

# Exogenous Surfactant in the Neonate

## Suggestions for its use in developing countries

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In spite of improvement in perinatal assistance, the frequency of Respiratory Distress Syndrome in preterm babies (NRDS) remains very high.

The estimated incidence of NRDS in babies with a birth weight of 500- 750 g (very low birth weight -VLBW-) reaches a value of over 80% and in babies with a birth weight between 1000 and 1500 g the frequency is over the 30% (1). Survival significantly improved with the introduction of new techniques of prevention and of treatment of the disease, in particular, after the introduction of the exogenous surfactant.

In the United States of America (USA), the neonatal mortality related to NRDS declined by 28% between 1988 and 1991; this data was temporally associated with widespread use of surfactant therapy and was the single most important factor for the reduction in overall neonatal mortality in the US. (1)

Now, the exogenous surfactant is in widespread use in many countries, however, there is great variability in its use, within and among countries, related not only to different medical strategies and organisations, but also to the costs. The surfactant preparations currently on the market are relatively expensive and their supply is relatively limited. Therefore an accurate planning of the indications is necessary.

### Prevention of NRDS

Two main strategies are available for the prevention of NRDS (prophylaxis):

-one is antenatal (before-birth) with the administration of corticosteroids to mothers, at risk of preterm delivery, thus accelerating fetal lung maturation and

-one is after birth, by giving in the delivery room, as soon as possible, exogenous surfactant to the new-borns.

### Antenatal prophylaxis

The antenatal corticosteroid treatment for prophylaxis of NRDS proposed by Liggins and Howie in 1972 is effective in reducing the frequency and the severity of the disease(2).

Moreover, use of steroids during the perinatal period affects almost all body systems, enhancing cell differentiation but reducing cell division.

Some negative side effects on growth, development and circulation have been described in animals and in humans. The most evident acute adverse effects on the fetus are: reduction of the fetal body and breathing movements, reduction in fetal heart rate variability. Other severe adverse effects reported are: fetal and placenta growth retardation, disturbances of growth and functional differentiation of the central nervous system, increase of pre-term delivery, increased susceptibility to infections, depression of adrenal function (low cortisol level in new-borns), and transient hypertrophic cardiomyopathy. The most

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important long term adverse effects are related to the neurological system with abnormal neurological development, cerebral palsy and they suggest a warning against indiscriminate use of steroids during fetal life.

The prenatal prophylaxis of the NRDS with steroids presents important advantages such as; easy administration, very low costs, reduction in the need of intensive care, reduction in mortality and morbidity, therefore, a single course of corticosteroids is recommended for mothers at risk of preterm delivery and who are between 24 and 34 weeks gestation(3).

Repeated antenatal courses must be avoided, they may have lasting negative side effects on fetal grow and neurological development without clear benefits for the fetus. (4)

Betamethasone has more pronounced side effects but also more beneficial effects than dexamethasone, therefore, it is the drug of choice.

The main scheme for prenatal prophylaxis foresees the administration of betamethasone at the dose of 12 mg repeated after 12 or 24 hrs (5).

### Postnatal prophylaxis

A new way to prevent NRDS is the administration of exogenous surfactant to the newborn at birth, as soon as possible, in the delivery room.

Some experimental data suggest that it would be better to give the surfactant immediately after birth (6,7).

In fact, in surfactant deficient infants the leak of serum proteins into the alveoli inhibits the endogenous surfactant, moreover, surfactant deficient animals present necrosis and desquamation of bronchiolar epithelium already within a few minutes after the onset of ventilation.

Recently, Werner and Bjorklund demonstrated that in immature new-born animals the mechanical ventilation, also for a brief period, damages the lungs with a reduction of respiratory compliance that remains permanently lower than in the controls, also after surfactant administration (8).

In 1996, to evaluate the effects of an early administration of exogenous surfac-

tant in the delivery room (prophylaxis), to prevent NRDS, we performed a multicenter randomised clinical trial using a natural porcine exogenous surfactant (Curosurf) (9)

Before-birth babies with gestational ages between 24 and 30 weeks, were randomised (stratified in three groups on the basis of the gestational age) for prophylaxis or as controls.

In all the babies the rescue treatment was allowed in the cases of NRDS with need of mechanical ventilation.

We enrolled a total of 268 cases, 136 in the group of prophylaxis and 132 as controls.

The two groups were comparable in clinical characteristics.

In the group with prophylaxis mortality, grade III or IV NRDS and need of rescue treatment with surfactant were significantly lower than in the control group.

We observed, also, a reduction of other unfavourable clinical outcomes such as IVH, pneumotorax, interstitial emphysema and pneumonia, but the differences were not significative.

Combined unfavourable outcomes of mortality + BPD and mortality + BPD+IVH

**Table 1. Main Factors Predisposing an Infant to RDS**

1. Prematurity. Incidence of RDS increase with the decrease of gestational age (g.e.). Over 80% in infants with g.e. under 28 wks.
2. Male sex. Boys are more likely than girls to suffer from RDS and have a higher mortality.
3. Ethnic origin. RDS is more common in white than in non-white neonates.
4. Perinatal asphyxia. Increase the risk for RDS in both the term and preterm population.
5. Maternal Diabetes. Insulin delays the maturation of alveolar Type II cells.
6. Multiple pregnancies. Mainly related to low gestational age.
7. Caesarean section. Mainly related to low gestational age.
8. Familial disposition. If a women has one baby with RDS the risk in subsequent pregnancies increase. Surfactant protein B deficiency is an autosomal recessive condition, which presents as severe and persistent RDS, resulting in death.
9. Antenatal corticosteroids. The administration of corticosteroids to a mother who subsequently delivers a preterm baby, reduce the risk of developing RDS and mortality.

*These factors are considered indicators of the need for prophylactic surfactant.*

and retinopathy of the prematurity (ROP) were also significantly lower in prophylaxis than in the control group.

The prophylaxis with surfactant in the delivery room is more effective than rescue treatment and it "saves about seven more lives than rescue treatment for every one hundred babies treated".(10-14)

The prophylaxis, however, increases the number of unnecessary treatments. A percentage of babies, ranging from 20% to 40 %, depending on the gestational age, will receive the treatment without need because they never should have developed NRDS. This means an increase in surfactant's consumption and costs.

With regards to the problem of costs, Morley estimated that "prophylactic surfactant would cost about seven more doses of surfactant for every extra life saved."(10)

All these advantages and disadvantages must be taken into account, in particular, with planning of neonatal assistance in the developing countries.

A suggestion may be to reserve the prophylaxis for the babies with gestational ages between 26 and 28 weeks and for babies with gestational ages over 28 wks. that require intubation for management or for resuscitation in the delivery room.

Moreover, there are some predisposing factors that can help to choose prophylaxis or rescue treatment (Tab. 1).

In extremely low gestational new-born ages (<26 wk.) the surfactant administration, as prophylaxis or as rescue treatment, must be evaluated case by case and discussed with the parents, because of the poor outcomes of these babies.

In our study on prophylaxis in the delivery room with exogenous surfactant, considering the three different subgroups stratified at randomisation on the basis of the gestational age, we observed that prophylaxis reduces severe NRDS in the same way in the different gestational ages, but the mortality is only slightly reduced in the lower gestational ages. These babies, probably, suffer from other problems than lung immaturity.

The prophylaxis is more effective than rescue treatment but it is necessary to con-

sider, additionally, the cost and the availability of exogenous surfactant preparations for each country before recommending it for the prevention of NRDS. The surfactant preparations currently on the market are relatively expensive and the supply is relatively limited.

A low dose of surfactant for prophylaxis of NRDS should be sufficient (15)

### Rescue treatment

Exogenous surfactant is the drug of choice for the treatment of established NRDS.

Surfactant replacement therapy improves lung function, reduces mortality and incidence of air-leak complications.

These beneficial effects have been obtained with human surfactant isolated from amniotic fluid, modified natural surfactant of bovine or of porcine origin, as well as with protein free synthetic surfactant, although natural surfactants are more effective than artificial ones. (14, 15-17)

To evaluate the efficacy of surfactant treatment of severe NRDS, in 1988, we performed a randomised multicenter trial, involving the collaboration of eight European neonatal intensive care: 146 patients with a mean gestational age of 28.4 to 28.8 wks. and a mean birth weight of 1246 to 1182 g were enrolled. 77 babies received a large single dose (200 mg/ kg) of a natural porcine surfactant preparation (Curosurf) and 69 infants, that resulted at randomisation as controls, received the same assistance as the treated babies with the exception that no surfactant was instilled into the air-ways (16).

Babies receiving surfactant showed, within a few minutes, a dramatic improvement of oxygenation as reflected by a near threefold increase of the PaO<sub>2</sub>/FiO<sub>2</sub> ratio, neonatal mortality (28 days) decreased from 51% to 31% (P<. 05), incidence of pulmonary interstitial emphysema (23% v 39% P<. 05) and pneumothorax (18% v 35% P<. 05)

Many other randomised clinical trials have definitively demonstrated the efficacy of surfactant treatment of NRDS, however, the best timing of surfactant administration, in clinical practice, has not yet been clearly established (14). The early administration offers the advantage in

that the disease is less severe, however, there exists varying percentages of unnecessary treatment and of surfactant consumption similarly as in prophylaxis (9,11).

To evaluate the effects of a precocious treatment with exogenous surfactant of babies with NRDS we performed, in 1993 (in 8 different states in Europe), a multicenter randomised trial involving a total of 182 new-borns with NRDS and needing mechanical ventilation with an  $FiO_2$  between 0,40 and 0,59.

The new-borns of the "early treatment" group received, immediately after randomisation, a single dose (200 mg /Kg bw) of a natural porcine surfactant (Curosurf), while in the control group the treatment was reserved for those babies who needed mechanical ventilation with a  $FiO_2$  above 0.60.

The babies enrolled were comparable with regards to clinical characteristics, in particular, regarding gestational ages and birth weights(18).

The most impressive effects of the precocious treatment was a significant reduction in mortality, in IVH grade III or IV and death + BPD.

The duration of oxygen therapy and of IPPV was also reduced (in the babies with early treatment).

On the basis of these results we concluded that early treatment is better than the delayed one and it is recommended for babies with lower gestational ages.

Similarly, an early treatment with exogenous surfactant of pre-term infants (<30 wk. gestational age) receiving nasal continuous positive airway pressure (CPAP) reduces mortality and the need of mechanical ventilation (19).

### Conclusions

In summary, the suggestions for the developing countries should be:

- Prenatal prevention of NRDS with a single course of corticosteroids for mothers at risk of a pre-term delivery and that are between 24 and 34 week's gestation must be recommended. Repeated antenatal courses must be avoided.

- Postnatal prophylaxis with exogenous surfactant can be reserved for babies with

gestational ages between 26 and 28 weeks with evidence of high risk for NRDS (male sex, perinatal asphyxia, need of intubation at birth, incomplete course of antenatal corticosteroids, caesarean section, multiple pregnancies, maternal diabetes) and for babies with gestational ages over 28 wks. that require intubation.

- For prophylaxis a low dose of surfactant can be used.

Rescue treatment with exogenous surfactant is recommended for new-borns with gestational ages between 26-28 wks. with clinical evidence of NRDS. The early administration of a single low dose of surfactant improves the outcomes and the results are more effective than delayed treatment and, therefore, it is recommended.

- The rescue treatment of new-borns with NRDS who need intermittent positive pressure ventilation (IPPV) with a  $FiO_2$  > 40%, is mandatory.

- The replacement therapy of established NRDS, should be initiated as soon as possible even only on the basis of a clinical diagnosis.

- In new-borns with gestational ages > 28 weeks with NRDS, treatment may be delayed to reduce the number of unnecessary administrations and reserved for babies that need intermittent positive pressure ventilation (IPPV). In these cases the full dosage of the available surfactant is mandatory.

- In new-borns with extremely low gestational ages (<26 wk.) the surfactant administration must be evaluated case by case and discussed with the parents because of the poor outcomes of these babies.

- Surfactant administration, after a brief intubation, in the spontaneously breathing babies treated with CPAP might be useful to avoid mechanical ventilation

- Surfactant must be administered by qualified physicians trained in neonatal intensive care and in management of mechanical ventilation of VLBW infants.

- Supplementary surfactant should be used routinely only in institutions having all the necessary facilities for the management of VLBW infants and for mechanical ventilation.

- In some circumstances, the surfactant administration should be done in periphe-

ral hospitals, to WLBW infants waiting to be transferred to a NICU.

A clinical study we conducted in Rumania in 1996, at a time when neonatal respirators and NICUs too, were not available in that country- showed an improvement of clinical and respiratory conditions in new-borns with a mean gestational age of 30 wks, receiving surfactant supplementation in the first minutes of life with respect to the control group (20).

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