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Invited Review

# The use of surfactant in the neonatal period- the known aspects, those still under research and those which need to be investigated further

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## Abstract

Respiratory distress syndrome is pulmoner insufficiency caused by the lack of surfactant and the main reason of morbidity and mortality in preterm infants. Mothers at high risk of preterm birth should be transferred to perinatal centers with experience for respiratory distress syndrome and antenatal steroids should be given before 35 weeks' of gestational age. Surfactant treatment should be applied to babies with or at high risk for respiratory distress syndrome. Prophylaxis should be given to infants of <26 weeks of gestational age and to infants requiring entubation in the delivery room. Nasal continuous positive airway pressure should be considered in infants with complete steroid treatment and without entubation need. Early surfactant may be given if entubation is performed during follow-up. Natural forms of surfactant should be preferred when needed. If the infant is stable, early extubation and non-invasive respiratory support should be considered. In this review, the recent studies' current data about surfactant treatment will be discussed. (Türk Ped Arş 2014; 49: 1-12)

**Key words:** Newborn, respiratory distress syndrome, surfactant

Respiratory distress syndrome (RDS) is a pulmonary insufficiency picture which starts at delivery or in a short time after delivery and which gradually becomes more severe in the first two days of life and is the main reason of morbidity and mortality in preterm babies (1). This picture arises from structural immaturity of the lung and alveolar surfactant deficiency. Therefore, the frequency of RDS increases with the decrease in the gestational week. The frequency has been reported to be 91% at the 23-25$^{th}$ gestational week, 88% at the 26-27$^{th}$ gestational week, 74% at the 28-29$^{th}$ gestational week and 52% at the 30-31$^{st}$ gestational week (2). In our country, approximately 17 000 of 1,5 million babies born in one year die in the first month of life and preterm delivery and related RDS constitute 25% of the reasons of death (3). In this review article, it was aimed to give general and simple information about surfactant treatment with which a new era began in RDS treatment and thus in decreasing neonatal morbidity and mortality rates.

About 50 years ago, the importance of primary surfactant deficiency in the pathogenesis of neonatal RDS was found by Avery and Mead (4). In the following years, it was reported that administration of natural surfactant to the trachea of immature rabbits provided success in treatment of RDS (5). No medical discovery, drug or medical procedure which has started in the laboratory setting and reached clinical practice has directly affected human life in such a positive way as surfactant. Currently, surfactant is not only used in treatment of RDS in the neonatal period, but it is also used with success in many clinical conditions including lung hemorrhage, meconium aspiration syndrome, neonatal pneumonia, genetic surfactant deficiency and acute lung damage.

Surfactant which is required for normal lung function provides gas exchange by preventing alevolar collapse with its effect to decrease surface tension. In the 18$^{th}$ week of gestation, a portion of the epithelial cells transform into Type 1 cells and another portion transforms into Type 2 cells, while the asinuses develop. Type 1 cells cover 96% of the alveolar wall and are primarily responsible of gas exhange. Type 2 cells are responsible of production and storage of surfactant. In the intrauterine period, effective gas exchange begins in the 24$^{th}$ week, although the blood-gas border develops in the 19-20$^{th}$ weeks. In the 24$^{th}$ week, the Type 1 cells and mesenchyme become thin, the structural development required fo gas echange is provided with formation of a higher number of alveoles

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and approach of the cappillaries to the vessel lumen. Surfactant is synthesized in Type 2 pneumocytes in the 20-24th weeks, is stored in the lamellary bodies after the 24th week and secreted after the 28-30th weeks (6).

Surfactant synthesis starts in the 20th week and gradually accelerates after the 24th week. 80% of surfactant which is lipoprotein complex is composed of lipid, 12% is composed of protein and 8% is composed of neutral fats. 80-85% of the lipids are composed of phspholipids. 7% of these phospholipids is composed of phosphatidylcholine (PTC) and 8-12% is composed of phosphatidylglycerol (PTG), phosphatidylinositol (PTI) and phosphatidylethanolamine (PTE). 60% of phosphatidylcholine is composed of dipalmitoilphosphatidylcholine (DPPC) and is involved in decreasing the surface tension. Dipalmitoilphosphatidylcholine is the content of surfactant which can decrease the surface tension up to zero in the air-water interaction area in the alveole. Dipalmitoilphosphatidylcholine is synthesized in the endoplasmic reticulum and carried to the lammellary bodies with surfactant protein-B (SP-B) and SP-C. Phosphatidylglycerol provides extension of surfactant in the alveole (6). The elements in the structure of surfactant and percent values are shown in Table 1.

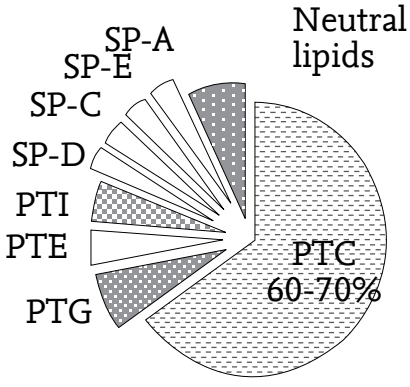
Surfactant proteins SP- A and SP-D are synthesized in and secreted from epithelial Type 2 cells of the alveole and Clara cells which are bronchial cells without cilia. These two hydrophilic proteins are found in the secretory granules in Clara cells and are released as acute phase reactants in presence of infectious agents. Therefore, SP-A and SP-D play a role in host defence of the upper airway tracts. Although it is thought that they are specific for the lung, especially SP-D is formed in many tissues including mainly the gastric and intestinal mucosa (7). Surfactant protein-A is additionally responsible of formation of tubular myelin and resynthesis of surfactant. Hydrophilic surfactant proteins SP-B and SP-C constitute the keystones of the mechanism in the development of RDS. While surfactant protein-B provides extension of surfactant in the alveolar surface and trasfer to the surface, SP-C provides adherence and extension of phospholipids to the surface (Table 2) (6, 7).

Sufficient endogeneous lung surfactant protects against collapse by decreasing the surface tension of the alveoles. In Figure 1, it is observed that the alveoles have been markedly collapsed during inspiration in a preterm baby with a diagnosis of RDS in whom surfactant treatment was not administered compared to normal inspiration and expiration in a term baby.

The picture of RDS develops as a natural result of surfactant deficiency. Clinially, RDS is a picture of respiratory distress which is characterized with cyanosis, wheezing, retractions and tacypnea and which develops in the early period. This picture is confirmed with clinical and radiological findings (Figure 2). All interventions required to prevent respiratory distress syndrome should be performed starting from the prenatal period. Babies who will be delivered prematurely with a risk of respiratory distress syndrome should be delivered in centers where respiratosy support, intubation, surfactant and mechanial ventilation can be performed.

After Avery and Mead and Enhorning et al. (5) showed that the main mechanism in RDS was surfactant deficiency, exogenous surfactant was used in treatment by Fujiwara et al. (8) in 1980. With exogeneous surfactant administration lung adaptation develops, oxygen requirement ($FiO_2$) decreases, oxygenation increases, air leakages like pneumothorax decrease and the survival rate increases. With surfactant administration pneumothorax decreases by 30-65% and the mortality rate decreases by 40% compared to the untreated groups or the groups in whome placebo is administered (9). These results show that surfactant administration in treatment of RDS is one of the main factors in saving life and decreasing the possibility of persistent disease.

**Table 1. Components included in the structure of surfactant and their percentages (6)**




| Component | % |
|---|---|
| Phospholpids | (80-85%) |
| Phosfatidylcholine (PTC) | 70% |
| Saturated phosphatidylcholine (sPTC) | 52% |
| Unsaturated phosphatidylcholine (uPTC) | 18% |
| Phosphatidylglycerol (PTG) | 8% |
| Phosfatidylethanolamine (PTE) | 4% |
| Phosfatidylinositol (PTI) | 2% |
| Sphyngomyelin | 1% |
| Proteins | (10%) |
| Specific glycoproteins (SP-A, SP-D ) | |
| Hydrophobic glycoproteins (SP-B, SP-C) | |
| Neutral lipids | (5-10%) |
| Cholesterol | |
| Diacylgylcerol | |

**Table 2. Main proteins included in the structure of surfactant and their properties (6, 7)**

| Protein | Solubility | Presence in commercial preparations | Function-importance |
|---|---|---|---|
| Surfactant Protein-A (SP-A) | Hydrophilic | Absent | Is involved in formation of myelin, resynthesis of surfactant and host defense mechanism and increases macrophage phagocytosis |
| Surfactant Protein-B (SP-B) | Hydrophobic | Present at different ratios | Provides extension of surfactant on the alveolar surface and penetration to the surface and is involved in ideal formation of the lipid layer |
| Surfactant Protein-C (SP-C) | Hydrophobic | Present at different ratios | Provides adherence of phospholipids on the surface and extension of phospholipids |
| Surfactant Protein-D (SP-D) | Hydrophilic | Absent | Is involved in microorganism adhesion and in host defense mechanism |


**Figure 1. The state of alveoles during inspiration in a preterm baby diagnosed with RDS in whom surfactant treatment was not administered and in a term baby according to normal inspiration and expiration**
RDS: respiratory distress syndrome

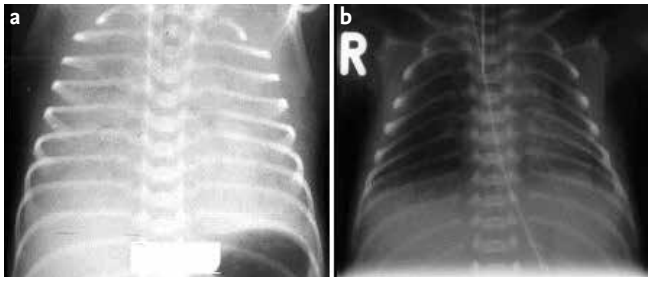



**Figure 2. a, b. Lung graphy of the preterm baby before and after surfactant treatment**

However, dicussions about surfactant treatment are still continuing. In the following parts, the literature data which try to find answers to questions related with surfactant treatment will be explained.

Surfactant preparations are divided into two groups as natural ansd synthetic surfactant. In Turkey, only Survanta and Curosurf which are natural surfactant preparations are available. Natural surfactant preparations are obtained from porcine or cattle and include only SP-B and SP-C. While the old synthetic preparations included only phospholipids without protein, the new ones include recombinant surfactant proteins or sysnthetic peptides. All commercial surfactant types and simple contents and preparation methods are shown in Table 3. the properties of the surfactants used in newborns are shown in Table 4 (10-12).

**Which one is more efficient? Natural? Synthetic? Semi-synthetic?**
In use of natural and synthetic perparations of surfactant, it has been found that both groups are efficient in prevention and treatment of RDS. However, in clinical studies performed using natural surfactant, it has been shown that the action is more rapid, requirement for ventilatory support decreases earlier compared to synthetic surfactant, the rate of pneumothorax is decreased and neonatal morbidity rates are decreased. This is related with tha fact that natural preparations act more rapidly because they contain SP-B and SP-C. With natural preparations the survival rates without development of bronchopulmonary dysplasia are also higher. In the literature, there are contradictory studies which report a decrease, stability or increase in the risk of intraventricular hemorrhage with administration of natural surfactant (13). However, in the studies which reported an increase, it was observed that these hemorrhages were limited to lower stages. Therefore, in clinical evaluation, use of natural surfactant is considered more appropriate compared to use of present synthetic surfactants (13).

**Table 3. Surfactant preparations used worldwide and their simple content properties**

| Commercial names | Generic name | Content |
|---|---|---|
| Natural surfactants | | |
| HL-10 | ? | Porcine-lung tissue |
| Curosurf | Poractant alpha | Porcine-lung tissue |
| Alveofact | SF-RI 1 | Cattle-lung lavage |
| BLES | Bovine Lipid Extract Surfactant | Porcine-lung lavage |
| Infasurf | Calfactant CLSE | Porcine-lung lavage |
| Newfacten | ? | Porcine-lung |
| Surfacten | Surfactant- TA | Porcine-lung homogenate |
| Survanta | Beractant | Porcine-lung tissue |
| Synthetic surfactants which do not contain protein | | |
| Adsurf | Pumactant (ALEC) | Synthetic (DPPC, PTG) |
| Exosurf | Colfosceril palmitate | Synthetic (DPPC) |
| Synthetic surfactants which contain peptide | | |
| Venticute* | rSP-C surfactant (Lusupultite) | Synthetic (DPPC, POPG, PA, rSPC) |
| Surfaxin | Lucinactant | Synthetic (DPPC, POPG, PA, KL4) |

* Is not used clinically in the neonatal period. It was only used for the purpose of the study
DPPC: dipalmitoylphosphatidylcholine; PTG: phosphatidylglycerol; POPG: palmitoyl-oleoyl phosphatidylglycerol; PA: palmitic acid; rSPC: recombinant Surfaktan Protein-C; KL4: abbreviation of the peptide structure

**Table 4. Structural properties and content percentages** of the commercial surfactant preperations used in the neonatal period* with alphabetical order**

| | Alveofact | Curosurf | Eksosurf | Infasurf | Survanta | Surfaksin |
|---|---|---|---|---|---|---|
| Amount (mL) | 1.2 | 1.5-3 | 8 | 6 | 4-8 | 10 |
| Concentratio (mg PL/mL) | 40 | 76 | 13.5 | 35 | 25 | 30 |
| DPPC (%) | 84 | 40-50 | 100 | 40-60 | 45-75 | 75 |
| Total dose (mL/kg) | 1.2 | 1.25-2.50 | 5 | 3 | 4 | 5.8 |
| Total dose (mg PL/kg) | 50 | 200 as the first dose and 100 as the repeated dose | 67.5 | 105 | 100 | 175 |
| Dose range | 12 hours | 12 hours | 12 hours | 12 hours | 6 hours | 6 hours |
| SP-B (mcprot/mmol L) | 2-5.8 | 2-3.7 | - | 5.4 | 0-1.3 | 19.8 |
| SP-C (mcprot/mmol L) | 1-12 | 5-11.6 | - | 8.1 | 1-20 | Palmitik asit |

*Venticute (Lusupultite): Synthetic surfactant preparation,it is not used clinically in the neonatal period and contains 50 mg/mL phospholipid (PL) and only recombinant surfaktan protein-C (SP-C). DPPC / POPG: 7/3
** The data have been obtained from product nomograms and reference (Guttentag S, Foster CD. Update in Surfactant Therapy NeoReviews 2011;12;e625-e634. DOI: 10.1542/neo.12-11-e625. http://neoreviews.aappublications.org/cgi/content/full/neoreviews;12/11/e625).

In the final Cochrane meta-analysis in which synthetic surfactants containing protein were compared with natural surfactants, it was noted that synthetic surfactants and natural surfactants were similar in terms of chronic lung disease and other outcomes of premature delivery, but a significant decrease was observed with synthetic surfactants in the rates of necrotizing enterocolitis and neonatal mortality in two recent studies (14). However, it was stated that further studies were needed in this area.

**Which natural surfactant preparation should we prefer?**

When the whole world is considered, the most widely uıed surfactant preparations include *poractant* and *beractant*. As a result of this, the comparison studies in the literature are mostly related with these two preparations. In the study of Malloy et al. (15) in which these two perparations were compared, it was found that $FiO_2$ requirement in the first 48 hours was lower in the group in which *poractant* (200 mg/kg) was administered and the rate of patent ductus arteriosus (PDA) was lower in this group. Similarly, in the *poractant-beractant* comparison study performed by Ramanathan et al. (16), the requirement for repeated dose of surfactant was found to be decreased with an initial *poractant* dose of 200 mg/kg. Use of *poractant* with an initial dose of 200 mg/kg resulted in more decrease in requirement of oxygen compared to *beractant* in preterm babies with RDS below the 35 gestational week. In addition, a statistically significant decrease in the mortality rate was observed in preterm babies born before the 32$^{th}$ gestational week compared to 100 mg/kg *poractant and beractant*. Gharehbaghi et al. (17) found no significant difference between the clinical and laboratory results except for shorter intubation times with *poractant* in the *poractant- beractant* comparison study which they conducted with babies born before the 32$^{nd}$ gestational week.

In a review published recently, the mortality rate, the rate of repeated dose administration, times of mechanical ventilation and/or the rate of oxygen treatment were found to be statistically significantly lower with use of 200 mg/kg *poractant* compared to use of 100 mg/kg *beractant* when rescue treatment was administered, but this difference was not observed especially in terms of mortality when equal doses were used according to the results of five randomized controlled studies including 529 newborns. When use of oxygen in the corrcted 36th week was examined, no difference was found between use of *poractant (for all doses*) and use of *beractant* (18).

When the surfactant studies performed in Turkey are examined, it is observed that there are three national and international studies comparing three natual surfactant types presented to the market so far (*SFRI 1, Beractant, Poractant*).

In the study performed by Yalaz et al. (19) in which *SF-RI 1(Alveofact®*) and *Beractant (Survanta)* were compared, it was shown that $FiO_2$ (fractional concentration of oxygen) and MAP (Mean airway pressure) values were significantly lower in the second hour of surfactant administration with *SF-RI 1*, but the $a/APO_2$ (arterial/alveolar oxygen pressure) ratio was lower in the second hour of administration with use of *Beractant*. The changes found in the second hour were eliminated in the sixth hour of surfactant administration. In this study, no statistically significant difference was found between the two groups in terms of the rates of pneumothorax, sepsis, intraventricular hemorrhage and bronchopulmonary dysplasia, mechanical ventilation time, hospitalization time and neonatal mortality rate.

Similarly, in the *SF-RI 1 - Beractant* comparison performed by Sarıcı et al. (20), it was observed that MAP values and $FiO_2$ requirement decreased significantly in the first 48 hours after surfactant administration with *Beractant,* the mechanical ventilation time was significanly shorter in the *Beractant* group and the frequencies of chronic lung disease and PDA were lower in the *Beractant* group.

In the study performed by Dizdar et al. (21), use of *Poractant* (200 mg/kg) and use of *Beractant* (100 mg/kg) were compared and a significantly lower rate of oxygen requirement after treatment, a significantly lower rate of repeated dose administration, a significantly higher rate of extubation in the first three days and a significantly higher rate of survival without bronchopulmonary dysplasia with use of *Poractant* was found. However, no difference was found in the rate of reintubation in the first 14 days, total ventilation time, total respiratory support of any kind, hospitalization time, first oral feeding and full oral feeding, hemodynamic support rates and finally mortality rates.

In the review published by Ramanathan (22) in 2009, it was reported that treatment of preterm babies with RDS or preterm babies carrying a risk for RDS with natural surfactant yielded better clinical outcomes. When poractant alpha is used at a dose of 200 mg/kg, a greater decrease in mortality rates can be obtained. Poractant can be considered as the first option according to the results of these clinical studies. Further studies on development of synthetic surfactant which could provide these conditions should be conducted.

The major limitations of both national and international studies comparing the efficiencies of different surfactant preparations include lack of being "blind" when giving these preparations because of the properties of these preparations and inability to demonstrate the efficiency of the preparation "simply" in terms of morbidity and mortality, because the prognosis is affected seperately by many factors including PDA, asphyxia, prenatal and postnatal infection, genetic factors, respiratory support type preferred (CPAPA (continuous positive airway pressure), nasal CPAP, nasal SIMV (synchronized intermittent forced ventilation), mechanical ventilation), different mechanical ventilator types and inter-personal, inter-clinic protocol differences which may have an direct impact on the efficiency of the exogeneous surfactant administered and which may affect the general health status of the baby in terms of ideal results.

**What is the ideal administration method for exogeneous surfactant?**

Surfactant should be cleanly administered in the endotracheal tube. It may be administered with a catheter into the lower part of the trachea or upper part of the carina as a bolus or infusion or with the help of specially produced adaptors like Trach-care MAC after the baby is intubated. In the study performed by Zola et al. (23), no difference was found between the two groups in whom bolus and infusion was used in terms of FiO2, MAP and $a/APO_2$ values in the 72$^{nd}$ hour as well as air leakage, pulmonary interstitial emphysema or neonatal mortality rates. However, desaturation develops more frequently after bolus administration. It has been observed that slow administration is as efficient as

bolus administration, but the frequency of surfactant reflux into the airway increases with this method (24).

During administration, airway obstruction may develop as well as arterial desaturation. In such a case, the administration rate should be reduced, the positive inspiratory pressure should be increased if surfactan is administered by adaptor, $FiO_2$ should be increased slightly and the baby should be ventilated with bag-valve-mask method for a short time if surfactant is administered by a catheter. The distribution of surfactant in the lung mostly depends on the gravity. The position of the thorax does not affect the distribution.

In our study which investigated if peripheral tissue oxygenation changed during administration of two different surfactant preparations [Beractant (n=20)-Poractant (n=19)] using pulsatile and perfusion index methods, no significant difference was found, although administration positions were the same and administration times were different by definiton. However, it was found that tissue perfusion was disrupted in the first few minutes and could reach back to the baseline value in the first 5 minutes with both preparations and the importance of the methods which might lead to less hypoxia compared to bolus administration methods (25).

As a result of administration of surfactant by way of double lumen endotracheal tube, decrease in hypoxia periods and less reduction in heart rate and oxygen saturation was observed. The group who received surfactant from double lumen required oxygen support with a lower rate, but no difference was found between long-term outcomes (26).

Besides endotracheal tube, administration of surfactant by aerosolization, nebulization and in utero administration are in the experimental phase. In addition to administration by gastric tube and laryngeal mask, use as aerosol which has been studied recently will eliminate the need for intubation. The clinical use of Aerosurf® which is the aerosol form of Lucinactant (Surfaxin®), which was produced by Mazela et al. (27) and is in the experimental stage has not been approved yet. In this pilot application, Aerosurf was administered as prophylactic treatment in 17 patients who were born between the 29 and 32$^{nd}$ gestational weeks. Treatment was administered in the first 30 minutes, the study was continued until the 48$^{th}$ hour and three applications were allowed at most. At the end of the study, all babies survived, RDS developed in only four of them and treatment was unsuccessful in three patients. Although this study in which no significant problem was found was encouraging, the study had no control group.

Further studies are needed to determine the best dose of aerolized surfactant and the particle size and to investigate the surfactant formula which preserves its efficiency when aerolized. In a recent review in this area, Pillow et al. (28) examined the subject of aerosol surfactant and compared ultrasonic, jet, oscillating membrane nebulizators in this application. Although the aerosol distribution of ultrasonic nebulizators is better in vivo and in vitro compared to jet nebulizators, the fact that aucistic waves of medium-high frequency lead to a high temperature to change the properties of surfactant proteins and to phospholipid loss is regarded as a disadvantage. Although the technique of jet nebulizators of administration of the drug by pulling by kinetic energy has a low cost is an advantage, a large portion of the dose which will be administered may remain in the device or expired into the airway. In this area, certain advences have been provided with oscillating membrane nebulizators for effective aerosolization. With this device an increase was observed in the amount of aerosol drug which reached the newborn. Capillary aerosol production technology is a promising technology with low flow, high efficiency and adaptable particle size in surfactant aerosolization (28).

In recent years, administration of surfactant by way of laryngeal mask to avoid invasive procedures including intubation has come to the forefront and studies related with this subject have been published. In the study performed by Attridge et al. (29), a total of 26 preterm babies below the age of 72 hours with a birth weight below 1200 g with RDS findings receiving nasal CPAP were divided into two grouphs. While nasal CPAP was continued in one group, calfactant (Infasurf) was administered by laryngeal mask and subsequently nasal CPAP was inititated in the other group. A marked decrease in oxygen consumption was shown in preterm babies receiving surfactant by laryngeal mask. Although no side effect related with use of laryngeal mask is found in these subjects, the major limitation of the technique is the fact that even the most appropriate device for the procedure is large for preterm babies below the 30-32$^{nd}$ gestational week. Larger case series are needed in terms of application by laryngeal mask (29)

No evidence supporting or opposing to intrapartum pharyngeal surfactant administration could be found in randomized controlled studies related with this application (30). In addition to these methods, more non-invasive methods including surfactant administration without intubation by direct placement of catheter into the trachea with the aim to avoid invasive procedures including intubation have been used in some studies published recently. This subject is explianed in detail in the remaining part of the article.

**When should it be administered after delivery?**

Exogeneous surfactant is used in two ways according to the related guidelines in RDS treatment (31).

1. Preventive treatment: Administration of surfactant in the first 15-30 minutes after delivery in very small preterm babies born below the 28$^{th}$ gestational week or in babies with a lecithin/sphyngomyelin ratio below 2 in the amniotic fluid (if it can be measured).
2. Rescue (selecvtive) treatment: Adminsitration of surfactant in the first two hours in the early form and after the first two hours in the late form in babies with a clinical and radiological diagnosis of RDS who are ventilated.

In administration of protective surfactant, surfactant which is administered when the lungs are filled with fluid is distributed homogeneously. Since apllication of mechanical ventilation even for 15-30 minutes before surfactant leads to alveolar cap-

illary injury and release of inflammatory mediators, protective surfactant decreases barotrauma and lung damage. A decrease in need for mechanical ventilatory support is also provided with use of protective surfactant (24).

Administration of synthetic surfactant as preventive treatment provides a decrease in the risk of pneumothorax, pulmonary interstitial emphysema and neonatal mortality. With preventive treatment the risk of pneumothorax decreases by 5%, the risk of pulmonary interstitial emphysema decreases by 6% and the neonatal mortality rate decreases by 7% (32).

In treatment of respiratory distress syndrome, the objective includes treatment of all babies who carry a risk for development of RDS and therefore babies who carry a high risk should receive surfactant treatment before the diagnosis of RDS is made radiologically as recommended from of old. In a large analysis study which compared preventive treatment and rescue treatment, a decrease was found in the frequencies of RDS, pneumothorax, pulmonary interstitial emphysema, mechanical ventilation, bronchopulmonary dysplasia and in the neonatal mortality rate, while the frequencies of necrotizing enterocolitis, PDA and intraventricular hemorrhage did not change (33). With preventive administration, there is a risk of unnecessary intubation and surfactant administration, a risk of unnecessary use of surfactant in patients who will not develop RDS in the future and thus an increase in cost.

When early and late administration of exogenous surfactant for rescue treatment of RDS were compared, a marked decrease was found in the frequencies of pneumothorax, pulmonary interstitial emphysema, chronic lung disease and in the neonatal mortality rate with early administration, while no impact of the time of administration was found on pulmonary hemorrhage, PDA, retinopathy of prematurity, necrotizing enterocolitis and intraventricular hemorrhage (34).

Therefore, administration of surfactant with the INSURE (Intubation, Surfactant, Extubation) technique has come to the forefront and the need for mechanical ventilation decreased with this technique. Although repeated dose of surfactant is required more frequently with rapid extubation after early surfactant administration and inititation of CPAP, the need for mechanical ventilation and the frequency of bronchopulmonary dysplasia is decreased (35, 36).

In the recent COIN study which is related with administration of nasal CPAP in the delivery room instead of preventive surfactant, 610 preterm babies with spontaneous respiration between 25 gestational weeks and 28 weeks and 6 days were randomly divided into two groups as the nasal CPAP in the fifth minute of life group and the intubation-mechanical ventilation group. In the follow-up of these groups, 46% of the subjects in the nasal CPAP group required intubation in the first five days of life. In spite of this, the number of days of mechanical ventilation and the need for mechanical ventilation were found to be lower in this groups (37). In the SUPPORT study of Finer et al. (38) which included 1316 preterm babies aged between the 24$^{th}$ gestational week and 27 weeks and 6 days, no difference was found in terms of neonatal mortality and bronchopulmonary dysplasia between administration of surfactant by intubation in the first hour in the delivery room and nasal CPAP with 5 cm$H_2O$ pressure alone. In addition, the frequency of intubation, the frequency of postnatal steroid treatment and the number of days of mechanical ventilation were found to be lower in the nasal CPAP group.

In the CURPAP study conducted by Sandri et al. (39) and published in 2010, 208 preterm babies between 25 weeks and 28 weeks 6 days who did not require intubation in the delivery room were randomly divided into two groups as the nasal CPAP in the first 30 minutes group and preventive surfactant group. Poractant alpha was administered at a dose of 200 mg/kg by intubation in the preventive surfactant group and nasal CPAP was inititated again in the shortest time possible. In these subjects who had spontaneous respiration, no difference was found in terms of need for mechanical ventilation in the first 5 days, prematurity diseases in the 28$^{th}$ day and postmenstruel 36$^{th}$ week and mortality. Therefore, these results obtained in the study showed that treatment could be started with nasal CPAP in the delivery room and surfactant could be administered when RDS findings developed (39).

In the study of Kandraju et al. (40) published recently, a decrease in need for mechanical ventilation was shown with early rescue treatment compared to late rescue treatment in babies in whom nasal CPAP was inititated as from the delivery.

In previous studies in which preventive surfactant administration to all newborns with a risk of RDS was compared with early rescue treatment, preventive administration was shown to provide a decrease in air leakage syndromes and mortality rates, but the studies published recently showed that the results with postnatal CPAP management together with prenatal steroid use with a higher rate were different compared to previous studies. A decrease in the risk of chronic lung disease and in the mortality rate was shown with management with early CPAP after delivery and selective surfactant administration only in the subjects who need intubation (41).

In this new era in which use of prenatal steroid administraiton increased, the results of the SUPPORT study related with regular nasal CPAP in the delivery room and the Vermont Oxford Network (VON) Delivery Room Management study were added to the studies performed before 1990 and no difference was found between use of preventive surfactant and CPAP + use of surfactant when necessary (38, 42). While preterm babies with a gestational age between 24 weeks and 27 weeks and 6 days were included in the SUPPORT group, Dunnet al. (42) included preterm babies with a gestational age between 26 weeks and 29 weeks and 6 days in the VON group. When these two studies were examined seperately from the other studies, a decrease in the risk of chronic lung disease and mortality was observed.

In terms of the method of administration, the advantages of administration of less surfactant are also being investigated. Kribs et al. (43) found the need for mechanical ventilation, the rate of bronchopulmonary dysplasia and the mortality rate to be low-

er in the first 72 hours of life in the group in which surfactant was administered by a flexible feeding catheter when the baby was receiving nasal CPAP compared to the group in which surfactant was administered by endotracheal tube after intubation. The negative aspect of the method is the fact that placement of flexible catheter throogh the vocal cords using Magill forceps and keeping it at the appropriate place is difficult and requires experience (43, 44).

Therefore, a new alternative method was developed by Dargaville et al. (45) and surfactant was administered by passing a narrow, semi-rigid vascular catheter through the vocal cords without a need for Magill forceps with this technique which is named as the Hobert method. During this lowest surfactant treatment (MIST) administered by Dargaville et al. (45), preterm babies between 25 and 28 weeks with any CPAP and $FiO_2$ value and with a CPAP requirement of ≥7 $cmH_20$ and a $FiO_2$ requirement of ≥%35 and an 16G catheter was passed through the vocal chords by direct visualization in these subjects. After administration of porcine-derived surfactant at a dose of 100 mg/kg/dose, a decrease in $FiO_2$ and CPAP requirement was observed in the subjects. In the group in which surfactant was administered, the rate of intubation requirement in the first 72 hours was lower and oxygen treatment was needed for a shorter time in this group.

One of the studies related with non-invasive administration of exogeneous surfactant is the amniotic fluid volume (AMH) study. This study is based on avoidance of mechanical ventilation in preterm babies with spontaneous respiration. The AMH study which was published by Göpel et al. (47) in 2011 is a randomized, controlled parallel-group study conducted in 12 neonatal intensive care unists (tertiary care) in Germany. In this study, postantal CPAP treatment (≥4 $cmH_2O$) was initiated in preterm babies in the first 12 hours of life with a gestational age between 26 weeks and 28 weeks and 6 days and a birth weight below 1500 g. The subjects were not intubated only for surfactant administration. The subjects who had severe RDS or asphyxia requiring intubation and mechanical ventilation, who had a $FiO_2$ requirement of >30%, who had acidosis and a high carbondioxide value were intubated. In the subjects who had spontaneous respiration and a $FiO_2$ requirement of >30% at nasal CPAP, a thin catheter (2.5-5 Fr) was placed with the help of a laryngoscope through the vocal cords and 100 mg/kg surfactant was administered. In this group, the total number of days of mechanical ventilation and need for oxygen were found to be lower compared to the control group (46).

In in the TAKE-CARE study conducted by Erdeve et al. (47) in our country which is still continuing, 100 mg/kg/dose surfactant was administered as bolus by intratracheal catheter during spontaneous respiration in a group of newborns below 32 weeks and 1500 g who were diagnosed with RDS with clinical and laboratory findings and nasal CPAP was initiated subsequently. It was planned to compare the data obtained with the group in whom INSURE was administered with the same dose of surfactnat. According to the primary data, requirement for respiratory support and the rates of BPD were found to be decreased markedly with TAKE-CARE technique compared to INSURE technique (47).

As a further step of the study published by Dargaville et al. (44) in 2011 the OPTIMIST study came to the forefront considering also the results of the AVM study. Newborns receiving 5-8 $cmH_2O$ CPAP treatment with a gestational age between 25 weeks and 28 weeks an a $FiO_2$ requirement of ≥ 30% (OPTIMIST-A) in the first 6 hours of life and a gestational age between 29 weeks and 32 weeks and a $FiO_2$ requirement of ≥30% (OPTIMIST-B) in the first 12 hours of life will be included. While nasal CPAP is planned to be continued in a group of these subjects, 200 mg/kg/dose poractant administration with Hobart method is planned in another group. Completion of the results of the study is expected.

In the final European Consensus Report published recently, preventive surfactant treatment is recommended as a standard for preterm babies who need intubation for stabilization in the delivery room and for excessively preterm babies born from mothers who have not received prenatal steroid therapy and early rescue treatment is recommended for preterm babies below the 30th gestational week, when necessary. Early rescue treatment should be considered when a requirement for >30% $FiO_2$ continues in babies born before the 26$^{th}$ gestational week and a requirement for >40% $FiO_2$ continues in babies born after the 26$^{th}$ gestational week. In this report, INSURE technique was recommended and it was stated more mature babies can be switched to nasal CPAP or nasal IPPV (48).

Administration of surfactant before transportation was found to be safe especially in newborns who would be transported. This application which did lead to an increase in morbidity and mortality rates resulted in lower oxygen requirement during transportation and a decrease in the number of days of ventilation in the follow-up. A decrease in the risk of pneumothorax after surfactant treatment is an expected benefit (49).

**Administration of repeated dose?**

In treatment, repeated doses may be needed in some cases in patients with RDS. In randomized studies, it was proved that two doses were better compared to a single dose in surfactant administration. In multiple-single dose comparison, it was observed that the rates of pneumothorax and mortality were decreased with administration of multiple doses (50). The surfactant dose should be repeated in all babies with RDS with persistent or repeated oxygen and ventilator requirement in the first 72 hours of life. In babies in whom the dose is administered again, oxygen and ventilator requirement decreases in the first week and the mortality rates are lower in the 28$^{th}$ day and at the age of one year (49). The second dose is generally administered 6 hours after the first dose. In the study of Figueras-Aloy et al. (51), the second dose of beractant was administered in the second hour in the first group and in the sixth hour in the second group. It was found that the rate of improvement in the ratio of a/APO2 12 hours after the first dose was higher in the group in whom the second dose was administered in the second hour among preterm babies below 1000 g. It was stated that the second dose could be given earlier in this group. However, in the study of Köksal et al. (52), no difference was found between surfactant administered in the second hour and in the sixth hour in terms

of clinical efficiency and RDS problems. It was reported that a second an deven third dose of surfactant should be administered in case of RDS findings including continuing oxygen requirement and mechanical ventilation requirement according to the European Consensus Report 2013 (48).

When the group in whom early extubation for nasal CPAP was performed after early surfactant trreatment and short-term (<1 hour) mechanical ventilation was compared with the group who received late rescue surfactant and longer mechanical ventilation, the frequencies of BPD and air leakage syndrome were found to be lower in the first group (53).

Although imporvement in RDS is observed with response to surfactant treatment in many preterm babies, a portion of these give weak response to surfactant and/or develop early exacerbation. In this group with weak response, a high rate of congenital infection, exposure to severe chorioamnionitis, pneumonia and suffocation during delivery were defined. Additionally, lack of structural pulmonary maturation, PDA, oxygen toxicity and barotrauma may be observed in early respiratory failure. Therefore, an inflammatory process may be triggerred and the immature air ways and/or alevolocappillary area may be damaged. As a result of this, plasma proteins which leak into the air space may disrupt the efficiency of the surfactant system and trigger dysfunction (54).

**What are the other areas of use of exogeneous surfactant?**

Surfactant treatment is currently used to save life in respiratory diseases other than RDS with relative indication (12, 20).

1. **Persistent pulmonary hypertension (PPHN):** Persistent pulmonary hypertension develops as a result of insufficiency of transition to normal circulation after delivery. Marked pulmonary hypertension leads to hypoxemia and extrapulmonary right to left shunt of the blood. As a result of inappropriate pulmonary hemorrhage, refractory hypoxemia, RDS and acidosis develop in the newborn. Persistent pulmonary hypertensiyon develops as a result of medical problems including mecınium aspiration syndrome, pneumonia, sepsis and congenital diaphragm hernia and surfactant treatment was shown to be beneficial.
2. **Meconium aspiration syndrome (MAS):** In the picture of meconium aspiration syndrome, especially free fatty acids in the meconium (palmitic acid, stearic acid, oleic adic) have a higher surface tension compared to surfactant and therefore elevate surfactant from the alveolar surface. Meconium is a strong inflammatory stimulus which leads to PAF (platelet activating factor) and TNF-alpha (tumor necrotizing factor) release from the alveolar macrophages depending on the dose and time (54). Although bolus administration of regular surfactant is not recommended in subjects with meconium aspiration, it should be used in selected subjects with predominant parenchymal disease and in cases of severe respiratory failure (56).

Among many pulmonary diseases in which washing treatment is administered, meconium aspiration syndrome has the highest potential for efficiency. In subjects in whom surfactant washing is administered, it was shown that oxygenation and pulmonary mechanics were better after washing compared to the control group and this group was even shown to be superior compared to the group in whom surfactant treatment was administered as bolus in terms of these aspects.

The total washing volume ranges between 5 and 80 mL/kg in experimental studies, but the values of 20-30 mL/kg are usually compared in studies. Dargaville et al. (44) compared different doses in an animal example and showed that the dose of 30 mL/kg provided the balance between the capacity of cleaning the lung from meconium and washing retention remained in the lung. In addition, in an experimental example, it was reported that oxygenation and lung compliance were better after washing with a washing volume of 20-30 mL/kg compared to a washing volume of 10 mL/kg.

It was shown that meconium cleaning was increased with a single application of 15 mL/kg during washing procedure. According to experimental data, a content of 5 mg/mL surfactant appears to be optimum.

In this way MAS leads to severe respiratory failure and secondary surfactant failure. Surfactant washing provides benefit in this issue and leads to a decrease especially in the mortality rate and pneumothorax. However, washing treatment should be performed by experienced individuals and these individuals should be educated in this area (44).

3. **Neonatal pneumonia and bronchiolitis:** This leads to surfactant failure like meconium aspiration syndrome and gas exchange imporves with surfactant treatment. Pneumonia and bronchiolitis are also included in the relative indications in the neonatal period, since surfactant treatment contibutes to surfactant synthesis of the baby and regulates pulmonary functions and provides synthesis of natural SP-A and SP-D subsequently, though it is not included in the hydrophylic SP-A and SP-D commercial preparations which have an important place in the natural immune system recognizing the carbonhydrate structures on bacteriae and viruses. In a review including 79 subjects with a diagnosis of respiratory syncytial virus bronchiolitis, it was reported that respiratory variables imporved with surfactant treatment and mechanical ventilation and hospitalization periods were decreased (57).
4. **Congenital diaphragm hernia (CDH):** Respiratory failure and surfactant failure develop becasue of change of lung formation due to hernia. Although large-sclae, multi-center studies are lacking, retrospective studies have not shown a clear benefit. Therefore, surfactant treatment may be tried in special cases and as recue treatment, though it is not recommended as a part of regular treatment in CDH.
5. **Lung hemorrhage:** Hemorrhage develops in preterm babies who are ventilated, have severe RDS and PDA in association. The reason of hemorrhage is increased left to right shunt by

way of PDA due ot a rapid fall in intrapulmonary pressures and increase in the pulmonary blood flow. In lung hemorrhage, the blood leads to secondary surfactant failure. However, there is no definite recommendation for use of surfactant treatment except for trial as a life-savng treatment in lung hemorhhage.

4. **Bronchopulmonary dysplasia (BPD):** Although type II alveolar cells are hyperplasic, it has been shown that these cells do not have normal functions. There is no controlled retrospective study related with BPD. However, there are publications of case reports reporting that surfactant treatment improves respiratory functions, but it is not possible to associate this with only surfactaant treatment, since the patients usually receive multiple therapies.

**What are the side effects of surfactant use?**

When the side effects of surfactant are examined, bradycardia, hypoxemia, and blockage in the endotracheal tube may develop during administration in the acute period. A rapid change in gas exhange occurs in newborns with surfactant failure who have received surfactant treatment. subsequently, dramatic changes occur in static pulmonary compliance. The frequency of lung hemorrhage may increase after surfactant treatment, but an increase in the mortality rate related with lung hemorrhage has not been found. The mortality rates decrease with surfactant treatment (23, 30, 49, 54).

Questions related with the immunologic effects of surfactant in the long term emerge. However, no evidence of immunological changes has been found. Circulating immune complexes directed to surfactant proteins have been reported in babies with RDS. One should be careful about microbiological safety in surfactant preparations (49).

**How should surfactant be used in RDS treatment conclusively?**

- According to the European Consensus and Canada Pediatrics Association reports, management of newborns with RDS and prenatal and postnatal evidence-based treatment approaches for exogenous surfactant treatment which will be administered at this time should be as follows: (31, 48, 49).
- Mothers who carry a high risk for premature delivery should be referred to prenatal centers experienced in RDS.
- Prenatal corticosteroid should be definetely administered in all pregnant women below the 34 gestational week, if premature delivery is in question.
- Surfactant treatment should be administered, if there is RDS or a risk for RDS in the baby delivered.
- Preventive surfactant should be administered in the delivery room in all babies with a gestational age below 26 weeks. In addition, preventive treatment should be administered in all preterm babies with RDS with a requirement of intubation for stabilization independent of the gestational week. In addition, surfactant should be administered in the delivery room as preventive treatment in excessively preterm babies born from mothers in whom prenatal steroid regime had not been completed.
- However, nasal CPAP is initiated in babies in whom prenatal steroid treatment is completed and who do not need intubation because of RDS in the delivery room and early rescue treatment may be administered, if intubation is required in the follow-up. Early rescue treatment should be planned in preterm babies with a gestational age of <26 weeks and a $FiO_2$ requirement of >30% and with a gestational age of >26 weeks and a $FiO_2$ requirement of >40%.
- Early rescue treatment should be administered in babies who have not received treatment before, but have evidence of RDS.
- Natural surfactant forms should be preferred. Definite and evidence-based data in relation with the question of which preparation should be used are still lacking. Each center should make a decision considering the degree of the underlying disease, present additional comorbidities, assitive respiratory support devices and probably the cost and all benefits and establish a procedure.
- If the baby is stable, non-invasive respiratory support (nasal CPAP or nasal IPPV) should be initiated together with early extubation following surfactant administration.
- In case of persistent oxygen requirement and mechanical ventilation requirement, a second and even a third dose may be needed sometimes, if the RDS findings persist.
- Repeated doses of surfactant can be administered in infants with persistent or resurrent oxygen and ventilator requirement in the first 72 hours of life.
- If persistent or recurrent oxygen requirement above 30% continues, a second dose of surfactant may be administered at least 2 hours after the first dose or frequently 4-6 hours after the first dose.
- All newborns below the 30th week who would not need mechanical ventilation, but carry a risk of RDS should receive perinatal nasal CPAP and followed up at CPAP until their clinical states become clear.
- If preventive surfactant treatment is needed, the objective after administration of surfactant is rapid extubation and switching to non-invasive nasal or IPPV treatment.
- Use of nasal CPAP together with early rescue treatment should be considered in all babies with respiratory distress syndrome in order to decrease the need for mechanical ventilation.
- Babies who are diagnosed with respiratory distress syndrome and have been intubated in the delivery room should receive exogeneous surfactant before transportation.

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