

Surfactant Replacement therapy in Newborns

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Abstract: Hyaline membrane disease is the most common respiratory disorder of the infants. It mainly affects the preterm babies below 35 weeks of gestation and is the major cause of mortality in this age group. Hyaline membrane disease is characterized by respiratory distress starting almost immediately after birth or maximum within first 6-8 hours of life. The basic defect in HMD is alveolar collapse secondary to surfactant deficiency. Surfactant has become the routine care in the management of preterm babies with HMD. After ventilation, surfactant has been proven to be the most important agent, which has improved the survival in preterm infants. Natural surfactant has been proven to be better than synthetic surfactant. Prophylactic surfactant usage should be restricted to babies less than 28-29 weeks of gestation, in older gestations it should be delivered early in the course of disease for optimal action. Surfactant therapy is definitely cost effective and without significant side effects. The surfactant usage is currently being extended to other neonatal respiratory disorders.

Introduction

Hyaline membrane disease is the most common respiratory disorder of the neonates. It mainly affects the preterm babies below 35 weeks of gestation and is the major cause of mortality and morbidity in this age group. It can also affect more mature babies born to diabetic mothers, suffering from birth asphyxia or having congenital deficiency of surfactant apoprotein B. Hyaline membrane disease is characterized by respiratory distress starting almost immediately after birth or maximum within first 6-8 hours of life in a preterm baby. The clinical hallmark is grunting respiration, hypoxia, increased oxygen and artificial ventilation requirement in a significant proportion of cases.

The basic defect in HMD is alveolar collapse secondary to surfactant deficiency. A very and Mead first described this association in 1959 (1). They reported that the lungs of preterm infants with HMD lacked the surface tension lowering agent characteristic of pulmonary surfactant. It took almost 20 years before Fujiwara et al, 1980(2) reported the clinical use of surfactant in preterm babies with HMD. They treated 10 neonates with surfactant prepared from solvent extract of bovine lungs and observed that it improved the oxygenation and decreased mortality and incidence of pneumothorax.

First randomized controlled trial to test its efficacy was done in 1984 and after that over 80 such trials have been done. Metanalysis of these trials show a decrease in oxygen requirement, ventilatory support, pneumothorax and mortality related to respiratory failure has drastically come down by 40%. Even larger trials involving 4000-5000 infants with weight <1500gms have shown a reduction in mortality by 30%. No consistent effect has been observed in the incidence of retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC) and bronchopulmonary dysplasia (BPD). Surfactant therapy is now the routine care in the management of preterm babies with HMD. After ventilation, surfactant has proved to be the most important agent, which has improved the survival in preterm infants.

Composition of surfactant(3) : Lipid constitute the major fraction of surfactant (nearly 90%), dipalmitoylphosphatidylcholine (DPPC) is the most active substance, which lowers surface tension. DPPC can reduce surface tension to zero but it requires surface active proteins for

its adsorption (SP-B and SP-C) and other unsaturated phospholipids for its spread. DPPC is synthesized in the endoplasmic reticulum and fetal lung accumulates large amount of DPPC in the last trimester. 90% of the total surfactant pool is recycled requiring surface-active proteins for this action. Though a term neonate's surfactant pool is 10 times more than that of adult lungs but preterm babies are deficient in surfactant pool. In addition in preterm neonates, surfactant has decreased biophysical function and is more sensitive to inactivity by inhibitors. In neonate recovering from RDS, concentration of DPPC increases over 4-5 days to normal infants. Surfactant pool in a term neonate is about 100mg/kg of phospholipids and this is the dose delivered to these babies.

Effects on lung mechanics⁴

Surfactant deficient lungs have poor compliance and low functional residual capacity. There is alveolar collapse at the end of expiration leading to low FRC and ventilation perfusion mismatch resulting in intrapulmonary right to left shunting. Surfactant helps in prevention of alveolar collapse at the end of the expiration, leading to improvement in FRC and thereby improving the compliance (5). As a result there is improvement in oxygenation and ventilation requirement goes down substantially. It is not very effective late in the course of the disease, as by that time hyaline membrane is already formed and surfactant cannot reach the alveolar air fluid interface.

Types of surfactant

It has two broad categories. (1) *Natural* (2) *Synthetic*

Natural surfactant is obtained mainly from either bovine or porcine lungs. Beractant (Survanta) and surfactant TA (surfacten) are lipid extracts of bovine lung mince with added DPPC, tripalmitoylglycerol and palmitic acid. Other natural surfactants are curosurf (porcine lung mince), Infracurf (calf lung surfactant extract). All natural surfactants contain SP-B and SP-C. The purification procedure that includes extraction with organic solvents removes the hydrophobic proteins SP-A and SP-D.

Synthetic surfactant - Exosurf consists of 85% DPPC, 9% hexadecanol, 6% tyloxapol (a spreading agent). Other is pumactant, which is a 7:3 mixture of DPPC and phosphatidylglycerol. Neither of these two synthetic surfactants contains any of the phospholipids and apoproteins.

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Two other synthetic surfactants that are likely to be available for human use soon are lucinactant and venticute, which contains genetically engineered recombinant apoproteins SP-B and SP-C respectively.

Use of surfactant

Various clinical trials have proved that surfactant therapy definitely improves the outcome in preterm babies by decreasing the incidence of pneumothorax, PIE and mortality. Various issues have been raised to find out the best use of surfactant. These issues are: whether to use natural or synthetic surfactant, what is better prophylactic or rescue treatment, what should be the timing, dose of surfactant in cases of established HMD and how effective is the combination therapy i.e. use of maternal corticosteroids and surfactant. All these issues are discussed below one by one.

Natural Vs Synthetic therapy⁶

Natural surfactant has been documented in various clinical trials to be better than the synthetic surfactant because of its rapid onset of action, sustainability of action because of apoproteins and decrease in the frequency of pneumothorax and mortality.

Prophylactic Vs Rescue treatment

Trials have been conducted to find out the best timing for giving surfactant. Prophylactic therapy means delivery of surfactant before baby develops respiratory distress. The rationale for the use of prophylactic therapy was that in animal models when surfactant was given immediately after birth there was more uniform and homogenous distribution of surfactant in fluid filled lungs leading to less acute lung injury. Systematic review by CJ Morley 1997(7) concluded that prophylactic treatment saved seven more lives than rescue treatment for every 100 babies treated. But this approach destabilizes the patient and surfactant is received by a group of preterm babies who do not require it leading to the wastage. Another issue in prophylactic therapy is, whether to deliver surfactant with the first breath even before resuscitation or delay it after baby has been resuscitated. This issue has been looked into by Kendig et al 1988(8) and he concluded that surfactant may be administered with equal or greater efficacy after initial resuscitation and confirmation of endotracheal tube.

Early Vs Late rescue therapy of HMD⁹

The rescue therapy means delivery of surfactant after baby starts having respiratory distress. The recommendation is to give surfactant therapy as soon as possible, as even minimal mechanical ventilation in a very short time can cause acute lung injury. The results of metaanalysis of various studies have shown decrease in the risk of pneumothorax, pulmonary interstitial emphysema and mortality if given within 2 hrs of birth (early) vs >3 hrs of birth (late).

Combination Therapy¹⁰

The incidence of hyaline membrane disease has been reduced after universal introduction of antenatal steroids in suspected preterm births. Surfactant therapy is definitely beneficial in babies with respiratory distress. The combination therapy i.e. the use of maternal corticosteroids with surfactant has even better outcomes. In a trial from Finland in

1994, Kari and associates (11) found that infants with RDS randomized to receive maternal corticosteroids showed better response compared to infants who did not receive prenatal corticosteroids. In another metaanalysis of randomized multicentric trials it was observed that when maternal corticosteroids and surfactant therapy were used alone results were quantitatively similar in terms of improving the respiratory outcome but when used together there was better outcome. Death decreased significantly from 19.6% in the group receiving neither surfactant nor corticosteroids to about 7% in a group receiving either treatment. No infant died of respiratory distress that received combined treatment.

Guidelines for use of surfactant

The preterm babies below or equal to 28-29 weeks of gestation with no history of maternal corticosteroids should be given surfactant immediately after birth after initial resuscitation (prophylactic therapy). Babies who are ≥ 30 weeks of gestation should be clinically assessed and if they are having respiratory distress, requiring intubation with chest x-ray picture showing feature of HMD, should be given surfactant as early as possible, i.e. within 2 hrs. In preterm babies who are more than 32 weeks surfactant therapy should be given if baby is having $FiO_2 > 0.4$ and $MAP > 7$ cm of H₂O and clinical picture is suggestive of HMD.

Dose of Surfactant

Surfactant dose is 100mg/kg of phospholipids, which is the surfactant pool of term neonate. In surfactant this is equal to 4ml/kg and in exosurf 5ml/kg.

Repeat dose of surfactant¹²

There is controversy regarding the number of doses of surfactant required for the best results. Various trials have been conducted to find out the answer. As surfactant is rapidly metabolized, only 20-30% of dose can be recovered from the air spaces after 24 hrs of ventilation, improve after a single dose is unsustainable and its function can be inhibited by proteins in small airways, so multiple doses can overcome this functional inactivation. In the OSIRIS trial two dose treatment schedule was found to be equivalent to a treatment schedule of four doses.

Side effects of surfactant

Surfactant is so far a safe drug with minimal side effects. It may have transient side effects like cyanosis, bradycardia, increased oxygen requirements, hypoxemia, increased PaCO₂ during administration¹³, which can be minimized after careful monitoring. It also increases the risk of pulmonary hemorrhage, which is 5-7% with natural surfactant and 3-5% with synthetic surfactant. The pulmonary hemorrhage is nothing but hemorrhagic pulmonary edema and is so more often seen in presence of a patent ductus arteriosus. Careful monitoring and faster weaning after surfactant therapy can minimize it. There are no long-term side effects like neurodevelopmental delay, growth retardation and late allergic and respiratory disorders attributable to surfactant alone.

Method of administration of surfactant

Surfactant administration should take precedence over admission procedure, putting long lines and nursing care. The whole procedure should be carried out under aseptic precautions.

Method of delivering exogenous surfactant to the affected lungs consists of the following steps:

- (1) **Stabilize the patient hemodynamically. Never give surfactant to a baby who is desaturating or is in shock.**
- (2) **Keep the baby in supine position. Previously the baby's position used to be changed during administration but the latest recommendation is not to change the position as changing the position destabilizes the baby and does not lead to better spread.**
- (3) **Intubate the baby with dual lumen endotracheal tube and confirm the position clinically.**
- (4) **Fill the surfactant from the bottle with wide bore needle into the 10ml syringe. Don't shake the bottle as it leads to foth formation.**
- (5) **Deliver surfactant through the side port of the Endotracheal tube in 4 boluses of 1ml/kg each over a total of 10-15 minutes making a total dose of 4ml/kg.**
- (6) **During administration don't disrupt mechanical ventilation as constant PEEP help in better dispersion of the surfactant.**
- (7) **Monitor baby's saturation, blood pressure (ideally invasive), heart rate and Transcutaneous PaCO₂ throughout the procedure.**
- (8) **Constantly monitor the ventilatory settings as surfactant rapidly improves the compliance of the lung necessitating rapid decrease in the ventilatory settings.**
- (9) **In face of nonavailability of transcutaneous PaCO₂ monitor, a blood gas after 15-20 minutes is mandatory to see PaCO₂.**

Cost of surfactant

Natural imported surfactant is available at the rate of Rs. 13000-15000/vial while synthetic surfactant is available at the rate of Rs. 25000/vial. An Indian company has come up with a *synthetic* surfactant available at the cost of Rs.4500/vial. The effectiveness of this surfactant is being tried in a clinical trial at present. Surfactant replacement therapy for neonatal respiratory distress syndrome has the potential to reduce morbidity and mortality of very premature infants. A study was done¹⁴ to investigate whether surfactant replacement therapy reduces hospital charges for these infants. They compared the hospital charges incurred by a group of patients treated with surfactant with hospital charges for the control group who did not receive surfactant. Average daily charges in the surfactant treated patients were 25% less than for the control patients. Most of the savings in daily charges were due to a 52% reduction in daily charges for laboratory, X-ray, respiratory therapy and other ancillary services. This study showed reduction in neonatal mortality and morbidity from respiratory distress syndrome, and it also significantly reduced requirement of ancillary services and so their charges. In this way surfactant therapy is cost effective by improving survival without increasing overall hospital costs.

Expanded Use of surfactant

After successful use of surfactant in hyaline membrane disease, it has been used in a number of other neonatal respiratory disorders like meconium aspiration syndrome, congenital diaphragmatic hernia¹⁵, pulmonary hemorrhage¹⁶, acute lung injury¹⁷, acute respiratory disorder syndrome¹⁸, pneumonia and sepsis. There are some trials supporting its use in MAS and acute lung injury. There are only few small prospective, randomized, controlled trials supporting surfactant use in non-HMD cases. Use of surfactant Therapy for any disorder other than HMD must be considered "Off the shelf" and experimental and should be decided on case to case basis.

Conclusion

The use of surfactant has revolutionized care of preterm babies suffering

from hyaline membrane disease. Its judicious use with careful monitoring has improved survival, decreased incidence of air leak syndrome but has not affected the incidence of chronic lung disease, NEC, ROP and IVH. Natural surfactant has been proved to be better than the synthetic surfactant. Prophylactic surfactant usage should be restricted to babies less than 28-29 weeks of gestation. In older gestations it should be delivered early in the course of disease for optimal action. In other neonatal disorders surfactant is being used on experimental basis only.

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