Neonatology

Cochrane Review Update

Neonatology 2013;104:124–126
DOI: 10.1159/000353673

Published online: July 24, 2013

Early versus Delayed Selective Surfactant Treatment for Neonatal Respiratory Distress Syndrome

Cochrane Abstract

Background: Clinical trials have confirmed that surfactant therapy is effective in improving the immediate need for respiratory support and the clinical outcome of premature newborns. Trials have studied a wide variety of surfactant preparations used either to prevent (prophylactic or delivery room administration) or treat (selective or rescue administration) respiratory distress syndrome (RDS). Using either treatment strategy, significant reductions in the incidence of pneumothorax, as well as significant improvement in survival, have been noted. It is unclear whether there are any advantages to treating infants with respiratory insufficiency earlier in the course of RDS. ***Objectives:*** To compare the effects of early versus delayed selective surfactant therapy for newborns intubated for respiratory distress within the first 2 h of life. Planned subgroup analyses included separate comparisons for studies utilizing natural surfactant extract and synthetic surfactant. ***Search Methods:*** We searched 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 handsearching in the English language. For the updated search in April 2012, we searched the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, 2012, Issue 1) and PubMed (January 1997 to April 2012). ***Selection Criteria:*** Randomized and quasi-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 h of life versus delayed selective surfactant administration to infants with established RDS were considered for review. ***Data Collection and Analysis:*** Data regarding clinical outcomes were excerpted from the reports of the clinical trials by the review authors. Subgroup analyses were performed based on type of surfactant preparation, gestational age, and exposure to prenatal steroids. Data analysis was performed in accordance with the standards of the Cochrane Neonatal Review Group. ***Main Results:*** Six randomized controlled trials met selection criteria. Two of the trials utilized synthetic surfactant (Exosurf Neonatal) and four utilized animal-derived surfactant preparations. The meta-analyses demonstrate significant reductions in the risk of neonatal mortality (typical risk ratio (RR) 0.84; 95% confidence interval (CI) 0.74–0.95; typical risk difference (RD) –0.04; 95% CI –0.06 to –0.01; 6 studies; 3,577 infants), chronic lung disease (typical RR 0.69; 95% CI 0.55–0.86; typical RD –0.04; 95% CI –0.06 to –0.01; 3 studies; 3,041 infants), and chronic lung disease or death at 36 weeks (typical RR 0.83; 95% CI 0.75–0.91; typical RD –0.06; 95% CI –0.09 to –0.03; 3 studies; 3,050 infants) associated with early treatment of intubated infants with RDS. Intubated infants randomized to early selective surfactant administration also demonstrated a decreased risk of acute lung injury including a decreased risk of pneumothorax (typical RR 0.69; 95% CI 0.59–0.82; typical RD –0.05; 95% CI –0.08 to –0.03; 5 studies; 3,545 infants), pulmonary interstitial emphysema (typical RR 0.60; 95% CI 0.41–0.89; typical RD –0.06; 95% CI –0.10 to –0.02; 3 studies; 780 infants), and overall air leak syndromes (typical RR 0.61; 95% CI 0.48–0.78; typical RD –0.18; 95% CI –0.26 to –0.09; 2 studies; 463 infants). A trend

1661–7800/13/1042–0124$38.00/0

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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 to –0.00; 3 studies; 3,039 infants). No differences in other complications of RDS or prematurity were noted. Only two studies reported on infants under 30 weeks' gestation. Decreased risk of neonatal mortality and chronic lung disease or death at 36 weeks' postmenstrual age was noted.

Reviewers' 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 worsening RDS.

Bahadue FL, Soll R: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database Syst Rev. 2012 Nov 14;11:CD001456. DOI: 10.1002/14651858.CD001456.pub2.

Commentary

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Surfactant is effective in reducing the immediate need for respiratory support and improving clinical outcome of preterm newborns. Although surfactant is proven to be effective, the timing of surfactant remains unclear. Recent large randomized, controlled trials as well as meta-analyses have demonstrated that the need for aggressive resuscitation, intubation and surfactant treatment in infants at risk of RDS is probably no longer indicated in this day of increased utilization of antenatal steroids and improved stabilization on less invasive methods of respiratory support [1, 2]. However, these studies do not address the issue of the timing of surfactant administration in intubated infants.

Bahadue [3] has updated the Cochrane Review of 'Early versus delayed surfactant treatment for neonatal respiratory distress syndrome'. There is not a great deal of new information to comment on but it is worthwhile to remind readers of previous findings. Six randomized, controlled trials met the selection criteria but two of them utilized synthetic surfactant preparations which are no longer part of routine care. That said, there is a significant reduction in the risk of neonatal mortality (fig. 1), chronic lung disease, and chronic lung disease or death (fig. 2) associated with earlier treatment of intubated infants. In addition, there is a significantly decreased risk of pneumothorax, pulmonary interstitial emphysema and overall air leak syndromes. Although only two studies reported on infants less than 30 weeks' gestation, a decreased risk of neonatal mortality and chronic lung disease was noted in this population.

Although we do not need to be in such a rush to intubate infants for the purposes of surfactant therapy, once intubated, those infants should be given surfactant in a timely way. This is reflected in current practices in neonatal intensive care units. In the Vermont Oxford Network, the use of intubation in the delivery room has decreased over the past decade but the percentage of those infants who are intubated who received surfactant in the delivery room has increased [4]. This represents appropriate uptake of the currently available information. We await further studies about less invasive methods of delivering surfactant to spontaneously breathing infants [5–7] but, until that point in time, it seems wise that, in intubated infants with or at high risk for respiratory distress syndrome, we administer surfactant in a timely fashion.

Acknowledgment

Editorial support of the Cochrane Neonatal Review Group has been funded with Federal Funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health, USA, under Contract No. HHSN275201100016C.

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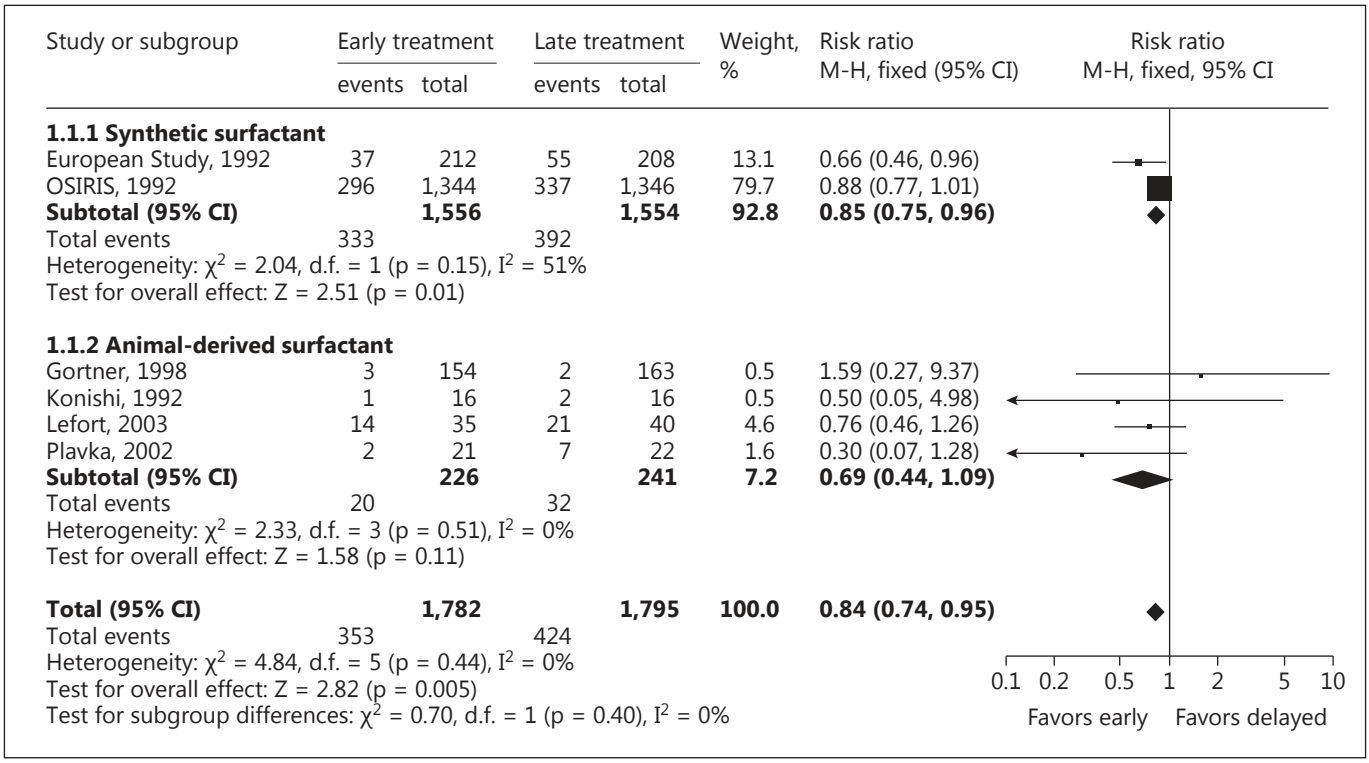

Fig. 1. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Effect on neonatal mortality.

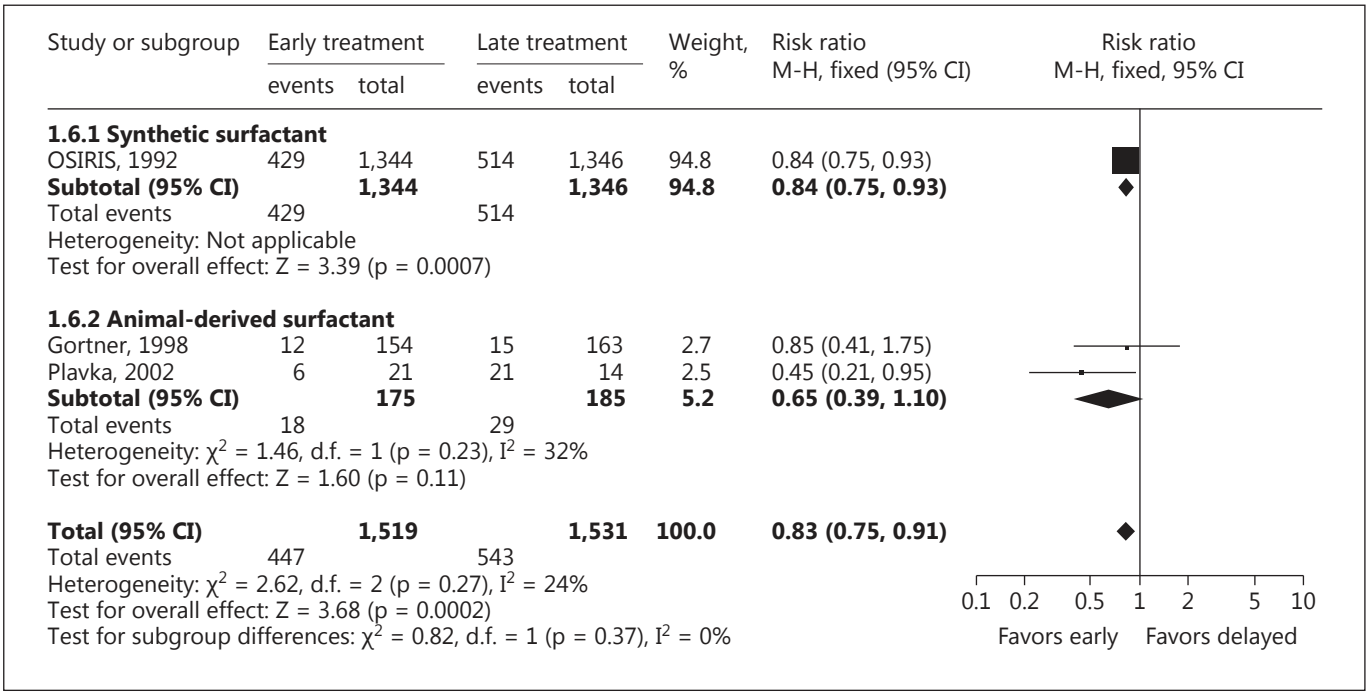

Fig. 2. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Effect on chronic lung disease or death.