

**PHARMACOKINETICS OF SURFACTANT AND SUBSTANCES,  
STIMULATING ITS SYNTHESIS IN TREATMENT OF  
PREMATURELY BORN CHILDREN**

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**Abstract:** *our research were conducted in the Republic perinatal centre. 42 preterm children including 27 boys and 15 girls were given surfactant. We divided babies by gestational period into 3 groups: extremely preterm, very preterm and moderate to late preterm. Less than 28 weeks of gestation: 3 girls and 8 boys; 28 – 32 weeks of gestation: 10 girls and 15 boys; 32-37 weeks of gestation: 2 girls and 4 boys. 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.*

**Keywords:** *surfactant, premature babies, treatment, prevention.*

**Introduction.** Every year, an estimated 15 million babies are born preterm (before 37 completed weeks of gestation), and this number is rising [1-5]. Infant respiratory distress syndrome (IRDS) is a syndrome in premature infants caused by developmental insufficiency of pulmonary surfactant production and structural immaturity in the lungs [4-13]. The incidence decreases with advancing gestational age, from about 60% in babies born at 28 weeks, to about 15-20% at 32–36 weeks. Around 1 million preterm babies die each year. Those babies who survive can face lifelong physical, neurological or learning disabilities, often at great cost to families and society [12-20]. The number of premature babies in Uzbekistan amounted to nearly 37000 every year. 30 % babies has RDS (per 1000). Surfactant preparations are very expensive [19-21]. So, since this year purchase of surfactant is included in State program.

**Purpose of investigation:** evaluation of the effectiveness of the surfactant preparations based on pharmacokinetics and determine methods of treatment of preterm babies with IRDS.

**Materials and methods of investigation.** Our research were conducted in the Republic perinatal Centre. 42 preterm children including 27 boys and 15 girls were given surfactant. We divided babies by gestational period into 3 groups: extremely preterm, very preterm and moderate to late preterm. Less than 28 weeks of gestation: 3 girls and 8 boys; 28 – 32 weeks of gestation: 10 girls and 15 boys; 32-37 weeks of gestation: 2 girls and 4 boys. By birth weight babies were divided into 3 groups: 500-999g – 7 girls and 5 boys; 1000-1499g – 5 girls and 15 boys; 1500-2499g – 3 girls and 7 boys.

**Discussion.** Surfactant reduces the surface tension of fluid in the lungs and helps make the small air sacs in the lungs (alveoli) more stable. This keeps them from collapsing when an individual exhales. Preterm babies often lack adequate surfactant and must receive surfactant replacement therapy immediately after birth in order to breathe. Surfactant which is required for normal lung function provides gas exchange by preventing alveolar collapse with its effect to decrease surface tension. In the 18<sup>th</sup> week of gestation, a portion of the epithelial cells transform into type 1 cells and another portion transforms into type 2 cells, while the alveoli develop. Type 1 cells cover 96% of the alveolar wall and are primarily responsible of gas exchange. Type 2 cells are responsible of production and storage of surfactant. In the intrauterine period, effective gas exchange begins in the 24<sup>th</sup> week, although the blood-gas border develops in the 19–20<sup>th</sup> weeks. In the 24<sup>th</sup> week, the Type 1 cells and mesenchyme become thin, the structural development required for gas exchange is provided with formation of a higher number of alveoles and approach of the capillaries to the vessel lumen. Surfactant is synthesized in Type 2 pneumocytes in the 20–24<sup>th</sup> weeks, is stored in the lamellary bodies after the 24<sup>th</sup> week and secreted after the 28–30<sup>th</sup> weeks. Surfactant synthesis starts in the 20<sup>th</sup> week and gradually accelerates after the 24<sup>th</sup> 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 phospholipids. 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. Dipalmitoilphosphatidylcho-line is the content of surfactant which can decrease the surface tension up to zero in the air-water interaction area in the alveole. Dipalmitoil phosphatidyl choline is synthesized in the endoplasmic reticulum and carried to the lamellary bodies with surfactant protein-B (SP-B) and SP-C. Phosphatidyl glycerol provides extension of surfactant in the alveoli. Surfactant is a complex naturally occurring substance made of six lipids (fats) and four proteins that is produced in the lungs. It can also be manufactured synthetically.

Without adequate surfactant, a baby works much harder to breathe, becomes exhausted, and does not get enough oxygen. Babies that do not have enough surfactant to breathe normally at birth are said to have infant respiratory distress syndrome (RDS). Conception asserting that development of IRDS at new-born is based on structural-functional immaturity of lungs and system of surfactant, is leading, and its positions became stronger since data appeared about successful application of exogenous surfactant. 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 whom placebo is administered. 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.

Surfactant preparations are divided into two groups as natural and synthetic surfactant. 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 synthetic peptides. 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 the 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.

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 after the baby is intubated. 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.

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.

Exogenous surfactant is used in two ways according to the related guidelines in RDS treatment. 1. Preventive treatment: Administration of surfactant in the first 15–30 minutes after delivery in very small preterm babies born below the 28<sup>th</sup> gestational week or in babies with a lecithin/sphingomyelin ratio below 2 in the amniotic fluid (if it can be measured). 2. Rescue (selective) treatment: Administration 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 application of mechanical ventilation even for 15–30 minutes before surfactant leads to alveolar capillary 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.

Therefore, administration of surfactant with the INSURE (Intubation, Surfactant, Extubation) technique has come to the fore-front 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 initiation of CPAP, the need for mechanical ventilation and the frequency of bronchopulmonary dysplasia is decreased.

Treatment could be started with nasal CPAP in the delivery room and surfactant could be administered when RDS findings developed. 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 exchange occurs in newborns with surfactant failure who have received surfactant treatment. The most widely used surfactant preparations over the world: poractant  $\lambda$  (Curosurf), beractant (Survanta) and bovactant (Alveofact). Methods of surfactant's administration: INSURE (Intubation, SURfactant, Extubation), LISA (Less Invasive Surfactant Administration), MIST, laryngeal mask. Applied dose of surfactant: 100 mg/kg – prophylactic dose, 200 mg/kg – therapeutic dose. In our investigation poractant  $\lambda$  (Curosurf) was applied to 26 babies; bovactant (Alveofact) applied to 16 babies. Surfactant in our investigation was used only in therapeutic dose – 200 mg/kg. We used 2 methods of administration: INSURE and LISA to 21 babies, respectively. Study showed that LISA is less invasive and more effective method.

Surfactant is effective only within “an gold hour”. Side effects were not noted. The mortality rates decrease with surfactant treatment. 5 children after surfactant therapy died. It was connected with untimely therapy and receptors of some babies are not sensitive to surfactant. Preferred method of administration is LISA in therapeutic dose. Using surfactant is impossible without CPAP and required hardware. Effectiveness of Curosurf and Alveofact in our study is 88%

**Conclusions:** - Prenatal corticosteroid should be definitely 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. - 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. - If the baby is stable, non-invasive respiratory support (nasal CPAP or nasal IPPV) should be initiated together with early extubation following surfactant administration. - Repeated doses of surfactant can be administered in infants with persistent or recurrent oxygen and ventilator requirement in the first 72 hours of life. - 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 exogenous surfactant before transportation.

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