Review article

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THERAPEUTIC APPROACH TO A CHILD WITH ACUTE RESPIRATORY DISTRESS SYNDROME: A REPORT OF TWO CASES

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The course of a respiratory disorder in a child may end up in respiratory failure. There are also acute non-respiratory diseases which have a great influence on the respiratory functions and often lead to the acute lung injury and sometimes to the acute respiratory distress syndrome (ARDS). A feature of respiratory function deterioration is changed in the surfactant system. We often see inhibition of its synthesis or damage to its structure. Therapy of children suffering from ARDS should be complex and rapid. Despite many recently published studies explaining the principle of this disorder, the mortality of ARDS is still very high (30-50\%). There are several studies documenting successful administration of exogenous surfactant as part of a complex combined therapy of patients with ARDS, which leads to decreased mortality, improved oxygenation, and decreased need for aggressive artificial pulmonary ventilation. The authors of this article present their own experience with administration of exogenous surfactant in therapy of children with ARDS.

Key words: ARDS, children, drowning, exogenous surfactant, sepsis

INTRODUCTION

Respiratory diseases are frequent, particularly in children. In some cases, a respiratory disorder develops into a full-blown, gradual or sudden, respiratory failure. There are also many acute non-respiratory diseases which have a great influence on the respiratory functions and frequently lead to respiratory failure. A therapeutic approach to a child with progressive respiratory failure involves a
continuing intensive care which is a basis for successful and effective treatment. Children have to be intubated and artificially ventilated. The main goal of therapy should be the treatment of the main disease (aspiration pneumonia, sepsis) and a decrease of the risk for the development of multiple organ dysfunction syndrome (MODS) or ventilator-induced lung injury (VILI). During the progression of respiratory failure, the surfactant system is subject to early changes consisting of inhibition of its synthesis and damage to its structure (1).

**Pulmonary surfactant**

Pulmonary surfactant has a substantial influence on the ventilatory mechanics. Surfactant is a lipoprotein complex covering the alveolar surface. It maintains the terminal airway lumen in the open state and prevents the alveolar collapse. Surfactant creates the border between water molecules and alveolar surface, which allows alveolar ventilation and normal gas exchange in the lungs (2). Pulmonary surfactant consists mainly of lipids (90%) and in a smaller part of proteins (10%). Phospholipids are the main part of surfactant lipids (80-90%). There were four specific surfactant apoproteins detected: SP-A, SP-B, SP-C, and SP-D. SP-B and SP-C are extremely hydrophobic low-molecular proteins, whereas SP-A and SP-D are, conversely, high-molecular hydrophilic proteins (3). Nowadays, several types of surfactant are commercially available for therapeutic use: Curosurf® (extracted from porcine lungs), Survanta® (extracted from bovine lungs), Alveofact® (prepared by lavage of bovine lungs), and finally Exosurf® (synthetic surfactant). The first three preparations contain apoproteins B and C because the apoproteins A and D are eliminated during the production process. Synthetic surfactant contains added proteins. All the four mentioned preparations are successfully used in the treatment of ARDS. According to the clinical experience, the naturally occurred surfactant preparations exert more beneficial effects (2, 4).

**Acute respiratory distress syndrome**

According to the most recent international consensus, ARDS represents a subgroup of acute lung injury, having the following characteristic clinical symptoms: acute onset of respiratory distress, bilateral X-ray pulmonary infiltrates, and the absence of left-atrial hypertension. The difference between ARDS and acute lung injury (ALI) lies in the disease severity, expressed by the oxygenation index (\( \text{PaO}_2/\text{FiO}_2 \)). In children, the corresponding values are less than 200 for ARDS and in a range of 200 to 300 for ALI.

ARDS can be induced either by a direct lung damage (pulmonary form of ARDS), or by indirect pulmonary damage (extrapulmonary ARDS). The predisposing factors for ARDS in children are especially intracranial hypertension, administration of blood derivatives, catheter sepsis, pneumonia,
lung contusion, acute pancreatitis, endotoxemia, and pulmonary embolisms caused by amniotic fluid, bone fractures or aspiration of gastric contents (5).

ALI/ARDS have a typical course consisting of the three following phases: exudative, proliferative, and fibrotic. These phases can be overlapping or the disease stops at a particular point of time (6). For ARDS, increased capillary and/or alveolar permeability, loss of serum proteins primarily to the interstitium and later to alveoli, vasoconstriction and microembolism, increased pulmonary vascular resistance together with the redistribution of pulmonary perfusion, and finally alveolar instability with the atelectases formation are characteristic. All these processes cause the ventilation/perfusion imbalance which leads to the formation of intrapulmonary shunts. Subsequently, progressive proliferative process with the development of pulmonary fibrosis develops. Damage to phospholipid and protein compounds, with the inhibition of surfactant synthesis, leads to destruction of type I and II pneumocytes (3, 7).

There is no specific and uniform approach regarding the ARDS treatment. A complex therapy consists of many methods and approaches, but it is evident that only an early and accurate management of ARDS can prevent the complications and definitely improve the patient’s outcome. The basic principle of successful ARDS management is the treatment of its cause (e.g., sepsis, pneumonia) and the minimalization of the risk of multiple organ failure and ventilator-induced lung injury development (7).

The appropriate strategy of artificial pulmonary ventilation (APV) is still the unique confirmed approach with an evident influence on the mortality of patients with ALI/ARDS (ca more than 22%) (6). The most preferred kind of APV is so-called lung-protective ventilation, which means the ventilation with lower tidal volume (5-7 ml/kg of body weight) under higher ventilation pressures (positive-pressure inspiration, PPI, and positive end-expiratory pressure, PEEP). This strategy is called “open lung tool” (8). Nowadays, search for an ideal method for the estimation of the optimum PEEP value is underway. The measurement of pressure-volume dependence (so-called “pressure-volume tool”) seems promising in helping estimate the ideal lower and upper inflection point easily. Other artificial ventilation and therapeutic approaches worth mentioning are: balanced or even inverse inspiration/expiration ratio, recruitment maneuver (PEEP, sigh, and prone position), permissive hypercapnia, and ventilation with low oxygen fraction, high-frequency ventilation, airway pressure release ventilation (APRV), extracorporeal membrane oxygenation (ECMO), total or partial liquid ventilation (TLV/PLV) and nitric oxide inhalation. Important progress and improvement in the ARDS treatment has been noticed after the incorporation of exogenous surfactant into the therapeutic algorithm, which is administered directly endotracheally in the form of either diluted solution or bronchoalveolar lavage. There are reports demonstrating a rapid improvement of oxygenation, increase in oxygenation index, improvement of chest X-ray findings with pulmonary infiltrates regression in children with ARDS after surfactant
administration. A reduction in aggressive ventilation, a shorter artificial ventilation and time of hospitalization, and a lower mortality have been observed in connection with this therapy (9-11).

Case Report

One of our patients who suffered from ARDS was a 3-year old boy (body weight 18 kg). His family, epidemiologic and allergic histories were unremarkable. The child had been seen by a cardiologist because of stable arrhythmia and tendency to hypotension. In his personal history, recurrent upper respiratory infections and laryngitis were noted. Because of deterioration of his clinical status during the treatment of varicella, he was admitted to the Department of Infectious Diseases. At the beginning of hospitalization, hyperpyrexia, cervical lymphadenopathy, dysphagia and swollen right cheek were observed. On the second day, his condition worsened with the appearance of left retrotonsillar abscess and the development of upper mediastinitis, with subsequent tachycardia, tachypnea and dyspnea. Because of progressive respiratory failure, he was admitted to the Department of Pediatric Intensive Care Medicine. He was intubated and artificial pulmonary ventilation with P-SIMV regimen was started (PIP of 18 cmH\textsubscript{2}O, PEEP of 4 cmH\textsubscript{2}O, FiO\textsubscript{2} of 0.35, V\textsubscript{T} of 7 ml/kg, ventilatory rate of 20/min). Rapidly, sepsis developed with progression to septic shock. Because of hypotension, a combined inotropic therapy was administered (norepinephrin, dobutamine). Despite the therapy, the child’s condition worsened and the sings of MODS were clearly expressed (heart, renal, hepatic and respiratory failure, metabolic failure, and hypoxemia). Subsequently, the development of ARDS with low oxygenation index of 63 was confirmed. Despite aggressive APV (PIP of 44 cmH\textsubscript{2}O, PEEP of 12 cmH\textsubscript{2}O, FiO\textsubscript{2} of 0.75-1.00, V\textsubscript{T} of 7 ml/kg, ventilatory rate of 35/min) based on the principles of lung protecting ventilation (open lung tool) hypoxemia continued. Since standard therapeutic strategies failed, exogenous surfactant was introduced. The dose of 50 mg/kg of body weight was diluted in the 20 ml of physiologic saline and administered endotracheally twice. After surfactant application, the hypoxemia disappeared (SaO\textsubscript{2} increased from 86 to 96%), which allowed reducing the inspired oxygen fraction and then also the values of PIP (44 to 39 cmH\textsubscript{2}O), PEEP (12 to 10 cmH\textsubscript{2}O), and ventilatory rate (35 to 22/min) in a relatively short period of time (ca 20 min). The oxygenation index increased from 63 to 157 and the child’s condition became stable. A second dose of surfactant was administered 24 hours later, which was followed by further gradual stabilization of respiratory functions as expressed by normoxemia, correction of the oxygenation index (157 – 200 – 379), regression of X-ray signs of ARDS (Fig. 1) and a reduction of aggressive ventilation parameters. The signs of MODS disappeared and no further complications were observed. Improved ventilation allowed discontinuation of APT and extubation. The patient was transferred to the
Department of Pediatrics for further standard care and after being discharged from the hospital remains in good health without any complications or consequences of the previous disease.

**Case Report**

Another patient was a 17-year old boy (body weight 75 kg). His family, epidemiologic, and allergic histories were unremarkable. He underwent common infectious diseases of childhood. During the summer, he was swimming in a lake and suddenly started to drown. He was rescued after some minutes under water. Because of heart arrest and cessation of breathing, resuscitation was started which was successful after 7 min; artificial pulmonary ventilation was then introduced until the boy was transported to the nearest hospital. In the hospital, however, hypoxemia, hypotension, and metabolic failure continued. Aggressive ventilation, with inotropic support and cerebroprotective therapy, was started. The patient, in a critical condition, was moved to the Department of Pediatric Intensive Care Medicine. At admission, there was hypothermia, hypotension, tachycardia, circulatory shock, hypoxemia ($\text{SaO}_2$ 86-90%), and metabolic failure with the subsequent development of MODS (heart, renal, hepatic, respiratory failure, and disseminated intravascular coagulation). The signs of ARDS were presented on chest X-ray and the oxygenation index was extremely low (59). Parameters of artificial ventilation in the P-SIMV regimen were PIP of 42 cmH$_2$O, PEEP of 14 cmH$_2$O, FiO$_2$ of 1.00, and V$_T$ of 5 ml/kg. A complex therapy and intensive monitoring of the patient followed, with a partial clinical stabilization and increase in body temperature. Computed tomography of the brain showed no evident pathological changes, such as oedema, signs of intracranial hypertension, or hemorrhage. Because of persistent hypoxemia, metabolic acidosis, and a failure of conventional therapy, administration of exogenous surfactant was introduced. Surfactant in a dose of 25 mg/kg in 50 ml of physiologic saline was instilled bronchoscopically into the right and left main bronchus. In about 35 min after surfactant administration, hypoxemia retreated.

*Fig. 1.* Chest X-ray of 4 years old boy with ARDS as a consequence of serious septic status: a) before surfactant administration, b) 4 h after the first dose, c) 4 h after the second surfactant dose.
(SaO₂ 88 to 96%) and ventilatory parameters could be reduced: FiO₂ 1.0 to 0.5, PIP 42 to 34 cmH₂O, PEEP 14 to 8 cmH₂O, and ventilatory rate 25 to 14/min). The oxygenation index subsequently increased from 59 to 244. Despite the clinical improvement, the chest X-ray findings persisted. Therefore, we administered a second dose of surfactant after 24 hours from the first one in like manner. After that the respiratory function stabilized, the oxygenation index increased (from 244 to 434), the X-ray signs of ARDS disappeared (Fig. 2) and the ventilatory parameters were normalized as follows: PIP 34 to 18 cmH₂O, PEEP 8 to 3 cmH₂O, FiO₂ 0.5 to 0.21, V̇̇ down to 7 ml/kg (Table 2). The oxygenation index increased from 59 to 434. The patient became clinically stable (normothermia, normotension, normoxemia, without any metabolic changes). After another three days, however, a sudden change in the neurological status was observed, along with increased markers of inflammation in the peripheral blood. Because of fixed mydriasis, we performed an urgent CT of the brain, which showed cerebral oedema, a likely sequela of severe hypoxemia, post-resuscitation syndrome, and ischemic/reperfusion damage. After a complex examination of the patient, the brain death was pronounced. During several following days, the clinical signs of MODS progressed and the patient died.

**DISCUSSION**

Exogenous surfactant has been introduced into clinical practice several years ago and has now assumed an essential role in the neonatal medicine, but its administration is requires the fulfilment of special indications. The main problem for the approval of exogenous surfactant in later periods of life is an insufficient number of multicenter, controlled clinical trials that would elaborate the criteria for surfactant administration in older children and adolescents. The basic problem
with the meta-analysis of existing clinical studies is their non-homogeneity (different body weight, growth, and development of a child, non-homogeneity of provided doses, modes, and forms of application). The economic aspect of this therapy should also be taken into consideration. However, there are several reports demonstrating a good clinical experience with surfactant therapy in children with respiratory failure of various origins (12).

Despite recent progress in the understanding of ARDS and new therapeutic options, the mortality of children with ARDS is still high (30-50%). In the algorithm of ARDS therapy, exogenous surfactant is increasingly used. It should be emphasized, however, that its administration is only a part of multimodal complex therapy. There are several reports describing and evaluating the results of surfactant use in the ARDS management. Exogenous surfactant often causes a rapid improvement of oxygenation, regression of X-ray lung infiltrates, reduction of aggressive ventilation parameters, and shortens APT and hospitalization duration. The reports confirm that administration of exogenous surfactant should be one of the first steps and not be delayed until critical and advanced phases of this disease develop (9-11). Surfactant is usually given endotracheally or through bronchoalveolar lavage in the form of diluted saline solution. Direct bronchoscopic instillation of surfactant is used with increasing frequency, for the aim of surfactant therapy is its application directly to the terminal airways (alveoli). Up to now, many application modalities were used: nebulization, instillation of non-diluted or diluted surfactant into endotracheal cannula, direct bronchoscopic instillation of diluted surfactant, or bronchoalveolar lavage with diluted solution (volume lavage). Nebulization of surfactant is effective, but has some disadvantages of which the most important one is that only 5% of the dose administered reaches the alveoli. Direct endotracheal application seems more effective and advantageous. Administration of non-diluted surfactant, apart from being a very expensive treatment, causes that the dose is not homogenously distributed in terminal airways. The best results were obtained after surfactant application in the form of a diluted solution or bronchoalveolar lavage. Bronchoscopic application of surfactant into the damaged parts of lung parenchyma also seems promising (10, 13, 14).

While doses of exogenous surfactant in newborn age are clearly defined, no dosage scheme has by far been conclusively designed for later childhood. Here is no standardized application schema of exogenous surfactant concerning the value of a single dose, the number of doses and the inter-dose interval. According to the published data, a single dose is within a range from 25 to 300 mg/kg with the interval of application from 6 hours between the two doses or once daily administration until the disappearance of clinical and laboratory signs of ARDS. The surfactant administration scheme depends, to a great extent, the results of vital functions monitoring (10, 13, 15).

We can summarize that recently exogenous surfactant treatment is increasingly practiced in critically ill pediatric patients. Despite missing complex
clinical studies, increased number of reports point to its therapeutic efficacy, especially in children with acute lung damage. Our clinical experience, described in the present article, confirms the beneficial effects of exogenous surfactant in children. Surfactant, added to a complex intensive therapy of both presented patients, showed clinical benefits resulting in regression of ARDS symptoms. The death of a boy whose ARDS was induced by drowning was a consequence of later sequelae, such as prolonged hypoxia and ischemic-reperfusion brain damage, which developed after a transient improvement due likely to surfactant-related regression of pulmonary changes. Exogenous surfactant seems a promising, albeit still largely unexplored area of adjunctive treatment of severe pulmonary pathologies.

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