Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (Review)

Soll R

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Roger Soll[1]

[1]Division of Neonatal-Perinatal Medicine, University of Vermont, Burlington, Vermont, USA

Contact address: Roger Soll, Division of Neonatal-Perinatal Medicine, University of Vermont, Fletcher Allen Health Care, Smith 552A, 111 Colchester Avenue, Burlington, Vermont, 05401, USA. Roger.Soll@vtmednet.org.

Editorial group: Cochrane Neonatal Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.
Review content assessed as up-to-date: 12 July 1999.

Citation: Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 1999, Issue 4. Art. No.: CD001456. DOI: 10.1002/14651858.CD001456.

ABSTRACT

Background

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

Objectives

To compare the effects of early vs. delayed selective surfactant therapy for newborns intubated for respiratory distress within the first two hours of life. Planned subgroup analyses include separate comparisons for studies utilizing natural surfactant extract and synthetic surfactant.

Search strategy

Searches were made of the Oxford Database of Perinatal Trials, Medline (MeSH terms: pulmonary surfactant; text word: early; limits: age, newborn: publication type, clinical trial), PubMed, abstracts, conference and symposia proceedings, expert informants, and journal hand searching in the English language.

Selection criteria

Only randomized controlled clinical trials comparing early selective surfactant administration (surfactant administration via the endotracheal tube in infants intubated for respiratory distress, not specifically for surfactant dosage) within the first 2 hours of life versus delayed selective surfactant administration to infants with established respiratory distress syndrome were considered for review.

Data collection and analysis

Data regarding clinical outcomes including the incidence of pneumothorax, patent ductus arteriosus, pulmonary interstitial emphysema, pulmonary hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, intraventricular hemorrhage (any and severe IVH), bronchopulmonary dysplasia, chronic lung disease, neonatal mortality, mortality prior to hospital discharge, bronchopulmonary dysplasia or death, and chronic lung disease or death were excerpted from the reports of the clinical trials by the reviewers. Data regarding the average number of surfactant doses per infant were also analyzed. Further analysis of data with regard to surfactant type was performed. Data analysis was performed in accordance with the standards of the Cochrane Neonatal Review Group.

Main results

Four randomized controlled trials met selection criteria. Two of the trials utilized synthetic surfactant (Exosurf Neonatal) and two utilized a natural surfactant extract. The meta-analyses demonstrated significant reductions in risk of pneumothorax (Typical RR 0.70, 95%CI 0.59, 0.82; Typical RD -0.05, 95%CI -0.08, -0.03), and pulmonary interstitial emphysema (Typical RR 0.63, 95%CI 0.43, 0.93; Typical RD -0.06, 95%CI -0.10, -0.01) in infants randomized to early selective surfactant administration. Infants randomized to early selective surfactant administration also demonstrated a decreased risk of neonatal mortality (Typical RR 0.87, 95%CI 0.77, 0.99; Typical RD -0.03, 95%CI -0.06, -0.00), chronic lung disease (Typical RR 0.70, 95%CI 0.55, 0.88; Typical RD -0.03, 95%CI -0.05, -0.01), and chronic lung disease or death at 36 weeks (Typical RR 0.84, 95%CI 0.75, 0.93; Typical RD -0.06, 95%CI -0.09, -0.03). A trend toward risk reduction for bronchopulmonary dysplasia or death at 28 days was also evident (Typical RR 0.94, 95%CI 0.88, 1.00; Typical RD -0.04, 95%CI -0.07, -0.00). No differences in other complications of RDS or prematurity were noted.

Authors' conclusions

Early selective surfactant administration given to infants with RDS requiring assisted ventilation leads to a decreased risk of acute pulmonary injury (decreased risk of pneumothorax and pulmonary interstitial emphysema) and a decreased risk of neonatal mortality and chronic lung disease compared to delaying treatment of such infants until they develop established RDS.

PLAIN LANGUAGE SUMMARY

Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Giving early selective surfactant to newborn babies with early signs of respiratory distress syndrome reduces the risk of chronic lung disease. Pulmonary surfactant is a substance that prevents the air sacs of the lungs from collapsing by reducing surface tension. Surfactant is often lacking in the lungs of newborn babies with respiratory distress syndrome (RDS). The effectiveness of surfactant extracts in increasing their survival rate has been proven. The question remains about the best time to start giving surfactant. The review of trials compared early selective treatment of RDS (within the first two hours of life) to late selective treatment and found evidence of the benefit of early therapy. More research is needed.

BACKGROUND

Clinical trials have proven that surfactant therapy is effective in improving the immediate need for respiratory support and the clinical outcome of premature newborns (Soll 1992). Trials have studied a wide variety of surfactant preparations used either prophylactically or in the treatment of established respiratory distress syndrome. Using either treatment strategy, significant reductions in the incidence of pneumothorax as well as significant improvement in survival has been noted.

Although both prophylactic surfactant administration and surfactant treatment of infants with established respiratory distress syndrome are successful treatment strategies, prophylactic strategies appear to have greater clinical benefit. In a systematic overview of trials comparing prophylactic surfactant administration to surfactant treatment of established respiratory distress syndrome, infants who received prophylactic therapy had a decreased incidence of pneumothorax, pulmonary interstitial emphysema, and mortality (Soll 1999). However, the approaches used to select treatment vary greatly in these studies. Selective treatment in infants with respiratory distress syndrome ranged from 1.5 hours to 8 hours of age.

Earlier treatment of infants with evolving respiratory distress syndrome may offer many of the advantages of prophylactic therapy. Early treatment may decrease the need for ventilatory support and avoid barotrauma that results from even short periods of assisted ventilation (Nilsson 1978). However, surfactant treatment reserved for infants with more severe respiratory distress syndrome offers the advantage of treating only infants with serious clinical disease, eliminating the potential risks and costs of treating relatively mildly affected infants.

As noted above, previous reviews have addressed the clinical issue of prophylactic surfactant administration (intubation and surfactant administration to infants at high risk of developing RDS) compared to surfactant treatment of RDS (Soll 1999). This review will evaluate early selective treatment of RDS (within the first two hours of life) compared with late selective treatment in infants with established respiratory distress syndrome.

OBJECTIVES

To compare the effects of early versus delayed selective surfactant therapy for newborns intubated for respiratory distress within the first two hours of life. Planned subgroup analyses include separate comparisons for natural surfactant extract and synthetic surfactant.

METHODS

Criteria for considering studies for this review

Types of studies

Prospective randomized controlled clinical trials comparing early selective surfactant administration (surfactant administration via the endotracheal tube in infants intubated for respiratory distress, not specifically for surfactant dosage) within the first 2 hours of life with delayed selective surfactant administration to such infants when they develop established respiratory distress syndrome.

Types of participants

Premature infants with respiratory distress syndrome, requiring intubation and assisted ventilation at <2 hours of life.

Types of interventions

Early selective surfactant administration (surfactant administration via the endotracheal tube in infants intubated for respiratory distress, not specifically for surfactant dosage), within the first two hours of life, versus delayed selective administration to such infants when they develop established respiratory distress syndrome.

Types of outcome measures

Data of the following clinical outcomes are included in the meta-analyses:

1. Pneumothorax
2. Pulmonary interstitial emphysema
3. Pulmonary hemorrhage
4. Patent ductus arteriosus
5. Necrotizing enterocolitis
6. Intraventricular hemorrhage
7. Severe intraventricular hemorrhage
8. Retinopathy of prematurity
9. Bronchopulmonary dysplasia (oxygen requirement at 28 days of life)
10. Chronic lung disease (oxygen requirement at 36 weeks adjusted age)
11. Neonatal mortality
12. Mortality prior to hospital discharge
13. Bronchopulmonary dysplasia or death at 28 days of life
14. Chronic lung disease or death at 36 weeks adjusted age
15. Number of doses per infant

Search methods for identification of studies

Searches were made of the Oxford Database of Perinatal Trials, Medline 1985 through 1998 (MeSH terms: pulmonary surfactant; text word: early; limits: age, newborn: publication type, clinical trial), PubMed, abstracts, conference and symposia proceedings, expert informants, and journal hand searching 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 inclusion criteria including gestational age, postnatal age at the time of treatment, and disease severity criteria was noted. Information on clinical outcome was analyzed including number of doses, pneumothorax, pulmonary interstitial emphysema, pulmonary hemorrhage, patent ductus arteriosus, necrotizing enterocolitis, intraventricular hemorrhage (any intraventricular hemorrhage and severe intraventricular hemorrhage), retinopathy of prematurity, bronchopulmonary dysplasia, chronic lung disease, neonatal mortality, mortality prior to hospital discharge, bronchopulmonary dysplasia or death at 28 days, and chronic lung disease or death at 36 weeks adjusted age.

Subgroup analyses evaluated the effect of surfactant type (natural surfactant extract or synthetic surfactant).

RESULTS

Description of studies

See: Characteristics of included studies.

Studies included in this review: European Study 1992; Gortner 1998; Konishi 1992 and OSIRIS 1992. The details concerning each study are included in the "Characteristics of Included Studies" table and references.

While each of the studies sought to compare early with delayed surfactant administration, significant differences were noted in the timing of the first dose. Konishi (1992) administered the early dose of surfactant within the first 30 minutes of life. The European Exosurf Trial (1992) and the OSIRIS Trial (1992) both defined early treatment as prior to 2 hours of life. Gortner (1998) used 1 hour of life as the cut-off for early treatment.

All studies attempted to evaluate a population at high risk for RDS, but differed slightly in their inclusion criteria. Konishi 1992 included babies of 500-1500g whose weight was appropriate for gestational age and whose surfactant deficiency had to be documented by analysis of the gastric aspirate. The European Exosurf Trial (1992) included infants between 26 -29 weeks, while Gortner (1998) included 27-32 weeks and OSIRIS (1992) did not specify specific inclusion criteria for gestational age or weight. All studies excluded infants with pre or post-natal congenital anomalies, as well as infants with oligohydramnios or prolonged rupture of membranes > 72 hours; all studies required informed consent.

The surfactant preparations differed between studies. Konishi (1992) and Gortner (1998) used natural bovine surfactant extract, Surfactant TA and Alveofact respectively. The European Exosurf Trial (1992) and OSIRIS (1992) treated infants with Exosurf Neonatal, a synthetic surfactant containing dipalmitoylphosphatidyl choline, tyloxapol, and hexadecanol. This review includes sub-group analyses by surfactant type.

Primary outcomes were survival and survival without BPD in both the OSIRIS (1992) and European Exosurf trials (1992). In the studies utilizing a natural surfactant extract, Konishi (1992) measured ventilatory requirements in the first 7 days of life, and Gortner (1998) measured length of mechanical ventilation as primary outcomes. Secondary outcomes included complications of prematurity.

All studies reported incidence of antenatal steroid use in experimental and control groups and demonstrated no significant difference between the study groups. Gortner (1998) was the only included study carried out in a population where the majority of infants' mothers had received a complete course of antenatal steroids. Three of the studies allowed for multiple surfactant doses. Konishi (1992) gave only 1 surfactant dose to infants in control and experimental groups.

Risk of bias in included studies

Only randomized controlled studies comparing the effects of early selective surfactant administration (intratracheal surfactant at less than 2 hours of life in infants intubated for early respiratory distress) versus delayed selective surfactant administration for the treatment of established respiratory distress syndrome were included in the analysis. All studies were multicenter studies, with the exception of Konishi (1992).

Randomization: Methods varied between studies. Konishi (1992) did not describe any blinding of randomization, stating only that the 32 included infants were randomized after meeting inclusion criteria. Gortner (1998) provided randomization lists to the 6 participating centers from a central statistical center for medical informatics. The European Exosurf Trial (1992) generated a unique trial number corresponding to an opaque sealed envelope located at the various trial centers. OSIRIS (1992) randomized trial entrants by telephone from a central location after entry criteria were met and prognostic variables recorded.

Blinding of Treatment: Only the European Exosurf Trial (1992) maintained full blinding of treatment. Konishi (1992) and Gortner (1998) failed to comment on any blinding of treatment, and OSIRIS (1992) was unblinded to treatment by design.

Blinding of Outcome Assessment: The European Exosurf Trial (1992) demonstrated full blinding of outcome assessment. The sequential design of the trial allowed for assessment of the data by an independent, non-clinical analysis team after every 20th baby. Results that might warrant termination of the trial were to be submitted to an independent advisory board with authority to terminate the trial. The other trials did not comment on blinding at the outcome assessment level.

Exclusion after Randomization: All data were analyzed from an intent-to-treat perspective after initial randomization. The European Exosurf Trial (1992), Gortner (1998), and OSIRIS (1992) excluded no patients after the initial randomization. Konishi (1992) excluded 8 of 40 infants initially randomized, because they did not meet the prospective inclusion criteria.

The combined sample sizes of the trials using natural surfactant were approximately one tenth the size of the trials using synthetic surfactant (349 infants enrolled in trials utilizing natural surfactant compared to 3110 infants enrolled in trials utilizing synthetic surfactant).

Effects of interventions

PNEUMOTHORAX: Both trials of early selective synthetic surfactant treatment demonstrated a significant reduction in the risk of pneumothorax. The European Exosurf Trial (1992) noted a decrease in the risk of pneumothorax with early surfactant treatment (RR: 0.68, 95%CI 0.47, 0.98; RD: -0.09, 95%CI -0.16, -0.01). OSIRIS (1992) also demonstrated a significant decrease in the risk of pneumothorax with early surfactant administration (RR: 0.69, 95%CI 0.57, 0.83; RD: -0.05, 95%CI -0.08, -0.03). The sole trial of natural surfactant extract (Gortner 1998) did not demonstrate any effect of early natural surfactant extract administration on the risk of pneumothorax.

The meta-analysis of all trials supports a decrease in risk of pneumothorax with early selective surfactant treatment (Typical RR: 0.70, 95%CI 0.59, 0.82; Typical RD: -0.05, 95%CI -0.08, -0.03).

PULMONARY INTERSTITIAL EMPHYSEMA: Two studies reported on the incidence of pulmonary interstitial emphysema (PIE) with early versus delayed selective surfactant. The European Exosurf Trial (1992) showed a significant decrease in the risk of PIE with early surfactant treatment (RR: 0.62, 95%CI 0.40,0.94; RD: -0.08, 95%CI -0.16, -0.01). Gortner (1998) found no significant decrease in the risk of PIE with early surfactant treatment (RR: 0.71, 95%CI 0.26, 1.94; RD: -0.16, 95%CI -0.06, 0.03).

The meta-analysis supports a significant decrease in the incidence of PIE associated with early selective surfactant administration (Typical RR: 0.63, 95%CI 0.43, 0.93; Typical RD: -0.06, 95%CI -0.10, -0.01).

PULMONARY HEMORRHAGE: Gortner (1998) reported on the risk of pulmonary hemorrhage associated with early selective surfactant treatment and found no significant effect on pulmonary hemorrhage (RR: 0.21, 95%CI 0.01, 4.37; RD: -0.01, 95%CI -0.03, 0.01). OSIRIS (1992) also failed to document a significant increase in the risk of pulmonary hemorrhage with early surfactant administration (RR: 1.01, 95%CI 0.75, 1.37; RD: 0.00, 95%CI -0.02, 0.02).

The meta-analysis found no evidence of effect on pulmonary hemorrhage with early selective surfactant treatment (Typical RR: 0.99, 95%CI 0.73, 1.34; Typical RD: -0.00, 95%CI -0.02, 0.02).

PATENT DUCTUS ARTERIOSUS: None of the 4 studies supported a decrease in the risk of patent ductus arteriosus (PDA) with early selective surfactant administration.

The meta-analysis demonstrated no evidence of effect on the risk of PDA with early selective surfactant treatment (Typical RR: 1.03, 95%CI 0.92,1.15; Typical RD: 0.01, 95%CI -0.02, 0.04).

NECROTIZING ENTEROCOLITIS: Three studies evaluated the effect of early selective surfactant treatment on the incidence of necrotizing enterocolitis (NEC). None demonstrated a significant effect.

The meta-analysis demonstrated no evidence of effect on the risk of NEC with early selective surfactant treatment (Typical RR: 1.08, 95%CI 0.77, 1.51; Typical RD: 0.00, 95%CI -0.01, 0.02).

RETINOPATHY OF PREMATURITY (Stage III or greater): Three of the included studies reported on the incidence of retinopathy of prematurity (ROP) associated with early selective surfactant treatment. No significant effect was reported.

The meta-analysis demonstrated no evidence of effect on the risk of ROP with early surfactant therapy (Typical RR: 1.06, 95%CI 0.58,1.91; Typical RD: 0.00, 95%CI -0.01, 0.01).

INTRAVENTRICULAR HEMORRHAGE (all grades): Only Konishi (1992) reports on the incidence of any intraventricular hemorrhage (IVH) associated with early selective surfactant treatment. No significant change in the rate of any IVH was noted (RR: 1.00, 95%CI 0.30, 3.32; RD: 0.00, 95%CI -0.30, 0.30).

INTRAVENTRICULAR HEMORRHAGE (Severe): The OSIRIS trial (1992) and Gortner (1992) reported on the incidence of severe IVH (Grades 3 and 4) associated with early selective surfactant treatment. No significant change in the risk of severe IVH was detected.

The meta-analysis does not support a significant effect on the risk of severe IVH associated with early selective surfactant administration (Typical RR: 0.97, 95%CI 0.83,1.14; Typical RD: -0.01, 95%CI -0.03, 0.02).

BRONCHOPULMONARY DYSPLASIA: Three of the included studies reported on the effect of early selective surfactant treatment on bronchopulmonary dysplasia (BPD). The stated definition of BPD in all studies but Konishi (1992) was any oxygen supplementation at 28 days of life. Konishi (1992) defined BPD as FIO2 greater than or equal to 0.3 at 28 days of life. Using data provided by the Konishi (1992) study, the more liberal and standard definition of BPD was applied to their results and included in this review. No study documented a significant reduction in BPD with early selective surfactant treatment.

The meta-analysis found no evidence of a significant reduction in the risk of BPD with early selective surfactant (Typical RR: 0.97, 95%CI 0.88, 1.06; Typical RD: -0.01, 95%CI -0.05, 0.02).

CHRONIC LUNG DISEASE: Gortner (1998) reported on the effect on chronic lung disease (CLD) of early selective surfactant administration. Gortner defined CLD as a requirement for supplemental oxygen at 36 weeks adjusted age. No significant effect of early surfactant treatment was noted (RR: 0.62, 95%CI 0.25, 1.53; RD: -0.03, 95%CI -0.08, 0.02). OSIRIS (1992) defined CLD as a supplemental oxygen requirement at the "expected delivery date," and showed a significant reduction in risk of CLD associated with early surfactant treatment (RR: 0.70, 95%CI 0.55, 0.89; RD: -0.03, 95%CI -0.06, -0.01).

The meta-analysis estimated a significant reduction in CLD with early selective surfactant treatment (Typical RR: 0.70, 95%CI 0.55, 0.88; Typical RD: -0.03, 95%CI -0.05, -0.01).

NEONATAL MORTALITY: All four included studies reported on the effect of early selective surfactant administration on neonatal mortality. None of the four studies found a significant effect on neonatal mortality, although in each of two studies, the European Exosurf trial (1992) and OSIRIS (1992), there was a trend towards decreased neonatal mortality with early surfactant treatment.

The meta-analysis estimated a significant reduction in neonatal mortality with early selective surfactant therapy (Typical RR: 0.87, 95%CI 0.77, 0.99; Typical RD: -0.03, 95%CI -0.06, -0.00).

MORTALITY PRIOR TO DISCHARGE: Three included studies reported on mortality prior to discharge. OSIRIS (1992) demonstrated a trend toward decreased risk of mortality prior to discharge with early surfactant treatment (RR: 0.89, 95%CI 0.79, 1.01; RD: -0.03, 95%CI -0.07, 0.00).

The meta-analysis estimates a similar trend (Typical RR: 0.90, 95%CI 0.79, 1.01; Typical RD: -0.03, 95%CI -0.06, 0.00).

BRONCHOPULMONARY DYSPLASIA OR DEATH AT 28 DAYS: Only the European Exosurf Trial (1992) did not comment on the effect of early selective surfactant on BPD or death at 28 days. Of the other three studies, Konishi (1992) (RR: 0.54, 95%CI 0.29, 0.98; RD: -0.38, 95%CI -0.68, -0.07) and OSIRIS (RR:

0.94, 95%CI 0.88, 1.00; RD: -0.04, 95%CI -0.08, -0.00) both showed a trend toward reduction of BPD or death with early surfactant. Gortner (1998) failed to show any reduction in incidence of the two outcomes with early surfactant (RR: 1.09, 95%CI 0.74, 1.59; RD: 0.02, 95%CI -0.08, 0.12).

The meta-analysis estimates a trend towards reduction in BPD or death at 28 days (Typical RR: 0.94, 95%CI 0.88, 1.00; Typical RD: -0.04, 95 % CI -0.07, -0.00).

CHRONIC LUNG DISEASE OR DEATH: Two studies reported on CLD or death. Gortner (1998) failed to show any reduction in incidence of the two unfavorable outcomes at 36 weeks adjusted gestational age (RR: 0.85, 95%CI 0.41, 1.75; RD: -0.01, 95%CI -0.08, 0.05). OSIRIS (1992) showed significant reductions in the rate of CLD or death at the "expected delivery date" with early selective surfactant treatment (RR: 0.84, 95%CI 0.75, 0.93; RD: -0.06, 95%CI -0.10, -0.03).

The meta-analysis supports a significant reduction in CLD or death at 36 weeks with early selective surfactant therapy (Typical RR: 0.84, 95%CI 0.75, 0.93; Typical RD: -0.06, 95%CI -0.09, -0.03).

NUMBER OF DOSES: The OSIRIS Trial (1992) and the study of Gortner (1998) reported on the number of surfactant doses given to infants. In the OSIRIS trial, infants randomized to receive early surfactant treatment received more surfactant treatments (WMD 0.49 doses per infant, 95% CI 0.41, 0.47). Gortner (1998) found no evidence of effect on the number of surfactant treatments. There was marked statistical heterogeneity for this outcome, so no typical effect was calculated.

DISCUSSION

Surfactant replacement therapy has been shown to improve clinical outcome, whether given prophylactically to infants at high risk of developing RDS, or when given to infants with established RDS (Soll 1992). A broad range of criteria for both timing of treatment and disease severity (two related but clearly distinct clinical issues) has been successfully utilized. This leaves clinicians with uncertainty regarding the optimal timing of surfactant treatment.

In this review, we evaluate the merits of early selective surfactant treatment compared to delayed selective surfactant treatment in infants with RDS. Four studies were identified which compared the use of early versus delayed selective surfactant administration in a population of premature infants at risk for respiratory distress syndrome. Of the four studies, the OSIRIS trial (1992), which utilized synthetic surfactant, is by far the largest study, and dominates the estimates of the effect of these treatment strategies. Given the relatively small number of infants studied in the trials of natural surfactant extracts, it is hard to draw conclusions regarding any differences in the effects of natural vs. synthetic surfactant when used early in the treatment of respiratory distress. Overall, early selective surfactant administration decreased the risk of acute pulmonary injury (decreased risk of pneumothorax and pulmonary interstitial emphysema) and decreased the risk of neonatal mortality and chronic lung disease compared to delayed selective treatment of infants with established RDS. Based on these data, recommendations favoring earlier treatment seem reasonable.

It is hard to judge the relative value of early surfactant treatment compared to true prophylactic use of surfactant in the absence of any randomized trials that have directly compared these policies. Prophylactic rather than delayed administration of surfactant to all infants deemed at high risk for RDS reduces the risk of pneumothorax, pulmonary interstitial emphysema, bronchopulmonary dysplasia or death, as well as mortality (Soll 1999). Similar benefits are associated with early selective rather than delayed surfactant administration in premature infants intubated for respiratory distress within the first two hours of life. With prophylactic rather than delayed surfactant, the number of infants that would need to be treated to avoid one pneumothorax was 50, and only 20 to prevent one death; the present meta-analysis suggests that with early rather than delayed surfactant treatment, 20 infants need be treated to prevent one pneumothorax, and 35 to prevent one neonatal death.

Although there are no randomized trials that compare prophylactic surfactant treatment with early selective surfactant treatment, studies suggest that the greatest benefit may come from the earliest care. Prophylactic delivery room treatment is effective whether given before or after the onset of respiration. Kendig (1998) demonstrated that the benefits of prophylactic surfactant administration were preserved even if the initial therapy was delayed to the first 10 minutes of life.

However, even small delays in treating infants with established RDS appear to be clinically important. Kattwinkel (1993) conducted a study comparing prophylactic versus early surfactant therapy in the 29 - 32 week gestational age population of premature neonates. Criteria for intubation and early selective surfactant treatment were liberal; an FIO2 requirement of 0.30 with radiographic findings not consistent with another respiratory process prompted intubation for surfactant therapy. In the studies of early treatment, criteria for the early selective treatment group were frequently more stringent than in the selective treatment group of Kattwinkel (1993). OSIRIS (1992) required intubation for respiratory distress prior to surfactant dosing; no child was intubated for the sole purpose of surfactant administration. The European Exosurf Trial (1992) enrolled only infants at high risk for RDS and intubated for respiratory distress before two hours of life. Gortner (1998) administered the first dose of surfactant within the first hour of life if respiratory distress required intubation. Clearly, Kattwinkel (1993) had a lower threshold for selective surfactant treatment, and surfactant was given earlier than in most of the included studies in this review. The selective treatment group of Kattwinkel (1993) had a median time to first surfactant dose of

90 minutes versus the 118 minutes noted in the OSIRIS (1992) trial for early selective treatment. The meta-analysis of prophylactic versus delayed surfactant (Soll 1999) estimated a relative risk reduction of 41 % for neonatal mortality and 25 % for mortality prior to hospital discharge. The current analysis estimates a 13 % reduction in relative risk for neonatal mortality and a strong trend towards a 10 % reduction in relative risk of mortality prior to discharge with early versus delayed selective surfactant treatment.

This meta-analysis suggests that the substantial benefits accompanying early versus delayed selective surfactant therapy may be a part of the greater trend towards improved outcomes with earlier treatment. This is consistent with evidence of lung injury from animal studies that demonstrate leakage of proteins into the alveolar spaces of the surfactant deficient lung that act as surfactant inhibitors (Jobe 1983). Exogenous surfactant has reduced the leakage of such surfactant inhibiting proteins in animal models (Jobe 1983, Ikegami 1986).

Despite evidence supporting the efficacy of prophylactic and early surfactant therapy, estimates show that not all infants judged to be at high risk for RDS are surfactant deficient. Of the trials included in this meta-analysis, only Konishi (1992) estimated surfactant deficiency prior to surfactant administration. He found only 66% of those judged at risk for RDS based on a birth weight criterion of 500 - 1500 grams to have surfactant deficiency at birth. Kattwinkel (1993) noted that of those randomized to early selective surfactant treatment only 43% of 621 infants required surfactant as indicated by their admittedly liberal criteria. Clearly prophylaxis with surfactant would overtreat a large number of infants judged at risk for RDS, and this overtreatment may be justified to save the life of every 20th child. It appears, however, that treatment with surfactant within the first two hours of life in those infants intubated for respiratory distress confers the benefits of reduced mortality and pneumothorax while treating a substantially smaller portion of those infants judged at risk prenatally.

Antenatal steroids improve the outcome of premature infants at risk for RDS (Crowley 1998). Gortner (1998) provided the only included study carried out in a population where the majority of infants' mothers had received a complete course of antenatal steroids. He failed to document a significant reduction in rates of pneumothorax or neonatal mortality. The review of studies comparing prophylactic versus delayed selective surfactant administration was also carried out in populations not fully benefiting from the documented effects of antenatal steroids. Gortner questions the impact of prophylactic or early treatment in the population of steroid treated infants, who are at less risk of RDS. However, most other studies of surfactant replacement have suggested a synergistic effect of these two therapies (Jobe 1993).

AUTHORS' CONCLUSIONS

Implications for practice

Early surfactant administration significantly reduces the risk of key clinical outcomes including pneumothorax, PIE, chronic lung disease, and neonatal mortality. Given the efficacy of prophylactic surfactant therapy (Soll 1999), this meta-analysis suggests that early selective surfactant administration to intubated infants with early signs of RDS may be part of a clinical spectrum of improved outcomes with earlier treatment. The difficulty of judging which infant is at risk for surfactant deficiency continues. The meta-analysis would suggest that neonates with early respiratory distress should be given surfactant as early as possible.

Implications for research

Improved identification of the infant at risk for RDS will improve the selection criteria for prophylactic or early selective surfactant therapy. Given the difficulty in determining which infant is at risk for respiratory distress syndrome and the known over-treatment of some infants with prophylactic surfactant therapy, further comparison of prophylactic versus very early selective surfactant treatment might provide further insight into the optimal timing for surfactant treatment.

ACKNOWLEDGEMENTS

We would like to thank Nancy Moreland for her help in preparing the manuscript.

REFERENCES

References to studies included in this review

European Study 1992 *{published data only}*

European Exosurf Study Group. Early or selective surfactant (Colfosceril Palmitate, Exosurf) for intubated babies at 26 to 29 weeks gestation: A European double-blind trial with sequential analysis. *Online J Curr Clin Trials* 1992;**Nov 10**:Doc. No. 28.

Gortner 1998 *{published data only}*

Gortner L, et al.Early versus late surfactant treatment in preterm infants of 27 to 32 weeks' gestational age: A multicenter controlled clinical trial. *Pediatrics* 1998;**102**:1153–1160.

Konishi 1992 *{published data only}*

Konishi M, et al.A prospective randomized trial of early versus late administration of a single dose of surfactant-TA. *Early Human Development* 1992;**29**:275–282.

OSIRIS 1992 *{published data only}*

The OSIRIS Collaborative Group. Early versus delayed neonatal administration of a synthetic surfactant - The judgement of OSIRIS. *Lancet* 1992;**340**:1363–1369.

Additional references

Crowley 1999

Crowley P. Prophylactic corticosteroids for preterm delivery. *Cochrane Library* 1999, Issue 2.

Ikegami 1983

Ikegami M, Jacobs H, Jobe A. Surfactant function in respiratory distress syndrome. *J Pediatr* 1983;**102**:443–447.

Jobe 1993

Jobe AH, Mitchell BR, Gunkel JH. Beneficial effects of the combined use of prenatal corticosteroids and postnatal surfactant in preterm infants. *Am J Obstet Gynecol* 1993;**168**:508–513.

Kattwinkel 1993

Kattwinkel J, et al.Prophylactic administration of calf lung surfactant extract is more effective than early treatment of respiratory distress syndrome in neonates of 29 through 32 week's gestation. *Pediatrics* 1993;**92**:90–98.

Kendig 1998

Kendig JW, et al.Comparison of two strategies for surfactant prophylaxis in very premature infants: A multicenter randomized trial. *Pediatrics* 1998;**101**:1006–1012.

Nilsson 1978

Nilsson R, Grossman G, Robertson B. Lung surfactant and the pathogenesis of neonatal bronchiolar lesions induced by artificial ventilation. *Pediatr Res* 1978;**12**:249–255.

Soll 1992

Soll RF, McQueen MC. Respiratory distress syndrome. In: Sinclair JC, Bracken MB editor(s). *Effective Care of the Newborn Infant*. Oxford: Oxford University Press, 1992:325–358.

Soll 1999

Soll RF, Morley CJ. Prophylactic versus selective use of surfactant for preventing morbidity and mortality in preterm infants. *Cochrane Library* 1999, Issue 1.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

European Study 1992

Methods	Randomized Multicenter Trial. Blinding of randomization: Yes (sealed envelope) Complete follow-up : Yes. (follow up scheduled to extend through the first 2 years of life, but only data through 36 weeks gestational age reported). Blinding of Outcome Measurement: Yes. (Full blinding of the interventions achieved with single drug administrator delivering air placebo or surfactant. Drug administrator then without clinical responsibility for ensuing course. Clinical study administrators blinded to results of trial. All data submitted in a sequential analysis design for statistical analysis after each 20 babies. An independent advisory board notified of results possibly warranting termination of the trial). Stratification: Gestational age and gender.
Participants	Early selective treatment: 212 randomized Delayed selective treatment: 208 randomized Inclusion Criteria: 1. 26 -29 weeks gestation by reliable dates or ultrasound examination performed prior to 20 weeks estimated gestational age; 2. Intubation and mechanical ventilation required prior to 2 hours of life; 3. No stillbirths or major fetal anomalies noted at or prior to delivery; 4. No hydrops fetalis, documented intrauterine infection or proven chromosomal anomaly; 5. Informed consent obtained prior to delivery. Demographics of participants not statically different with respect to sex, gestational age (25 - 32 weeks), and antenatal steroid administration (24% in both early and delayed treatment arms).
Interventions	Early Treatment: blinded air placebo versus surfactant (Exosurf 5 ml/kg x 2 doses at < 2 hours and 18 hours of life if no unblinded surfactant rescue treatment needed between 2 and 18 hours of life). Surfactant administered without positional manipulation and delivered via special endotracheal tube adaptation without interruption of mechanical ventilation. Surfactant rescue treatment given for > 0.22 arterial/Alveolar ratio.
Outcomes	PRIMARY OUTCOME: Survival to 28 days of life with intact CNS survival. SECONDARY OUTCOMES: Incidence of RDS requiring rescue treatment, requirements for ventilatory support, and complications of prematurity.
Notes	

Gortner 1998

Methods	Randomized Multicenter Trial Blinding of Randomization: Yes. Blinding of Intervention: can't tell Complete Follow-up: Yes. Blinding of Outcome Measurements: can't tell. Stratification: None.

Gortner 1998 (*Continued*)

Participants	Early selective treatment: 154 randomized Delayed selective treatment: 163 randomized Inclusion Criteria: 1. Prenatal informed consent obtained. 2. Gestational age between 27 - 32 weeks. 3. No congenital anomalies leading to cardio-respiratory compromise detected at or before deliver. 4. No rupture of membranes with oligo-or poly-hydramnios > 3 weeks prior to delivery.
Interventions	Early Treatment: Intratracheal bovine surfactant (100 mg/kg) during first hour of life if intubation and mechanical ventilation required (FiO2 > 0.5, PaCO2 >60, pH< 7.25 during spontaneous respiration). Delayed Treatment: Intratracheal bovine surfactant (100 mg/kg) at 2-6 hours of life if intubated and requiring FIO2 > 0.4 to adequately oxygenate. Repeat surfactant administrations given as needed with cumulative dose ceiling of 200 mg/kg with 50 mg/kg repeat doses given no more frequently than every 8 hours.
Outcomes	PRIMARY OUTCOME: Duration of mechanical ventilation SECONDARY OUTCOMES: Survival, survival without BPD, and complications of prematurity.
Notes	

Konishi 1992

Methods	Randomized single Center Trial Blinding of Randomization: can't tell Blinding of Intervention: can't tell Complete follow-up: Yes Blinding of Outcome Measurement: can't tell Stratification: None.
Participants	Early selective treatment: 16 randomized Delayed selective treatment: 16 randomized Inclusion Criteria: 1. AGA 500 -1500 gram infants. 2. Intubated for early respiratory distress. 3. Immature surfactant assay of gastric aspirates. 4. No PROM > 72 hours, maternal fever prenatally, 5 minute Apgar score of 4 or less, oligo- or poly-hydramnios, congenital malformations, WBC > 10 per HPF in gastric contents. 5. Informed consent obtained.
Interventions	Early Treatment: Surfactant TA (3ml/kg) per ETT in 5 aliquots over 5 minutes given within the first 30 minutes of life. Average age of administration = 18 minutes. Delayed Treatment: Surfactant TA (3ml/kg() as above given around 6 hours of life. Average age of administration = 6 hours.
Outcomes	PRIMARY OUTCOMES: 1. a/A PO2 Gradient and Mean Airway Pressure over first 72 hours of life. 2. Ventilatory Index (FIO2 x MAP/ PaO2) 3. 5 Clinical Outcomes at 7 and 28 days of life (No support, O2, IMV with O2 < 0.3, IMV with O2 > 0.3, Death) SECONDARY OUTCOMES: Complications of Prematurity

Konishi 1992 (*Continued*)

Notes	

OSIRIS 1992

Methods	Randomized Multicenter Trial. Blinding of randomization: Yes. Blinding of Intervention: No. Complete Follow-up: Yes. Blinding of Outcome measurement: can't tell. Stratification: None
Participants	Early selective treatment: 1344 randomized Delayed selective treatment: 1346 randomized Inclusion criteria: 1. Informed Consent. 2. Premature infants with high risk of RDS. 3. Less than 2 hours of life old at trial entry. 4. Intubation for ventilatory assistance. 5. No major congenital malformations.
Interventions	Early Treatment: Exosurf (5ml/kg) x2 doses administered intratracheally in unblinded fashion at less than 2 hours of life. Delayed Treatment: same Exosurf dosage and protocol give to participants greater than 2 hours of age with clinical signs of RDS. Administration unblinded.
Outcomes	PRIMARY OUTCOMES: 1. Death or BPD at 28 days. 2. Death 3. Death or CLD at "expected delivery date." SECONDARY OUTCOME: Complications of prematurity.
Notes	

DATA AND ANALYSES

Comparison 1. Early vs delayed selective surfactant treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pneumothorax	3	3427	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.59, 0.82]
1.1 Synthetic surfactant	2	3110	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.58, 0.81]
1.2 Natural surfactant	1	317	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.35, 3.21]
2 Patent ductus arteriosus	4	3459	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.92, 1.15]
2.1 Synthetic surfactant	2	3110	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.91, 1.14]
2.2 Natural surfactant	2	349	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.78, 1.76]
3 Pulmonary interstitial emphysema	2	737	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.43, 0.93]
3.1 Synthetic surfactant	1	420	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.40, 0.94]
3.2 Natural surfactant	1	317	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.26, 1.94]
4 Pulmonary hemorrhage	2	3007	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.73, 1.34]
4.1 Synthetic surfactant	1	2690	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.75, 1.37]
4.2 Natural surfactant	1	317	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.37]
5 Necrotizing enterocolitis	3	3427	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.77, 1.51]
5.1 Synthetic surfactant	2	3110	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.75, 1.51]
5.2 Natural surfactant	1	317	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.32, 6.20]
6 Retinopathy of prematurity stage 3 or greater	2	3007	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.58, 1.91]
6.1 Synthetic surfactant	1	2690	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.59, 2.09]
6.2 Natural surfactant	1	317	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.12, 4.17]
7 Intraventricular hemorrhage (any)	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.30, 3.32]
7.1 Synthetic surfactant	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.2 Natural surfactant	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.30, 3.32]
8 Intraventricular hemorrhage (severe)	2	3007	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.83, 1.14]
8.1 Synthetic surfactant	1	2690	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.81, 1.12]
8.2 Natural surfactant	1	317	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [0.66, 4.74]
9 Bronchopulmonary dysplasia	3	3039	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.88, 1.06]
9.1 Synthetic surfactant	1	2690	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.88, 1.08]
9.2 Natural surfactant	2	349	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.63, 1.27]
10 Chronic lung disease	2	3007	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.55, 0.88]
10.1 Synthetic surfactant	1	2690	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.55, 0.89]
10.2 Natural surfactant	1	317	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.25, 1.53]
11 Neonatal mortality	4	3459	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.77, 0.99]
11.1 Synthetic surfactant	2	3110	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.77, 0.99]
11.2 Natural surfactant	2	349	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.27, 4.01]
12 BPD or death at 28 days	3	3039	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.88, 1.00]
12.1 Synthetic surfactant	1	2690	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.88, 1.00]
12.2 Natural surfactant	2	349	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.68, 1.31]
13 CLD or death	2	3007	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.75, 0.93]
13.1 Synthetic surfactant	1	2690	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.75, 0.93]
13.2 Natural surfactant	1	317	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.41, 1.75]

14 Mortality at discharge	3	3039	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.79, 1.01]
14.1 Synthetic surfactant	1	2690	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.79, 1.01]
14.2 Natural surfactant	2	349	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.39, 3.98]
15 Number of doses per infant	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.1 Synthetic surfactant	1	2690	Mean Difference (IV, Fixed, 95% CI)	0.49 [0.41, 0.57]
15.2 Natural surfactant	1	317	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.29, 0.15]

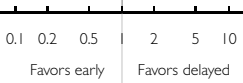
Analysis 1.1. Comparison 1 Early vs delayed selective surfactant treatment, Outcome 1 Pneumothorax.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early vs delayed selective surfactant treatment

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
1 Synthetic surfactant					
European Study 1992	38/212	55/208		18.9 %	0.68 [0.47, 0.98]
OSIRIS 1992	160/1344	232/1346		79.1 %	0.69 [0.57, 0.83]
Subtotal (95% CI)	**1556**	**1554**		**98.0 %**	**0.69 [0.58, 0.81]**
Total events: 198 (Treatment), 287 (Control)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 4.40 (P = 0.000011)					
2 Natural surfactant					
Gortner 1998	6/154	6/163		2.0 %	1.06 [0.35, 3.21]
Subtotal (95% CI)	**154**	**163**		**2.0 %**	**1.06 [0.35, 3.21]**
Total events: 6 (Treatment), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.10 (P = 0.92)					
Total (95% CI)	**1710**	**1717**		**100.0 %**	**0.70 [0.59, 0.82]**
Total events: 204 (Treatment), 293 (Control)					
Heterogeneity: Chi^2 = 0.57, df = 2 (P = 0.75); I^2 =0.0%					
Test for overall effect: Z = 4.32 (P = 0.000015)					



Analysis 1.2. Comparison 1 Early vs delayed selective surfactant treatment, Outcome 2 Patent ductus arteriosus.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early vs delayed selective surfactant treatment

Outcome: 2 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
1 Synthetic surfactant					
European Study 1992	72/212	76/208		16.8 %	0.93 [0.72, 1.20]
OSIRIS 1992	363/1344	351/1346		76.6 %	1.04 [0.91, 1.17]
Subtotal (95% CI)	**1556**	**1554**		**93.4 %**	**1.02 [0.91, 1.14]**
Total events: 435 (Treatment), 427 (Control)					
Heterogeneity: Chi^2 = 0.54, df = 1 (P = 0.46); I^2 =0.0%					
Test for overall effect: Z = 0.29 (P = 0.77)					
2 Natural surfactant					
Gortner 1998	24/154	21/163		4.5 %	1.21 [0.70, 2.08]
Konishi 1992	11/16	10/16		2.2 %	1.10 [0.67, 1.82]
Subtotal (95% CI)	**170**	**179**		**6.6 %**	**1.17 [0.78, 1.76]**
Total events: 35 (Treatment), 31 (Control)					
Heterogeneity: Chi^2 = 0.08, df = 1 (P = 0.78); I^2 =0.0%					
Test for overall effect: Z = 0.78 (P = 0.44)					
Total (95% CI)	**1726**	**1733**		**100.0 %**	**1.03 [0.92, 1.15]**
Total events: 470 (Treatment), 458 (Control)					
Heterogeneity: Chi^2 = 1.01, df = 3 (P = 0.80); I^2 =0.0%					
Test for overall effect: Z = 0.48 (P = 0.63)					

Analysis 1.3. Comparison 1 Early vs delayed selective surfactant treatment, Outcome 3 Pulmonary interstitial emphysema.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early vs delayed selective surfactant treatment

Outcome: 3 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
1 Synthetic surfactant					
European Study 1992	29/212	46/208		84.2 %	0.62 [0.40, 0.94]
Subtotal (95% CI)	**212**	**208**		**84.2 %**	**0.62 [0.40, 0.94]**
Total events: 29 (Treatment), 46 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.22 (P = 0.026)					
2 Natural surfactant					
Gortner 1998	6/154	9/163		15.8 %	0.71 [0.26, 1.94]
Subtotal (95% CI)	**154**	**163**		**15.8 %**	**0.71 [0.26, 1.94]**
Total events: 6 (Treatment), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					
Total (95% CI)	**366**	**371**		**100.0 %**	**0.63 [0.43, 0.93]**
Total events: 35 (Treatment), 55 (Control)					
Heterogeneity: Chi^2 = 0.06, df = 1 (P = 0.81); I^2 =0.0%					
Test for overall effect: Z = 2.30 (P = 0.022)					

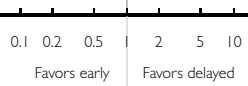
Analysis 1.4. Comparison 1 Early vs delayed selective surfactant treatment, Outcome 4 Pulmonary hemorrhage.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early vs delayed selective surfactant treatment

Outcome: 4 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
1 Synthetic surfactant					
OSIRIS 1992	80/1344	79/1346		97.0 %	1.01 [0.75, 1.37]
Subtotal (95% CI)	**1344**	**1346**		**97.0 %**	**1.01 [0.75, 1.37]**
Total events: 80 (Treatment), 79 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.09 (P = 0.93)					
2 Natural surfactant					
Gortner 1998	0/154	2/163		3.0 %	0.21 [0.01, 4.37]
Subtotal (95% CI)	**154**	**163**		**3.0 %**	**0.21 [0.01, 4.37]**
Total events: 0 (Treatment), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.01 (P = 0.31)					
Total (95% CI)	**1498**	**1509**		**100.0 %**	**0.99 [0.73, 1.34]**
Total events: 80 (Treatment), 81 (Control)					
Heterogeneity: Chi^2 = 1.02, df = 1 (P = 0.31); I^2 =2%					
Test for overall effect: Z = 0.06 (P = 0.95)					



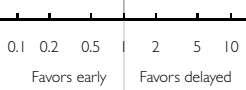
Analysis 1.5. Comparison 1 Early vs delayed selective surfactant treatment, Outcome 5 Necrotizing enterocolitis.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early vs delayed selective surfactant treatment

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
1 Synthetic surfactant					
European Study 1992	10/212	5/208		8.0 %	1.96 [0.68, 5.64]
OSIRIS 1992	54/1344	55/1346		87.3 %	0.98 [0.68, 1.42]
Subtotal (95% CI)	**1556**	**1554**		**95.4 %**	**1.07 [0.75, 1.51]**
Total events: 64 (Treatment), 60 (Control)					
Heterogeneity: Chi^2 = 1.47, df = 1 (P = 0.23); I^2 =32%					
Test for overall effect: Z = 0.36 (P = 0.72)					
2 Natural surfactant					
Gortner 1998	4/154	3/163		4.6 %	1.41 [0.32, 6.20]
Subtotal (95% CI)	**154**	**163**		**4.6 %**	**1.41 [0.32, 6.20]**
Total events: 4 (Treatment), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.46 (P = 0.65)					
Total (95% CI)	**1710**	**1717**		**100.0 %**	**1.08 [0.77, 1.51]**
Total events: 68 (Treatment), 63 (Control)					
Heterogeneity: Chi^2 = 1.60, df = 2 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 0.46 (P = 0.65)					



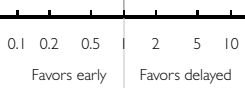
Analysis 1.6. Comparison 1 Early vs delayed selective surfactant treatment, Outcome 6 Retinopathy of prematurity stage 3 or greater.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early vs delayed selective surfactant treatment

Outcome: 6 Retinopathy of prematurity stage 3 or greater

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Synthetic surfactant					
OSIRIS 1992	20/1344	18/1346		86.1 %	1.11 [0.59, 2.09]
Subtotal (95% CI)	**1344**	**1346**		**86.1 %**	**1.11 [0.59, 2.09]**
Total events: 20 (Treatment), 18 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.33 (P = 0.74)					
2 Natural surfactant					
Gortner 1998	2/154	3/163		13.9 %	0.71 [0.12, 4.17]
Subtotal (95% CI)	**154**	**163**		**13.9 %**	**0.71 [0.12, 4.17]**
Total events: 2 (Treatment), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.38 (P = 0.70)					
Total (95% CI)	**1498**	**1509**		**100.0 %**	**1.06 [0.58, 1.91]**
Total events: 22 (Treatment), 21 (Control)					
Heterogeneity: Chi^2 = 0.22, df = 1 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 0.18 (P = 0.86)					



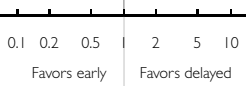
Analysis 1.7. Comparison 1 Early vs delayed selective surfactant treatment, Outcome 7 Intraventricular hemorrhage (any).

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early vs delayed selective surfactant treatment

Outcome: 7 Intraventricular hemorrhage (any)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Synthetic surfactant					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Natural surfactant					
Konishi 1992	4/16	4/16		100.0 %	1.00 [0.30, 3.32]
Subtotal (95% CI)	**16**	**16**		**100.0 %**	**1.00 [0.30, 3.32]**
Total events: 4 (Treatment), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Total (95% CI)	**16**	**16**		**100.0 %**	**1.00 [0.30, 3.32]**
Total events: 4 (Treatment), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					

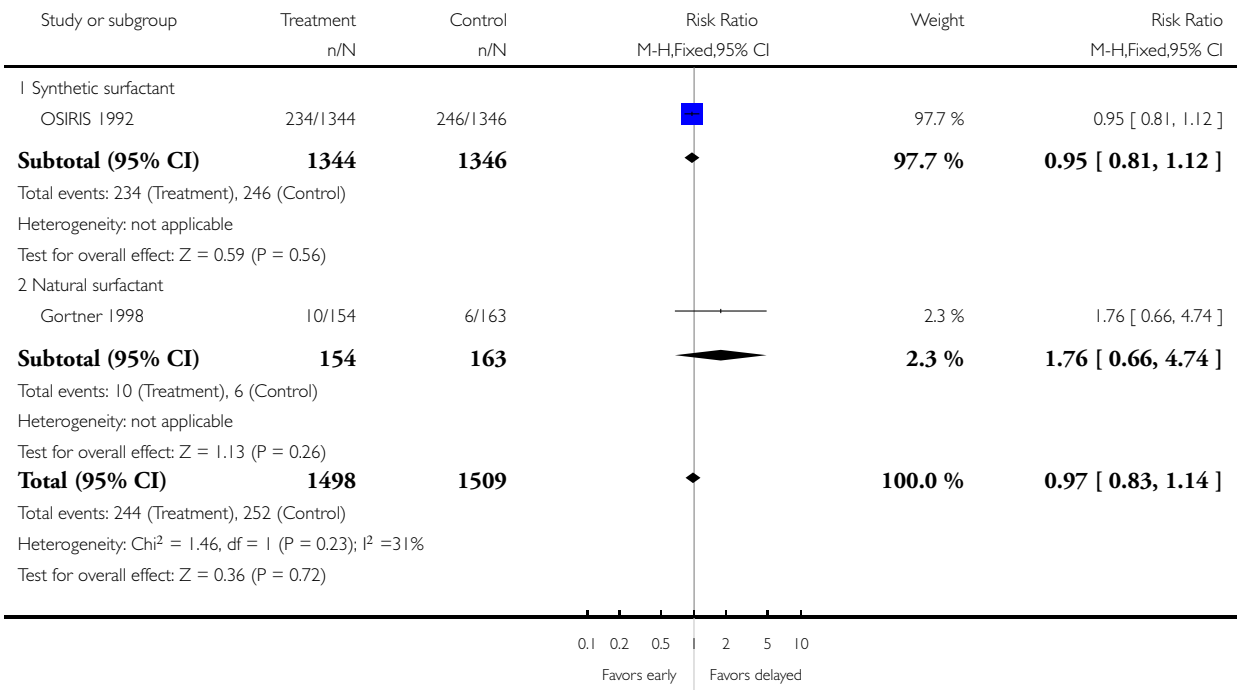


Analysis 1.8. Comparison 1 Early vs delayed selective surfactant treatment, Outcome 8 Intraventricular hemorrhage (severe).

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early vs delayed selective surfactant treatment

Outcome: 8 Intraventricular hemorrhage (severe)



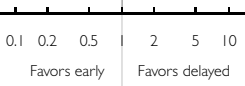
Analysis 1.9. Comparison 1 Early vs delayed selective surfactant treatment, Outcome 9 Bronchopulmonary dysplasia.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early vs delayed selective surfactant treatment

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
1 Synthetic surfactant					
OSIRIS 1992	483/1344	497/1346		91.2 %	0.97 [0.88, 1.08]
Subtotal (95% CI)	**1344**	**1346**		**91.2 %**	**0.97 [0.88, 1.08]**
Total events: 483 (Treatment), 497 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.53 (P = 0.59)					
2 Natural surfactant					
Gortner 1998	36/154	38/163		6.8 %	1.00 [0.67, 1.49]
Konishi 1992	6/16	11/16		2.0 %	0.55 [0.27, 1.11]
Subtotal (95% CI)	**170**	**179**		**8.8 %**	**0.90 [0.63, 1.27]**
Total events: 42 (Treatment), 49 (Control)					
Heterogeneity: Chi² = 2.17, df = 1 (P = 0.14); I² =54%					
Test for overall effect: Z = 0.61 (P = 0.54)					
Total (95% CI)	**1514**	**1525**		**100.0 %**	**0.97 [0.88, 1.06]**
Total events: 525 (Treatment), 546 (Control)					
Heterogeneity: Chi² = 2.52, df = 2 (P = 0.28); I² =21%					
Test for overall effect: Z = 0.69 (P = 0.49)					



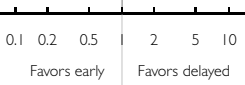
Analysis 1.10. Comparison 1 Early vs delayed selective surfactant treatment, Outcome 10 Chronic lung disease.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early vs delayed selective surfactant treatment

Outcome: 10 Chronic lung disease

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Synthetic surfactant					
OSIRIS 1992	106/1344	151/1346		92.8 %	0.70 [0.55, 0.89]
Subtotal (95% CI)	**1344**	**1346**		**92.8 %**	**0.70 [0.55, 0.89]**
Total events: 106 (Treatment), 151 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.92 (P = 0.0035)					
2 Natural surfactant					
Gortner 1998	7/154	12/163		7.2 %	0.62 [0.25, 1.53]
Subtotal (95% CI)	**154**	**163**		**7.2 %**	**0.62 [0.25, 1.53]**
Total events: 7 (Treatment), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					
Total (95% CI)	**1498**	**1509**		**100.0 %**	**0.70 [0.55, 0.88]**
Total events: 113 (Treatment), 163 (Control)					
Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 3.09 (P = 0.0020)					



Analysis 1.11. Comparison 1 Early vs delayed selective surfactant treatment, Outcome 11 Neonatal mortality.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early vs delayed selective surfactant treatment

Outcome: 11 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
1 Synthetic surfactant					
European Study 1992	37/212	45/208		11.8 %	0.81 [0.55, 1.19]
OSIRIS 1992	296/1344	337/1346		87.2 %	0.88 [0.77, 1.01]
Subtotal (95% CI)	**1556**	**1554**		**99.0 %**	**0.87 [0.77, 0.99]**
Total events: 333 (Treatment), 382 (Control)					
Heterogeneity: Chi^2 = 0.17, df = 1 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 2.10 (P = 0.036)					
2 Natural surfactant					
Gortner 1998	3/154	2/163		0.5 %	1.59 [0.27, 9.37]
Konishi 1992	1/16	2/16		0.5 %	0.50 [0.05, 4.98]
Subtotal (95% CI)	**170**	**179**		**1.0 %**	**1.04 [0.27, 4.01]**
Total events: 4 (Treatment), 4 (Control)					
Heterogeneity: Chi^2 = 0.61, df = 1 (P = 0.44); I^2 =0.0%					
Test for overall effect: Z = 0.05 (P = 0.96)					
Total (95% CI)	**1726**	**1733**		**100.0 %**	**0.87 [0.77, 0.99]**
Total events: 337 (Treatment), 386 (Control)					
Heterogeneity: Chi^2 = 0.83, df = 3 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 2.08 (P = 0.038)					

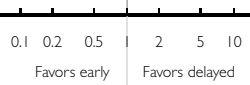
Analysis 1.12. Comparison 1 Early vs delayed selective surfactant treatment, Outcome 12 BPD or death at 28 days.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early vs delayed selective surfactant treatment

Outcome: 12 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
1 Synthetic surfactant					
OSIRIS 1992	779/1344	834/1346		94.2 %	0.94 [0.88, 1.00]
Subtotal (95% CI)	**1344**	**1346**		**94.2 %**	**0.94 [0.88, 1.00]**
Total events: 779 (Treatment), 834 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.11 (P = 0.034)					
2 Natural surfactant					
Gortner 1998	40/154	39/163		4.3 %	1.09 [0.74, 1.59]
Konishi 1992	7/16	13/16		1.5 %	0.54 [0.29, 0.98]
Subtotal (95% CI)	**170**	**179**		**5.8 %**	**0.95 [0.68, 1.31]**
Total events: 47 (Treatment), 52 (Control)					
Heterogeneity: Chi^2 = 3.85, df = 1 (P = 0.05); I^2 =74%					
Test for overall effect: Z = 0.33 (P = 0.74)					
Total (95% CI)	**1514**	**1525**		**100.0 %**	**0.94 [0.88, 1.00]**
Total events: 826 (Treatment), 886 (Control)					
Heterogeneity: Chi^2 = 3.80, df = 2 (P = 0.15); I^2 =47%					
Test for overall effect: Z = 2.12 (P = 0.034)					



Analysis 1.13. Comparison 1 Early vs delayed selective surfactant treatment, Outcome 13 CLD or death.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early vs delayed selective surfactant treatment

Outcome: 13 CLD or death

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Synthetic surfactant					
OSIRIS 1992	429/1344	514/1346		97.2 %	0.84 [0.75, 0.93]
Subtotal (95% CI)	**1344**	**1346**		**97.2 %**	**0.84 [0.75, 0.93]**
Total events: 429 (Treatment), 514 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.39 (P = 0.00069)					
2 Natural surfactant					
Gortner 1998	12/154	15/163		2.8 %	0.85 [0.41, 1.75]
Subtotal (95% CI)	**154**	**163**		**2.8 %**	**0.85 [0.41, 1.75]**
Total events: 12 (Treatment), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.45 (P = 0.65)					
Total (95% CI)	**1498**	**1509**		**100.0 %**	**0.84 [0.75, 0.93]**
Total events: 441 (Treatment), 529 (Control)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 3.42 (P = 0.00063)					

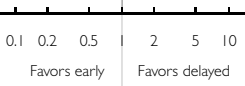
Analysis 1.14. Comparison 1 Early vs delayed selective surfactant treatment, Outcome 14 Mortality at discharge.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early vs delayed selective surfactant treatment

Outcome: 14 Mortality at 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
1 Synthetic surfactant					
OSIRIS 1992	354/1344	398/1346		98.8 %	0.89 [0.79, 1.01]
Subtotal (95% CI)	**1344**	**1346**		**98.8 %**	**0.89 [0.79, 1.01]**
Total events: 354 (Treatment), 398 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.86 (P = 0.062)					
2 Natural surfactant					
Gortner 1998	5/154	3/163		0.7 %	1.76 [0.43, 7.26]
Konishi 1992	1/16	2/16		0.5 %	0.50 [0.05, 4.98]
Subtotal (95% CI)	**170**	**179**		**1.2 %**	**1.25 [0.39, 3.98]**
Total events: 6 (Treatment), 5 (Control)					
Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² =0.0%					
Test for overall effect: Z = 0.38 (P = 0.71)					
Total (95% CI)	**1514**	**1525**		**100.0 %**	**0.90 [0.79, 1.01]**
Total events: 360 (Treatment), 403 (Control)					
Heterogeneity: Chi² = 1.14, df = 2 (P = 0.57); I² =0.0%					
Test for overall effect: Z = 1.79 (P = 0.073)					

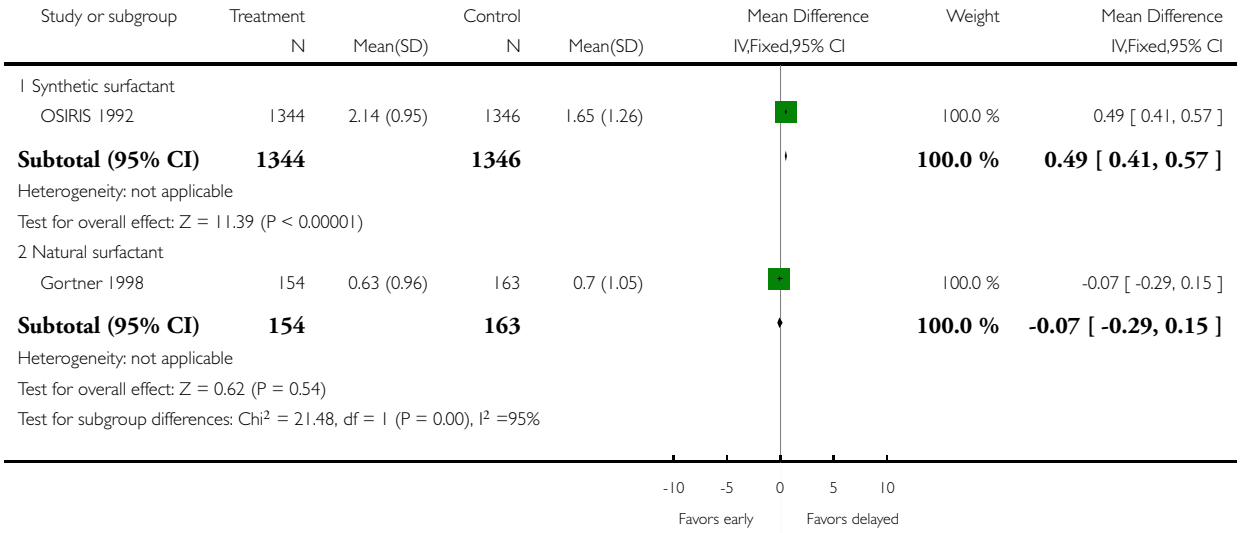


Analysis 1.15. Comparison 1 Early vs delayed selective surfactant treatment, Outcome 15 Number of doses per infant.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early vs delayed selective surfactant treatment

Outcome: 15 Number of doses per infant



WHAT'S NEW

Last assessed as up-to-date: 12 July 1999.

2 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 1999

Review first published: Issue 4, 1999

13 July 1999	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

Dr. R. Soll has acted as a paid 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

- No sources of support supplied

External sources

- [Information not provided], Not specified.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans