



**Evidence based
approach
to treat RDS**

Survanta Studies

Clinical Efficacy of Survanta in RDS

Annotated Bibliography

SURVANTA[®]

The Natural Surfactant

Med J Malaysia 1998 Dec;53(4):376-84

The effectiveness of surfactant replacement therapy for preterm infants with respiratory distress syndrome.

Lim WL, Lim CT, Chye JK.

Department of Paediatrics, University of Malaya, Kuala Lumpur.

Thirty preterm infants weighing ≥ 800 g with clinical and radiological evidence of respiratory distress syndrome (RDS) requiring mechanical ventilation with FiO_2 of $\geq 40\%$ were given modified bovine surfactant (SURVANTA). They were compared with equal number of historical controls. Infants who received surfactant showed prompt and highly significant improvement in FiO_2 , mean airway pressure, arterial/alveolar oxygen tension ratio and ventilatory index. There was significant improvement in mortality rate (10% vs 33%; $p = 0.03$). Among the survivors, surfactant-treated infants required shorter duration of continuous positive airway pressure (CPAP) (3.4 vs 9.6 days; $p = 0.04$). For survivors with birthweight of > 1000 g, surfactant-treated infants required shorter duration of ventilatory support (intermittent positive pressure ventilation + CPAP) (7.5 vs 18.9 days, $p = 0.02$). Overall, surfactant-treated infants achieved full enteral feeds sooner (15.7 days vs 24.6 days; $p = 0.03$) and required shorter duration of total parenteral nutrition (13.9 days vs 25.6 days; $p = 0.02$). We concluded that surfactant replacement therapy was effective in the treatment of preterm infants with RDS.

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Use of surfactant, particularly in the early phase of respiratory failure, significantly decreases the need for ECMO in the treatment of term newborns with respiratory failure, without increasing the risk of complications.

J Pediatr. 1999 Aug;135(2 Pt 1):267-8.

Multicenter study of surfactant (beractant) use in the treatment of term infants with severe respiratory failure. Survanta in Term Infants Study Group.

Lotze A, Mitchell BR, Bulas DI, Zola EM, Shalwitz RA, Gunkel JH.

Department of Pediatrics, Children's National Medical Center, Washington, D.C., USA.

OBJECTIVE:

The purpose of this study was to determine whether surfactant (SURVANTA) administration to term newborns in respiratory failure and at risk for requiring extracorporeal membrane oxygenation (ECMO) treatment would significantly reduce the incidence of severe complications through 28 days of age and the need for ECMO.

STUDY DESIGN:

A multicenter (n = 44), randomized, double-blind, placebo-controlled trial was conducted. Infants weighing 2000 gm or more with gestational ages of 36 weeks or greater were stratified by diagnosis (meconium aspiration syndrome, sepsis, or idiopathic persistent pulmonary hypertension of the newborn) and oxygenation index (15 to 22, 23 to 30, 31 to 39) and then randomly assigned to receive four doses of beractant, 100 mg/kg (n = 167), or air placebo (n = 161) before ECMO treatment and four additional doses during ECMO, if ECMO was required. The incidence of untoward effects (including hemorrhagic, neurologic, pulmonary, renal, cardiovascular, infectious, metabolic, and technical complications) occurring before and after randomization and through 28 days of age or discharge were recorded.

RESULTS:

The two treatment groups were comparable in baseline parameters, including birth weight, sex, gestational age, oxygenation index, and primary diagnosis. There was no difference in the incidence of severe complications. The need for ECMO therapy was significantly less in the surfactant group than in the placebo group (p = 0.038); this effect was greatest within the lowest oxygenation index stratum (15 to 22; p = 0.013).

CONCLUSIONS:

Use of surfactant, particularly in the early phase of respiratory failure, significantly decreases the need for ECMO in the treatment of term newborns with respiratory failure, without increasing the risk of complications.

Surfactant treatment in the neonate with severe respiratory distress syndrome.

Horpaopan S, Sangtaveesin V, Ratisawasdi V.

Neonatal Unit, Children's Hospital, Bangkok, Thailand.

Eighteen preterm infants severely ill with respiratory distress syndrome who required assisted ventilation were given modified natural surfactant (**SURVANTA**) endotracheally. They had a mean \pm SEM gestational age of 31.2 \pm 0.4 weeks (range 28-34) and a mean \pm SEM birthweight of 1562 \pm 71 g (range 1160-2010). Average time of initial surfactant administration was 15 \pm 1.7 hour (range 5-24). No significant side effects were found during surfactant instillation. Post surfactant, the air entry was improved, oxygenation and arterial/alveolar gradients increased, and the levels of inspired oxygen could be reduced. Some of the radiological abnormalities were resolved. In 13 infants, patent ductus arteriosus became clinically evident, seven of whom received Indomethacin. There were 4 cases of pulmonary air leak, 5 cases of pulmonary hemorrhage and 8 cases of bronchopulmonary dysplasia. Four infants expired, two were due to severe asphyxia/shock and two died of unrelated causes. Among the 14 survivors who came for follow-up, two cases of retinopathy of prematurity had gradually regressed, one had cerebral palsy and delayed development. Surfactant rescue therapy is a supplemental beneficial treatment for severe respiratory distress syndrome while newborn intensive care concept is necessary for efficient diagnosis and treatment of RDS.

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Outcome of infants with birth weights less than 1000 g with respiratory distress syndrome treated with high-frequency ventilation and surfactant replacement therapy.

Patel CA, Klein JM.

Department of Pediatrics, University of Iowa, Iowa City.

OBJECTIVE:

To compare outcomes in premature infants with respiratory distress syndrome who received surfactant replacement therapy and were treated with either high-frequency or conventional mechanical ventilation.

DESIGN:

Retrospective chart review of patient series.

SETTING:

Tertiary academic medical center.

PATIENTS:

One hundred fourteen extremely low-birth-weight infants (< 1000 g) with respiratory distress syndrome treated with surfactant replacement therapy (SURVANTA), consecutively admitted to the neonatal intensive care unit between September 1989 and August 1992.

INTERVENTIONS:

Treatment with either high-frequency ventilation (n = 46) or conventional mechanical ventilation (n = 68) after surfactant replacement therapy.

MAIN OUTCOME MEASURES:

Intraventricular hemorrhage and neurodevelopmental status.

RESULTS:

Infants who received high-frequency ventilation had significantly lower birth weights and were more premature than infants receiving conventional mechanical ventilation. Despite this, patients ventilated with high frequency had similar incidences of intraventricular hemorrhage and impaired neurodevelopmental outcomes when compared with the conventionally ventilated patients. As expected, the smaller and more premature infants receiving high-frequency ventilation required a longer duration of respiratory support (mechanical ventilation and nasopharyngeal continuous positive airway pressure). Additionally, multiple logistic regression analysis to control for differences in birth weight and gestational age between the two groups revealed a significant association between the combined use of high-frequency ventilation and antenatal corticosteroids and the absence of either intraventricular hemorrhage or pneumothorax.

CONCLUSION:

We conclude that high-frequency ventilation combined with surfactant therapy is as safe as conventional mechanical ventilation combined with surfactant therapy for treating respiratory distress syndrome in extremely low-birth-weight infants (< 1000 g) and does not increase the risk of either intraventricular hemorrhage or abnormal neurodevelopmental outcome.

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Effects of surfactant therapy on outcome of extremely premature infants.

Hoekstra RE, Ferrara TB, Payne NR.

Minneapolis Children's Medical Center, MN 55404.

Limits of viability of extremely premature infants have recently been addressed both in Europe and the United States. These reports, which demonstrate frequent adverse outcome of infants born before 26 weeks of gestation, have not considered the impact of surfactant therapy. We reviewed records of 445 infants born between 23 and 36 weeks gestation who were admitted to our nursery following the availability of surfactant treatment in 1986 through 1992. Two hundred and eighty-five infants were treated with surfactant (SURVANTA, Ross Laboratories) as part of controlled, prospective trials or as routine treatment under Food and Drug Administration approval. One hundred and fifty-six infants were unable to be treated with surfactant, as either they received placebo therapy during prospective trials or were born prior to approval of routine surfactant use in the United States. Four additional infants born following the commercial availability of surfactant did not receive surfactant therapy. Survival of untreated infants was 56% compared to 75% in treated infants ($P < 0.001$). Infants born at all gestational ages between 23 and 26 weeks had an increased likelihood of survival as a result of surfactant treatment. No differences in neurologic outcome between surfactant treated and non-treated infants were demonstrated at subsequent follow-up. We conclude that survival of extremely premature infants is improved following surfactant therapy and that subsequent neurologic outcome is not compromised as a result of this therapy.

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We conclude that multiple doses of Survanta given after diagnosis of respiratory distress syndrome reduce mortality and morbidity.

Pediatrics 1991 Jul;88(1):19-28

Reduction of neonatal mortality after multiple doses of bovine surfactant in low birth weight neonates with respiratory distress syndrome.

Liechty EA, Donovan E, Purohit D, Gilhooly J, Feldman B, Noguchi A, Denson SE, Sehgal SS, Gross I, Stevens D, et al.

Department of Pediatrics, Indiana University School of Medicine, Indianapolis.

To determine if outcomes of low birth weight neonates with respiratory distress syndrome can be improved by the administration of multiple doses of bovine surfactant, we conducted two identical multicenter, controlled trials, and the results were combined for analysis. Seven hundred and ninety-eight neonates weighing 600 to 1750 g at birth who had developed respiratory distress syndrome within 6 hours of birth were assigned randomly to receive either 100 mg of phospholipid/kg of SURVANTA, a modified bovine surfactant (n = 402), or a sham dosing procedure (n = 396). Neonates whose respiratory distress persisted could be given up to three more doses, with all doses to be given in the first 48 hours after birth. Dosing was performed by investigators not involved in the clinical care of the neonates; nursery staff were kept blinded as to the treatment assignment. Fewer Survanta-treated neonates died of any cause (18.4% vs 27.3%, $P = .002$), died of respiratory distress syndrome (9.0% vs 20.3%, P less than .001), and either died or developed bronchopulmonary dysplasia due to respiratory distress syndrome (51.2% vs 64.6%, P less than .001). Neonates who received Survanta also had greater improvement in their oxygenation and ventilatory status from baseline to 72 hours than did control neonates. Survanta-treated neonates were at lowered risk for developing pulmonary interstitial emphysema (18.6% vs 39.3%, P less than .001) and other pulmonary air leaks (11.5% vs 25.9%, P less than .001). We conclude that multiple doses of Survanta given after diagnosis of respiratory distress syndrome reduce mortality and morbidity.

Pediatrics 1991 Jul;88(1):10-8

Improved neonatal survival following multiple doses of bovine surfactant in very premature neonates at risk for respiratory distress syndrome.

Hoekstra RE, Jackson JC, Myers TF, Frantz ID 3rd, Stern ME, Powers WF, Maurer M, Raye JR, Carrier ST, Gunkel JH, et al.

Minneapolis Childrens Medical Center, Seattle, Washington.

To determine whether multiple doses of bovine surfactant would improve neonatal mortality in very premature neonates, we conducted two multicenter controlled trials under identical protocols; the results were combined for analysis. Four hundred and thirty neonates born between 23 and 29 weeks gestation and weighing 600 to 1250 g at birth were assigned randomly at birth to receive either 100 mg of phospholipids/kg of SURVANTA, a modified bovine surfactant (n = 210), or a sham air placebo (n = 220) within 15 minutes of birth. Neonates who developed respiratory distress syndrome and required mechanical ventilation with at least 30% oxygen could be given up to three more doses in the first 48 hours after birth. Dosing was performed by investigators not involved in the clinical care of the neonates; nursery staff were kept blinded as to the treatment assignment. Cause of death was determined by a panel of three independent, board-certified neonatologists after blindly reviewing case report forms and autopsy reports. Fewer Survanta-treated neonates died of any cause (11.4% vs 18.8%, P = .031), died of respiratory distress syndrome (1.9% vs 15.6%, P less than .001), and either died or developed bronchopulmonary dysplasia due to respiratory distress syndrome (39.5% vs 49.1%, P = .044). The incidence of respiratory distress syndrome was also lower in Survanta-treated neonates (28.0% vs 56.9%, P less than .001), and the Survanta-treated neonates' oxygenation and ventilatory status were improved significantly at 72 hours. Survanta-treated neonates were also at lowered risk of developing pulmonary interstitial emphysema (23.3% vs 36.9%, P = .002) and other forms of pulmonary air leaks (9.6% vs 20.8%, P .002)

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Multicenter trial of single-dose modified bovine surfactant extract (Survanta) for prevention of respiratory distress syndrome. Ross Collaborative Surfactant Prevention Study Group.

Soll RF, Hoekstra RE, Fangman JJ, Corbet AJ, Adams JM, James LS, Schulze K, Oh W, Roberts JD Jr, Dorst JP, et al.

Dept of Pediatrics, University of Vermont College of Medicine, Burlington 05405.

A multicenter, prospective randomized controlled trial was performed comparing the efficacy of a single intratracheal dose of modified bovine surfactant extract (SURVANTA, 100 mg/kg, Abbott Laboratory, North Chicago, IL) with air placebo in preventing respiratory distress syndrome. Infants were enrolled if they were estimated to be between 24 and 30 weeks' gestation, weighed between 750 and 1250 g, and were intubated and stabilized within 15 minutes after birth. A total of 160 infants were treated (79 with surfactant, 81 with air placebo) between 4 and 37 minutes after birth (median time 12 minutes). Of these, 5 infants were excluded from the final analysis. The 72-hour average values for the arterial-alveolar oxygen ratio, fraction of inspired oxygen, and mean airway pressure were calculated from the area under the curve of scheduled values measured throughout 72 hours. Clinical status was classified using five ordered categories (no supplemental oxygen or assisted ventilation, supplemental oxygen only, continuous positive airway pressure or assisted ventilation with intermittent mandatory ventilation less than or equal to 6 breaths/min, assisted ventilation with intermittent mandatory ventilation greater than 6 breaths/min, death). Chest radiographs at 24 hours were graded for severity of respiratory distress syndrome. Infants receiving Survanta had less severe radiographic changes at 24 hours of age and decreased average fraction of inspired oxygen (31% vs 42%, $P = .002$) compared with control infants. No differences were noted in the average arterial-alveolar oxygen ratio, mean airway pressure, or clinical status on days 7 and 28. A beneficial effect was noted in the incidence of pneumothorax ($P = .057$) and an increase was noted in the incidence of necrotizing enterocolitis ($P = .052$). No differences in incidence of patent ductus arteriosus, intraventricular hemorrhage, sepsis, or bronchopulmonary dysplasia were seen. According to results of a secondary analysis, there was improvement in the fraction of inspired oxygen and a greater number of survivors without bronchopulmonary dysplasia in the subgroup of infants weighing less than 1000 g who were treated with surfactant. It was concluded that a single dose of Survanta given shortly after birth resulted in decreased severity of chest radiographic findings 24 hours after treatment and improved oxygenation during 72 hours after treatment, but did not improve other acute measures of disease severity or clinical status later in the neonatal period. The group at highest risk for respiratory distress syndrome (infants with birth weights between 750 and 999 g) may benefit the most from preventive therapy.

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Single dose of Survanta given shortly after birth resulted in decreased severity of chest radiographic findings 24 hours after treatment and improved oxygenation during 72 hours after treatment

A European multicenter randomized controlled trial of single dose surfactant therapy for idiopathic respiratory distress syndrome.

Horbar JD, Soll RF, Schachinger H, Kewitz G, Versmold HT, Lindner W, Duc G, Mieth D, Linderkamp O, Zilow EP, et al.

Department of Pediatrics, University of Vermont College of Medicine, Burlington 05405.

We performed a multicenter prospective randomized controlled trial to determine the efficacy and safety of the surfactant preparation, SURVANTA (Abbott Laboratories, Chicago, USA), for 750-1750 g infants with idiopathic respiratory distress syndrome, (IRDS) receiving assisted ventilation with 40% or more oxygen. One hundred and six eligible infants from the eight participating centers were randomly assigned between March 1986 and June 1987 to receive either surfactant (100 mg phospholipid/kg, 4 ml/kg) or air (4 ml/kg) administered into the trachea within 8 h of birth (median time of treatment 6.2 h, range 3.2-9.1 h). Surfactant treated infants had larger average increases in the arterial-alveolar oxygen ratio, (a/A ratio) (P less than 0.0001), and larger average decreases in FiO₂ (P less than 0.0001) and mean airway pressure, (MAP) (P less than 0.017) than controls over the 48 h following treatment. The magnitude of the differences between the surfactant and control groups were 0.19 (SE = 0.03) for a/A ratio, -0.28 (SE = 0.04) for FiO₂ and -1.7 cm H₂O (SE = 0.70) for MAP. The clinical status on days 7 and 28 after treatment was classified using four predefined ordered categories: (1) no respiratory support; (2) supplemental O₂ with or without continuous positive airway pressure (CPAP); (3) intermittent mandatory ventilation; and (4) death. There were no statistically significant differences in the status categories on days 7 or 28 between surfactant and control infants.

Surfactant treated infants had larger average increases in the arterial-alveolar oxygen ratio, (a/A ratio) (P less than 0.0001), and larger average decreases in FiO₂ (P less than 0.0001) and mean airway pressure, (MAP) (P less than 0.017) than controls over the 48 h following treatment.

These results suggest that the increased survival rate associated with beractant treatment is followed through 2 years of adjusted age by outcomes equivalent to those of untreated control infants.

J Pediatr 1994 Jun;124(6):962-7

Two-year follow-up of infants treated for neonatal respiratory distress syndrome with bovine surfactant. Survanta Multidose Study Group.

In 1988 and 1989, a total of 1228 infants were studied in four double-blind, controlled, multidose clinical trials establishing the safety and efficacy of beractant (SURVANTA intratracheal suspension, Ross Products Division of Abbott Laboratories), a modified bovine lung extract, in prevention and treatment of neonatal respiratory distress syndrome in premature infants. Data on clinical status were collected for surviving infants at hospital discharge and at 6, 12, and 24 months of adjusted age. Significantly fewer beractant-treated infants required supplemental oxygen at discharge ($p = 0.036$). At 6 months of adjusted age, beractant-treated infants had more wheezing ($p = 0.023$) than control infants, a reduced need for supplemental oxygen ($p = 0.019$), and a lower incidence of cerebral palsy ($p = 0.020$). At 12 months of adjusted age, beractant-treated infants had less wheezing than control infants ($p = 0.005$), and this finding persisted at 24 months of adjusted age ($p = 0.008$). No circulating antibodies to the proteins present in beractant were found in serum samples at 6 and 12 months of age. These results suggest that the increased survival rate associated with beractant treatment is followed through 2 years of adjusted age by outcomes equivalent to those of untreated control infants.

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