and supplemental oxygen greater than 40%. Requirements for ventilatory support decreased significantly during the 72 hours after treatment. No other clinical benefit was noted.

Four large multicenter trials studied the effect of multiple doses of Exosurf Neonatal in the treatment of respiratory distress syndrome (Long 1991, US Exosurf Study 1991, McMillan 1995, Smyth 1995). These trials evaluated a wide range of infants with severe respiratory distress syndrome. The US Exosurf Study (1991) and McMillan (1995) (the Canadian Exosurf Neonatal Study Group) evaluated very low birthweight infants with respiratory distress syndrome (birthweight criteria: US Exosurf Study 700-1350 grams, McMillan/Canadian Exosurf Study 750-1249 grams). Infants were enrolled if they had respiratory distress syndrome requiring assisted ventilation, an arterial/alveolar ratio <0.22, and were between 2 and 24 hours of age. Both trials reported significant improvement in respiratory status during the first week of life. The US Exosurf Trial (1991) reported a decrease in mortality in surfactant treated infants. In both studies, a significant decrease in the incidence of pneumothorax and BPD or death at 28 days of age was noted.

Larger infants with respiratory distress syndrome were studied by the combined American and Canadian Exosurf Neonatal Study Group (1991). Entry criteria were similar to the other Exosurf treatment studies, except infants with birthweight >1250 grams were enrolled. Surfactant treated infants had significant improvement in respiratory status as well as improvement in long-term clinical outcome. A significant reduction in pneumothorax, intraventricular hemorrhage, bronchopulmonary dysplasia, and neonatal death was noted. As previously described in the smaller infants, an increase in apnea of prematurity was reported.

Smyth (1995) has reported on extremely low birthweight infants weighing 500-749 grams who met entry criteria similar to the other Exosurf treatment studies. No clinical improvement was associated with treatment.

Risk of bias in included studies

Randomized controlled trials which compared the effect of intratracheal synthetic surfactant treatment to control treatment (sham air treatment) in infants with established respiratory distress syndrome are included in the analysis. Specific methodologic issues regarding the six studies are discussed below:

RANDOMIZATION: All included studies allocated assigned treatment by randomization. In all six studies, sealed envelopes with randomly allocated treatment assignments were provided to participating centers.

BLINDING OF TREATMENT: Investigators attempted to blind treatment. Most studies relied on a drug administration team to administer the randomly allocated treatment. Individuals in this drug administration team were not responsible for ongoing care of the infant or for study evaluation.

BLINDING OF OUTCOME ASSESSMENT: Investigators who were not involved with treatment assessed study outcomes.

EXCLUSION AFTER RANDOMIZATION: Minimal exclusions were noted after randomization. All the trials report on the short term (in hospital) outcomes of virtually all randomized infants. However, long term follow-up for neurodevelopmental status (including evaluation for cerebral palsy) ranges from 84% to 100% of survivors.

Effects of interventions

Treatment of premature infants with established respiratory distress syndrome using complex synthetic surfactants (Exosurf Neonatal) leads to an improvement in oxygenation and ventilatory requirement. Synthetic surfactant treatment of premature infants with established respiratory distress syndrome has the following clinical impact:

PNEUMOTHORAX: Five of the randomized controlled trials reported on the incidence of pneumothorax. Long (1991), McMillan (1995), and the US Exosurf Study (1991) all demonstrated a decrease in the risk of pneumothorax associated with synthetic surfactant treatment. The typical estimate from the meta-analysis of all five trials suggests that synthetic surfactant extract treatment will lead to a significant reduction in the risk of pneumothorax (typical relative risk 0.64, 95% CI 0.55, 0.76; typical risk difference -0.09, 95% CI -0.12, -0.06).

PULMONARY INTERSTITIAL EMPHYSEMA: Four of the randomized controlled trials reported on the incidence of pulmonary interstitial emphysema. Long (1991), McMillan (1995), and the US Exosurf Study (1991) all reported a decrease in the risk of pulmonary interstitial emphysema associated with synthetic surfactant treatment. The typical estimate from the meta-analysis suggests that synthetic surfactant treatment will lead to a significant reduction in the risk of pulmonary interstitial emphysema (typical relative risk 0.62, 95% CI 0.54, 0.71, typical risk difference -0.12, 95% CI -0.16, -0.09).

PULMONARY HEMORRHAGE: Five of the randomized controlled trials reported on pulmonary hemorrhage. None of the individual trials reported a difference in the risk of pulmonary hemorrhage. The typical estimate from the meta-analysis suggests no effect of synthetic surfactant treatment on the risk of pulmonary

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hemorrhage (typical relative risk 1.44, 95% CI 0.68, 3.05; typical risk difference 0.00, 95% CI -0.00, 0.01).

PATENT DUCTUS ARTERIOSUS: Five of the randomized controlled trials reported on the incidence of patent ductus arteriosus associated with synthetic surfactant treatment. Long (1991) demonstrated a decrease in the risk of patent ductus arteriosus (relative risk 0.84, 95% CI 0.75, 0.95; risk difference -0.08, 95% CI -0.14, -0.03). The US Exosurf Study (1991) reported a trend towards decreased risk of patent ductus arteriosus. The typical estimate from the meta-analysis suggests that synthetic surfactant treatment of infants with established respiratory distress syndrome will lead to a significant reduction in the risk of patent ductus arteriosus (typical relative risk 0.90, 95% CI 0.84, 0.97; typical risk difference -0.06, 95% CI -0.10, -0.02).

NECROTIZING ENTEROCOLITIS: Five the randomized controlled trials reported on the incidence of necrotizing enterocolitis. None of the individual trials reported a difference in the risk of necrotizing enterocolitis and the typical estimate from the meta-analysis supports no difference in the risk of necrotizing enterocolitis (typical relative risk 1.32, 95% CI 0.76, 2.29; typical risk difference 0.01, 95% CI -0.01, 0.02).

APNEA OF PREMATURITY: Four trials reported on the risk of apnea of prematurity. The trials of Long (1991) and the US Exosurf Study (1991) both reported an increased risk of apnea of prematurity associated with synthetic surfactant treatment. The typical estimate from the meta-analysis suggests an increase in the risk of apnea of prematurity associated with synthetic surfactant treatment (typical relative risk 1.20, 95% CI 1.09, 1.31; typical risk difference 0.08, 95% CI 0.04, 0.12).

INTRAVENTRICULAR HEMORRHAGE: Four of the randomized controlled trials reported on the risk of intraventricular hemorrhage. Long (1991) reported a decrease in the risk of intraventricular hemorrhage associated with synthetic surfactant treatment (relative risk 0.76, 95% CI 0.61, 0.95; risk difference -0.06, 95% CI -0.10, -0.01). The typical estimate from the meta-analysis suggests a decrease in the risk of intraventricular hemorrhage (typical relative risk -0.88, 95 % CI 0.77, 0.99; typical risk difference -0.04, 95 % CI -0.08, -0.00).

SEVERE INTRAVENTRICULAR HEMORRHAGE: Five of the randomized controlled trials reported on the risk of severe intraventricular hemorrhage. None of the individual trials supports a difference in the risk of severe intraventricular hemorrhage and the typical estimate from the meta-analysis suggests no difference in the risk of severe intraventricular hemorrhage (typical relative risk 0.84, 95% CI 0.63, 1.12; typical risk difference -0.01, 95% CI -0.03, 0.01).

BRONCHOPULMONARY DYSPLASIA: Five randomized controlled trials reported on the risk of bronchopulmonary dysplasia. Long (1991) reported a decrease in the risk of bronchopulmonary dysplasia associated with synthetic surfactant treatment (relative risk 0.49, 95% CI 0.28, 0.86; risk difference -0.03, 95% CI -0.05, -0.01). The typical estimate from the meta-analysis suggests a decrease in the risk of bronchopulmonary dysplasia associated with synthetic surfactant treatment (typical relative risk 0.75, 95% CI 0.61, 0.92; typical risk difference -0.04, 95% CI -0.06, -0.01).

NEONATAL MORTALITY: All six randomized controlled trials reported on the risk of neonatal mortality. Long (1991) and the US Exosurf Study (1991) both reported a decrease in the risk of neonatal mortality associated with synthetic surfactant treatment. The typical estimate from the meta-analysis suggests a decrease in the risk of neonatal mortality associated with synthetic surfactant treatment (typical relative risk 0.73, 95% CI 0.61, 0.88; typical risk difference -0.05, 95% CI -0.07, -0.02).

BRONCHOPULMONARY DYSPLASIA OR DEATH: Four of the randomized controlled trials reported the combined outcome of bronchopulmonary dysplasia or death. Long (1991) and the US Exosurf Study (1991) both reported a decreased risk of bronchopulmonary dysplasia or death at 28 days in infants who received synthetic surfactant treatment. The typical estimate from the meta-analysis suggests a decreased risk of bronchopulmonary dysplasia or death at 28 days in infants who received synthetic surfactant treatment (typical relative risk 0.73, 95% CI 0.65, 0.83; typical risk difference -0.08, 95% CI -0.11, -0.05).

MORTALITY PRIOR TO HOSPITAL DISCHARGE: All six randomized controlled trials reported on the risk of mortality prior to hospital discharge. The US Exosurf study (1991) reported a decreased risk of mortality prior to discharge in infants who received synthetic surfactant treatment (relative risk 0.54, 95% CI 0.37, 0.80; risk difference -0.13, 95% CI -0.21, -0.05). The typical estimate from the meta-analysis suggests a decreased risk of mortality prior to hospital discharge in infants who received synthetic surfactant treatment (typical relative risk 0.79, 95% CI 0.68, 0.92; typical risk difference -0.05, 95% CI -0.07, -0.02).

RETINOPATHY OF PREMATURITY: Three trials reported on retinopathy of prematurity in followup evaluation of infants (McMillan 1995, Smyth 1995, US Exosurf 1991). A trend towards a decreased risk of retinopathy of prematurity was noted by Smyth (1995). The meta-analysis evaluates the risk of retinopathy in surviving infants who were examined. The typical estimate from the meta-analysis suggests no difference in the risk of any retinopathy (typical relative risk 0.93, 95% CI 0.80, 1.09; typical risk difference -0.03, 95% CI -0.11, 0.04) or in the risk of severe retinopathy of prematurity (typical relative risk 0.73, 95% CI 0.46, 1.17; typical risk difference -0.03, 95% CI -0.08, 0.02).

MORTALITY AT ONE YEAR: Four of the randomized controlled trials reported on mortality at one year of age. The US Exosurf Study (1991) reported decreased mortality at one year of age in infants who received synthetic surfactant (relative risk 0.57, 95% CI 0.39, 0.82; risk difference -0.13, 95% CI -0.21, -0.05). The typical estimate from the meta-analysis suggests a decreased risk of mortality in infants who received synthetic surfactant treatment (typical relative risk 0.80, 95% CI 0.69, 0.94; typical risk difference -0.04, 95% CI -0.07, -0.01).

FOLLOW-UP EVALUATION: Five of the randomized controlled trials reported on follow-up of infants enrolled in the trials. Wilkinson (1985) briefly notes the incidence of cerebral palsy in the primary report. Follow-up of infants of Long (1991) is reported by Sauve (1995) and Courtney (1995). Follow-up of the infants enrolled in the trial of McMillan (1995) is reported by Saigal (1995) and Courtney (1995). Follow-up of the infants enrolled in the study of Smyth (1995) is reported by Casiro (1995) and Courtney (1995). Infants from the US Exosurf Study (1991) are reported by Gong (1995) and Courtney (1995). Between 84% and 100% of survivors were

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evaluated in the studies. Completeness of follow-up was similar in the two treatment groups. The US Exosurf Study (1991) reports a decreased risk of cerebral palsy in infants who received synthetic surfactant treatment (relative risk 0.38, 95% CI 0.15, 0.98; risk difference -0.07, 95% CI -0.14, -0.01). The meta-analysis suggests no difference in the risk of cerebral palsy (typical relative risk 0.76, 95% CI 0.55, 1.05; typical risk difference -0.02, 95% CI -0.05, 0.00) or in the risk of moderate to severe cerebral palsy (typical relative risk 0.75 95% CI 0.48, 1.16; typical risk difference -0.01 95% CI -0.04, 0.01).

DISCUSSION

Six randomized controlled trials were identified which compared synthetic surfactant treatment of established respiratory distress syndrome to control treatment. Five of the randomized controlled trials utilized Exosurf Neonatal (dipalmitoylphosphatidylcholine, tyloxapol and hexadecanol). Only the small study of Wilkinson (1985) utilized dry powdered DPPC and phosphatidylglycerol (PG). Since investigators were treating infants with clinical signs and symptoms of respiratory distress syndrome, a broad range of gestational ages and birthweights are included. Only the study of Smyth (1995) focused on the extreme of very low birthweight (500-749 grams). The five studies of Exosurf Neonatal all enrolled infants prior to 24 hours of age. The larger studies of Exosurf Neonatal allowed for a repeat treatment 12 hours after the initial treatment if the infants remained on assisted ventilation (Long 1991, McMillan 1995, Smyth 1995, US Exosurf 1991). The larger studies of Exosurf Neonatal all report improvement in the immediate respiratory course. In the studies of Exosurf Neonatal, there are reports of improvement in oxygenation and ventilatory requirements in the 48-72 hours after treatment.

The meta-analysis suggests that synthetic surfactant treatment of established respiratory distress syndrome leads to a significant decrease in the risk of pneumothorax, pulmonary interstitial emphysema, patent ductus arteriosus, bronchopulmonary dysplasia, intraventricular hemorrhage, and mortality. The meta-analysis suggests that for every 100 infants given synthetic surfactant treatment of established respiratory distress syndrome, there will be 9 fewer pneumothoraces, 12 fewer cases of pulmonary interstitial emphysema, 6 fewer cases of significant patent ductus arteriosus, 4 fewer intraventricular hemorrhages, 4 fewer cases of bronchopulmonary dysplasia, and 5 fewer deaths.

Statistical non-homogeneity was noted in the analyses of the impact of synthetic surfactant treatment on pneumothorax, pulmonary interstitial emphysema, and bronchopulmonary dysplasia. The study of Wilkinson (1985) stands out as a uniquely different trial since the infants were not treated with Exosurf Neonatal. However, Wilkinson (1985) only contributed data to the analysis of bronchopulmonary dysplasia and is an extremely small trial, making it doubtful that this study is the source of heterogeneity. More likely the study of Smyth (1995), which included only extremely premature infants, represents the source of heterogeneity. This raises the question of the efficacy of synthetic surfactant in preventing these morbid outcomes in the extremely premature infant.

Individual studies as well as the meta-analysis suggests that there may be an increase in the risk of apnea of prematurity associated with synthetic surfactant treatment. The meta-analysis suggests that for every 100 infants treated with synthetic surfactant for established respiratory distress syndrome, there will be 8 more infants who demonstrate apnea of prematurity. This finding may be due to the increased survival rate and reduced need for assisted ventilation in surfactant treated infants. Unlike the trials of prophylactic synthetic surfactant (Soll 1998), a decrease in the risk of patent ductus arteriosus and no increase in the risk of pulmonary hemorrhage was demonstrated. In animals treated with surfactant products, earlier and more severe shunting through the patent ductus arteriosus has been noted. Pulmonary hemorrhage is thought to occur as a consequence of massive ductal shunting. Although not reported in the randomized controlled trials of synthetic surfactant treatment of established respiratory distress syndrome, pulmonary hemorrhage was addressed retrospectively in analyses by Raju (1993). The risk of pulmonary hemorrhage appears to occur with both synthetic surfactant products and natural surfactant extracts. In clinical practice, pulmonary hemorrhage may be preventable by aggressive treatment of the patent ductus arteriosus and appropriate ventilatory management. No other side effects of synthetic surfactant treatment were reported.

The trials included in this review compared synthetic surfactant treatment of established respiratory distress syndrome with no surfactant treatment. After the demonstration of the efficacy of surfactant in both preventing and treating respiratory distress syndrome, trials were conducted which compared the policies of prophylactic surfactant administration in infants at risk of RDS with selective treatment of infants who develop RDS. These trials were conducted using natural surfactant preparations. In these studies, prophylactic natural surfactant was noted to be superior to late selective treatment of babies with established RDS (Soll 1997a).

Studies have also evaluated the differences between synthetic surfactant and natural surfactant extract. These trials were only done in the context of treating established respiratory distress syndrome. In these studies, the use of natural surfactant extract appears superior in decreasing the risk of pneumothorax and increasing survival (Soll 1997b).

AUTHORS' CONCLUSIONS

Implications for practice

Synthetic surfactant treatment of infants with established respiratory distress syndrome has been demonstrated to improve clinical outcome. Infants who received synthetic surfactant treatment have a decreased risk of pneumothorax, a decreased risk of pulmonary interstitial emphysema, a decreased risk of intraventricular hemorrhage, a decreased risk of bronchopulmonary dysplasia, a decreased risk of neonatal mortality, a decreased risk of mortality prior to hospital discharge and at 1 year of age. Synthetic surfactant treatment of established respiratory distress syndrome may lead to an increase in apnea of prematurity. However, this complication does not overshadow the positive impact on outcome (including reductions in intraventricular hemorrhage, neonatal mortality and late mortality).

Implications for research

Synthetic surfactant treatment of established respiratory distress syndrome has been proven to improve clinical outcome. Further placebo controlled trials of synthetic surfactant are no longer warranted. Trials which compared the prophylactic treatment

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strategy to treatment of established disease have been tested using natural surfactant extract (see review: Prophylactic Surfactant vs. Treatment with Surfactant). Trials which have compared currently available synthetic surfactant to natural surfactant extract have been conducted. Overview analysis of these trials suggests that natural surfactant extract may be preferred to synthetic surfactant due to the decreased risk of pneumothorax associated with natural surfactant extract treatment (see review: Natural Surfactant Extract vs. Synthetic Surfactant). New formulations of synthetic surfactants, such as KL4, are promising and warrant further evaluation (Cochrane 1996).

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CHARACTERISTICS OF STUDIES

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

Long 1991

Methods	Randomized Multicenter Blinding of randomization: Yes (opaque, sealed envelopes Blinding of intervention: Yes (Drug administration team) Complete Follow-up: Short term: Yes Long term: 84% Blinding of outcome measurement: Yes Stratification: By birthweight and gender Long-term follow-up: Sauve 1995, Courtney 1995
Participants	Neonates Birthweight equal to or >1250 grams (Canada) Birthweight > 1350 grams (USA) Respiratory distress syndrome Assisted ventilation a/A ratio <0.22 No proven lung maturity No major congential anomaly No evidence of hydrops fetalis Age <24 hours Infants Randomized: Exosurf = 614

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Long 1991 *(Continued)*

	Control = 623
Interventions	Intratracheal Exosurf Neonatal (5 mg/kg) or sham treatment (air) Second dose 12 hours later if infant remained on assisted ventilation
Outcomes	PRIMARY OUTCOME: Neonatal death or survival with bronchopulmonary dysplasia SECONDARY OUTCOME cardiorespiratory support complications of Prematurity
Notes	Primary outcome (mortality and bronchopulmonary dysplasia) reported based on intention to treat. Other complications of prematurity reported based on treatment received.

McMillan 1995

Methods	Randomized Multicenter Blinding of randomization: Yes (opaque, sealed envelopes) Blinding of intervention: Yes (Drug administration team) Complete Follow-up: Short term: Yes Long term: 93% Blinding of outcome measurement: Yes Stratification: Based on birthweight and gender. Longterm Follow-up: Saigal 1995, Courtney 1995
Participants	Neonates Birthweight 750-1249 grams Respiratory distress syndrome Assisted ventilation a/A ratio <0.22 Age 2-24 hours Infants Randomized: Exosurf Neonatal = 176 Control = 168
Interventions	Intratracheal Exosurf Neonatal (5 ml/kg) or sham treatment (air) Second dose 12 hours later if infant remained on assisted ventilation
Outcomes	PRIMARY OUTCOME: Survival without bronchopulmonary dysplasia at 28 days SECONDARY OUTCOME cardiorespiratory support complications of prematurity
Notes	Primary outcomes (survival without BPD), BPD and neonatal mortality reported based on intention to treat. Other complications of prematurity reported based on treatment received.

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Phibbs 1991

Methods	Randomized Single Center Blinding of randomization: Yes (sealed envelopes) Blinding of intervention: No Complete Follow-up: Short term: Yes Long term: none Blinding of outcome measurement: No Stratification: Based on birthweight
Participants	Neonates Birthweight >650 grams Clinical diagnosis of hyaline membrane disease Ventilatory support for infants 650-1250 grams: (mean airway pressure equal to or >7 cm H20) FiO2 equal to or > 0.4 for infants >1250 grams: mean airway pressure equal to or >8 cm H2; FiO2 equal to or >0.5 Arterial catheter No major congenital anomaly No meconium aspiration Granulocyte count equal to or >1000/mm3 Age 4-24 hours Infants randomized: Exosurf = 57 Air placebo = 53
Interventions	Intratracheal Exosurf Neonatal (5ml/kg) given in 4 aliquots or sham treatment (air)
Outcomes	Incidence of major complications: chronic lung disease patent ductus arteriosus intracranial hemorrhage mortality ventilatory requirements
Notes	110 infants randomized 6 excluded from analysis (4 treated, 2 control)

Smyth 1995

Methods	Randomized Multicenter Blinding of randomization: Yes (opaque, sealed envelopes) Blinding of intervention: Yes (drug administration team) Complete Follow-up: Short term: Yes Long term: 96% Blinding of outcome measurement: Yes Stratification: Based on birthweight and gender

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Smyth 1995 *(Continued)*

	Long-term follow up: Casiro 1995, Courtney 1995
Participants	Neonates Birthweight 500-749 grams Respiratory distress syndrome Assisted ventilation a/A ratio <0.22 Age 2-24 hours Infants randomized: Exosurf Neonatal = 115 Control = 109
Interventions	Intratracheal Exosurf Neonatal (5 ml/kg) or sham treatment (air) Second dose 12 hours later if infant remained on assisted ventilation
Outcomes	PRIMARY OUTCOME: Neonatal mortality bronchopulmonary dysplasia survival at 28 days without BPD SECONDARY OUTCOMES cardiorespiratory support complications of prematurity
Notes	Primary outcome (neonatal mortality, BPD, survival without BPD) reported based on intention to treat. Other complications of prematurity reported based on treatment received.

US Exosurf 1991

Methods	Randomized Multicenter Blinding of Randomization: Yes (Opaque sealed envelopes) Blinding of Intervention: Yes (Drug Administration Team) Complete Follow-up: Short term: Yes Long term: 80% Blinding of Outcome Measurement: Yes Stratification: Based on birthweight and gender Long term follow-up: Gong 1995 Courtney 1995
Participants	Neonates Birthweight 700-1350 grams, inclusive Respiratory Distress Syndrome Assisted ventilation a/A ratio <0.22 No proven lung maturity No major congenital anomaly No evidence of hydrops fetalis No positive gram stain Age 2-24 hours Infants randomized: Exosurf Neonatal = 206 Control = 213

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US Exosurf 1991 *(Continued)*

Interventions	Intratracheal Exosurf Neonatal (5 ml/kg) or sham treatment (air) via side port adapter in 2 aliquots. Second dose 12 hours later if infant remained on assisted ventilation.
Outcomes	PRIMARY OUTCOME: Neonatal death or survival with bronchopulmonary dysplaisa SECONDARY OUTCOME: cardiorespiratory support complications of prematurity
Notes	Primary outcome (mortality and bronchopulmonary dysplasia) reported based on intention to treat. Unclear whether other complications of prematurity reported as intention to treat or treatment received.

Wilkinson 1985

Methods	Randomized Single center Blinding of randomization: Yes (sealed envelope) Blinding of intervention: Yes Complete Follow-up: Short term: Yes Long term: 100% Blinding of outcome measurement: Yes Stratification: Based on gender
Participants	Premature infants Gestational age <31 weeks Respiratory distress syndrome (clinical and radiologic evidence) Assisted ventilation L/S ratio <1.8 Not enrolled in delivery room study Infants Randomized: DPPC/PG = 12 Control = 12
Interventions	Intratracheal administration of dry powered dipalmitoylphosphatidylcholine and phosphatidylglycerol via modified resuscitation bag vs. manual ventilation with modified resuscitation bag.
Outcomes	cardiorespiratory variables requirement for respiratory support complications of prematurity
Notes	

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

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Study	Reason for exclusion
Chu 1967	Surfactant and route of administration inadequate
Robillard 1964	Surfactant and route of administration inadequate

DATA AND ANALYSES

Comparison 1. Synthetic surfactant vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pneumothorax	5	2328	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.55, 0.76]
2 Pulmonary interstitial emphysema	4	2224	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.54, 0.71]
3 Pulmonary hemorrhage	5	2328	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.68, 3.05]
4 Patent ductus arteriosus	5	2328	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.84, 0.97]
5 Necrotizing enterocolitis	5	2328	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.76, 2.29]
6 Apnea of prematurity	4	2224	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.09, 1.31]
7 Intraventricular hemorrhage	4	2224	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.77, 0.99]
8 Severe IVH	5	2328	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.63, 1.12]
9 Bronchopulmonary dysplasia	5	2248	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.61, 0.92]
10 Neonatal mortality	6	2352	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.61, 0.88]
11 BPD or death at 28 days	4	2224	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.65, 0.83]
12 Retinopathy of prematurity in survivors examined	3	605	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.80, 1.09]
13 Severe retinopathy of prematurity in survivors examined	3	605	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.46, 1.17]
14 Mortality prior to hospital discharge	6	2352	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.68, 0.92]
15 Mortality at 1 year	4	2224	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.69, 0.94]
16 Lost to follow-up	5	1819	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.85, 1.33]
17 Cerebral palsy in survivors examined	5	1557	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.55, 1.05]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18 Moderate - severe cerebral palsy in survivors examined	5	1557	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.48, 1.16]

Analysis 1.1. Comparison 1 Synthetic surfactant vs control, Outcome 1 Pneumothorax.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Long 1991	60/615	122/622		42.03%	0.5[0.37,0.66]
McMillan 1995	29/174	46/170		16.12%	0.62[0.41,0.93]
Phibbs 1991	27/53	28/51		9.89%	0.93[0.65,1.33]
Smyth 1995	30/113	31/111		10.84%	0.95[0.62,1.46]
US Exosurf 1991	40/206	62/213		21.12%	0.67[0.47,0.95]
Total (95% CI)	**1161**	**1167**		**100%**	**0.64[0.55,0.76]**
Total events: 186 (Treatment), 289 (Control)					
Heterogeneity: Tau^2=0; Chi^2=10.24, df=4(P=0.04); I^2=60.92%					
Test for overall effect: Z=5.32(P<0.0001)					

Analysis 1.2. Comparison 1 Synthetic surfactant vs control, Outcome 2 Pulmonary interstitial emphysema.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Long 1991	80/615	149/622		40.97%	0.54[0.42,0.7]
McMillan 1995	48/174	68/170		19.02%	0.69[0.51,0.93]
Smyth 1995	44/113	44/111		12.28%	0.98[0.71,1.36]
US Exosurf 1991	51/206	102/213		27.73%	0.52[0.39,0.68]
Total (95% CI)	**1108**	**1116**		**100%**	**0.62[0.54,0.71]**
Total events: 223 (Treatment), 363 (Control)					
Heterogeneity: Tau^2=0; Chi^2=10.94, df=3(P=0.01); I^2=72.58%					
Test for overall effect: Z=6.64(P<0.0001)					

Analysis 1.3. Comparison 1 Synthetic surfactant vs control, Outcome 3 Pulmonary hemorrhage.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Long 1991	6/615	1/622		8.69%	6.07[0.73,50.26]
McMillan 1995	3/174	1/170		8.84%	2.93[0.31,27.9]
Phibbs 1991	1/53	0/51		4.45%	2.89[0.12,69.32]
Smyth 1995	3/113	3/111		26.45%	0.98[0.2,4.76]
US Exosurf 1991	3/206	6/213		51.56%	0.52[0.13,2.04]

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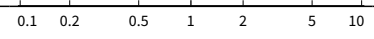
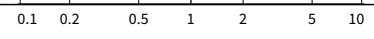
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)	**1161**	**1167**		**100%**	**1.44[0.68,3.05]**
Total events: 16 (Treatment), 11 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.71, df=4(P=0.32); I^2=15.1%					
Test for overall effect: Z=0.96(P=0.34)					



Favors treatment — Favors control

Analysis 1.4. Comparison 1 Synthetic surfactant vs control, Outcome 4 Patent ductus arteriosus.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Long 1991	279/615	334/622		49.49%	0.84[0.75,0.95]
McMillan 1995	120/174	111/170		16.73%	1.06[0.91,1.22]
Phibbs 1991	24/53	22/51		3.34%	1.05[0.68,1.62]
Smyth 1995	63/113	65/111		9.77%	0.95[0.76,1.19]
US Exosurf 1991	118/206	141/213		20.66%	0.87[0.74,1.01]
Total (95% CI)	**1161**	**1167**		**100%**	**0.9[0.84,0.97]**
Total events: 604 (Treatment), 673 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.62, df=4(P=0.16); I^2=39.62%					
Test for overall effect: Z=2.76(P=0.01)					



Favors treatment — Favors control

Analysis 1.5. Comparison 1 Synthetic surfactant vs control, Outcome 5 Necrotizing enterocolitis.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Long 1991	10/615	8/622		36.25%	1.26[0.5,3.18]
McMillan 1995	9/174	3/170		13.83%	2.93[0.81,10.64]
Phibbs 1991	2/53	1/51		4.64%	1.92[0.18,20.58]
Smyth 1995	2/113	4/111		18.39%	0.49[0.09,2.63]
US Exosurf 1991	6/206	6/213		26.89%	1.03[0.34,3.15]
Total (95% CI)	**1161**	**1167**		**100%**	**1.32[0.76,2.29]**
Total events: 29 (Treatment), 22 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.1, df=4(P=0.54); I^2=0%					
Test for overall effect: Z=1(P=0.32)					

Favors treatment — Favors control

Analysis 1.6. Comparison 1 Synthetic surfactant vs control, Outcome 6 Apnea of prematurity.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Long 1991	269/615	230/622		51.25%	1.18[1.03,1.36]

Favors treatment — Favors control

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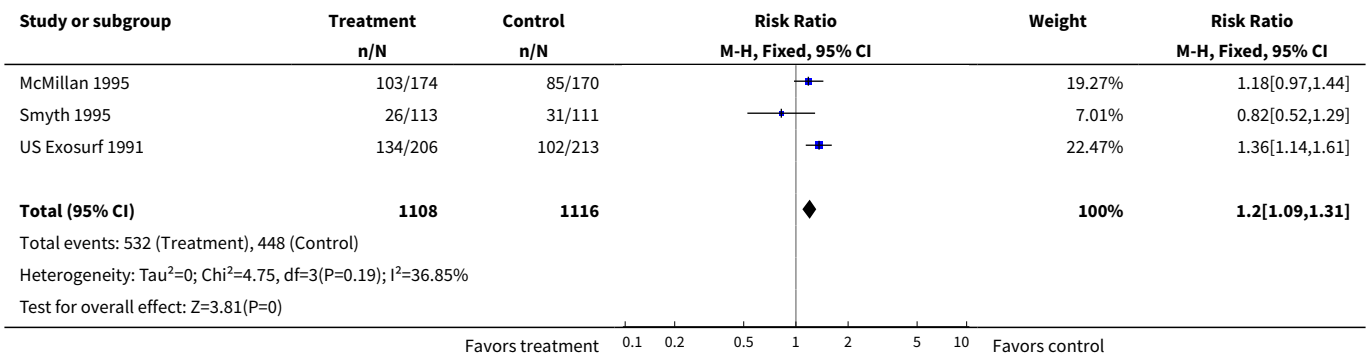
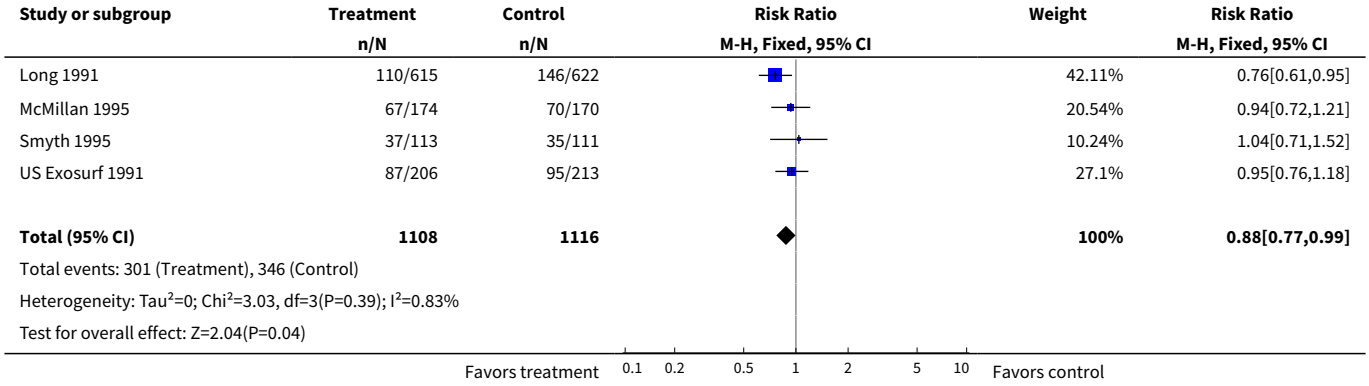
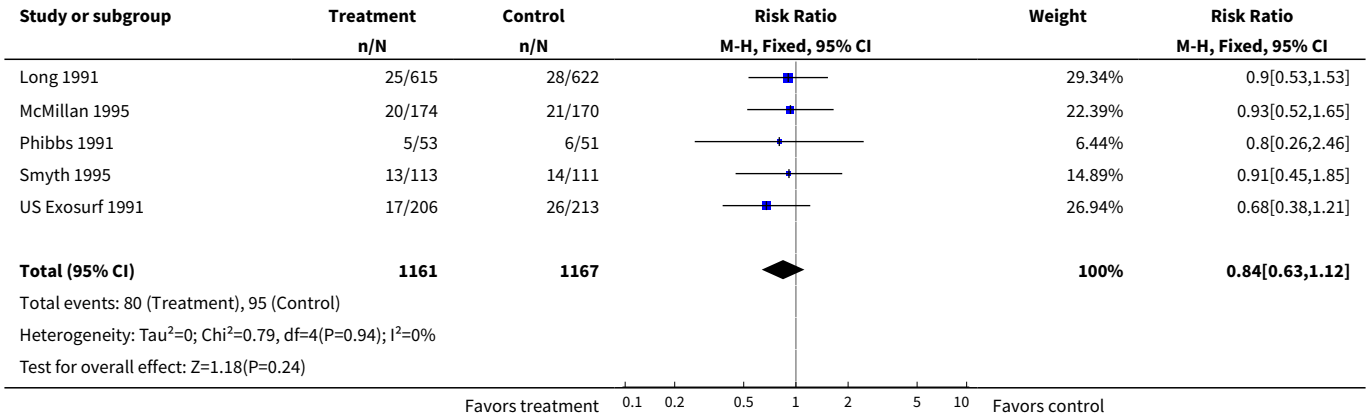


Analysis 1.7. Comparison 1 Synthetic surfactant vs control, Outcome 7 Intraventricular hemorrhage.



Analysis 1.8. Comparison 1 Synthetic surfactant vs control, Outcome 8 Severe IVH.



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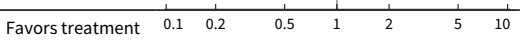
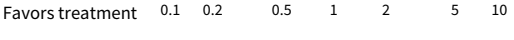
Analysis 1.9. Comparison 1 Synthetic surfactant vs control, Outcome 9 Bronchopulmonary dysplasia.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Long 1991	18/614	37/623		22.44%	0.49[0.28,0.86]
McMillan 1995	38/176	46/168		28.75%	0.79[0.54,1.15]
Smyth 1995	35/115	40/109		25.09%	0.83[0.57,1.2]
US Exosurf 1991	31/206	39/213		23.42%	0.82[0.53,1.26]
Wilkinson 1985	1/12	0/12		0.31%	3[0.13,67.06]
Total (95% CI)	**1123**	**1125**		**100%**	**0.75[0.61,0.92]**
Total events: 123 (Treatment), 162 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.51, df=4(P=0.48); I^2=0%					
Test for overall effect: Z=2.74(P=0.01)					



Analysis 1.10. Comparison 1 Synthetic surfactant vs control, Outcome 10 Neonatal mortality.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Long 1991	26/614	43/623		21.19%	0.61[0.38,0.99]
McMillan 1995	36/176	40/168		20.32%	0.86[0.58,1.28]
Phibbs 1991	9/53	11/51		5.57%	0.79[0.36,1.74]
Smyth 1995	53/115	54/109		27.53%	0.93[0.71,1.22]
US Exosurf 1991	23/206	50/213		24.41%	0.48[0.3,0.75]
Wilkinson 1985	2/12	2/12		0.99%	1[0.17,5.98]
Total (95% CI)	**1176**	**1176**		**100%**	**0.73[0.61,0.88]**
Total events: 149 (Treatment), 200 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.72, df=5(P=0.17); I^2=35.25%					
Test for overall effect: Z=3.34(P=0)					



Analysis 1.11. Comparison 1 Synthetic surfactant vs control, Outcome 11 BPD or death at 28 days.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Long 1991	42/614	74/623		22.37%	0.58[0.4,0.83]
McMillan 1995	69/176	81/168		25.24%	0.81[0.64,1.04]
Smyth 1995	85/115	91/109		28.45%	0.89[0.77,1.02]
US Exosurf 1991	47/206	80/213		23.95%	0.61[0.45,0.82]
Total (95% CI)	**1111**	**1113**		**100%**	**0.73[0.65,0.83]**
Total events: 243 (Treatment), 326 (Control)					
Heterogeneity: Tau^2=0; Chi^2=11.31, df=3(P=0.01); I^2=73.48%					
Test for overall effect: Z=4.91(P<0.0001)					

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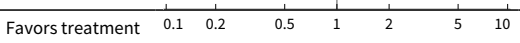
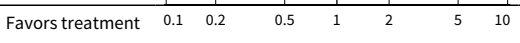
Analysis 1.12. Comparison 1 Synthetic surfactant vs control, Outcome 12 Retinopathy of prematurity in survivors examined.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
McMillan 1995	54/126	54/115		36.47%	0.91[0.69,1.21]
Smyth 1995	29/47	34/42		23.2%	0.76[0.58,1]
US Exosurf 1991	71/148	58/127		40.33%	1.05[0.82,1.35]
Total (95% CI)	**321**	**284**		**100%**	**0.93[0.8,1.09]**
Total events: 154 (Treatment), 146 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.04, df=2(P=0.22); I^2=34.27%					
Test for overall effect: Z=0.85(P=0.39)					



Analysis 1.13. Comparison 1 Synthetic surfactant vs control, Outcome 13 Severe retinopathy of prematurity in survivors examined.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
McMillan 1995	13/126	11/115		31.97%	1.08[0.5,2.31]
Smyth 1995	7/47	14/42		41.1%	0.45[0.2,1]
US Exosurf 1991	8/148	9/127		26.93%	0.76[0.3,1.92]
Total (95% CI)	**321**	**284**		**100%**	**0.73[0.46,1.17]**
Total events: 28 (Treatment), 34 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.44, df=2(P=0.29); I^2=18.13%					
Test for overall effect: Z=1.3(P=0.19)					



Analysis 1.14. Comparison 1 Synthetic surfactant vs control, Outcome 14 Mortality prior to hospital discharge.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Long 1991	44/614	59/623		23.23%	0.76[0.52,1.1]
McMillan 1995	47/174	47/170		18.86%	0.98[0.69,1.38]
Phibbs 1991	9/53	17/51		6.87%	0.51[0.25,1.04]
Smyth 1995	66/115	65/109		26.47%	0.96[0.77,1.2]
US Exosurf 1991	32/206	61/213		23.79%	0.54[0.37,0.8]
Wilkinson 1985	3/12	2/12		0.79%	1.5[0.3,7.43]
Total (95% CI)	**1174**	**1178**		**100%**	**0.79[0.68,0.92]**
Total events: 201 (Treatment), 251 (Control)					
Heterogeneity: Tau^2=0; Chi^2=10.37, df=5(P=0.07); I^2=51.76%					
Test for overall effect: Z=2.97(P=0)					

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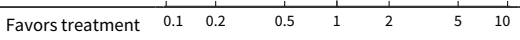
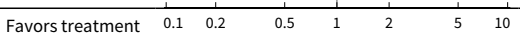
Analysis 1.15. Comparison 1 Synthetic surfactant vs control, Outcome 15 Mortality at 1 year.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Long 1991	44/615	59/622		24.99%	0.75[0.52,1.1]
McMillan 1995	47/174	47/170		20.25%	0.98[0.69,1.38]
Smyth 1995	64/113	67/111		28.79%	0.94[0.75,1.17]
US Exosurf 1991	34/206	62/213		25.97%	0.57[0.39,0.82]
Total (95% CI)	**1108**	**1116**		**100%**	**0.8[0.69,0.94]**
Total events: 189 (Treatment), 235 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.61, df=3(P=0.09); I^2=54.64%					
Test for overall effect: Z=2.69(P=0.01)					



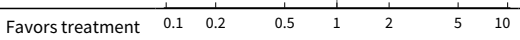
Analysis 1.16. Comparison 1 Synthetic surfactant vs control, Outcome 16 Lost to follow-up.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Long 1991	89/571	88/563		69.95%	1[0.76,1.31]
McMillan 1995	13/127	5/123		4.01%	2.52[0.93,6.85]
Smyth 1995	2/49	2/44		1.66%	0.9[0.13,6.11]
US Exosurf 1991	34/172	29/151		24.38%	1.03[0.66,1.61]
Wilkinson 1985	0/9	0/10			Not estimable
Total (95% CI)	**928**	**891**		**100%**	**1.06[0.85,1.33]**
Total events: 138 (Treatment), 124 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.12, df=3(P=0.37); I^2=3.75%					
Test for overall effect: Z=0.55(P=0.58)					



Analysis 1.17. Comparison 1 Synthetic surfactant vs control, Outcome 17 Cerebral palsy in survivors examined.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Long 1991	28/482	36/475		48.16%	0.77[0.48,1.24]
McMillan 1995	12/114	13/118		16.97%	0.96[0.46,2]
Smyth 1995	8/47	9/42		12.62%	0.79[0.34,1.87]
US Exosurf 1991	6/138	14/122		19.74%	0.38[0.15,0.96]
Wilkinson 1985	4/9	2/10		2.52%	2.22[0.53,9.37]
Total (95% CI)	**790**	**767**		**100%**	**0.76[0.55,1.05]**
Total events: 58 (Treatment), 74 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.69, df=4(P=0.32); I^2=14.63%					
Test for overall effect: Z=1.64(P=0.1)					



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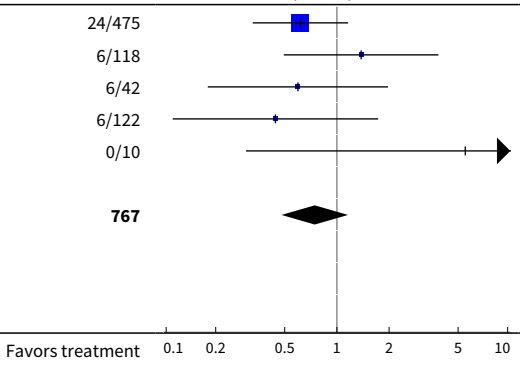
Analysis 1.18. Comparison 1 Synthetic surfactant vs control, Outcome 18 Moderate - severe cerebral palsy in survivors examined.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Long 1991	15/482	24/475		55.89%	0.62[0.33,1.16]
McMillan 1995	8/114	6/118		13.63%	1.38[0.49,3.85]
Smyth 1995	4/47	6/42		14.65%	0.6[0.18,1.97]
US Exosurf 1991	3/138	6/122		14.72%	0.44[0.11,1.73]
Wilkinson 1985	2/9	0/10		1.1%	5.5[0.3,101.28]
Total (95% CI)	**790**	**767**		**100%**	**0.75[0.48,1.16]**
Total events: 32 (Treatment), 42 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.24, df=4(P=0.37); I^2=5.64%					
Test for overall effect: Z=1.3(P=0.19)					



WHAT'S NEW

Date	Event	Description
28 February 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 1998
Review first published: Issue 3, 1998

Date	Event	Description
22 May 1998	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

Dr. R. Soll has acted as a consultant and invited speaker for several of the pharmaceutical companies which manufacture surfactant preparations (Abbott Laboratories, Ross Laboratories, Chiesi Pharmaceuticals, Dey Laboratories, Burroughs Wellcome).

SOURCES OF SUPPORT

Internal sources

- [Information not provided], Not specified.

External sources

- Neonatal Collaborative Review Group, NIH Contract #N01-MD-6-3253, USA.

INDEX TERMS

Medical Subject Headings (MeSH)

Infant, Premature; Pulmonary Surfactants [*therapeutic use]; Respiratory Distress Syndrome, Newborn [*drug therapy]

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MeSH check words

Humans; Infant, Newborn

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