Surfactant therapy for acute respiratory distress in children

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Abstract. In children with acute lung injury the endogenous surfactant system is altered via a variety of different mechanisms, including inflammation, vascular dysfunction, oxidant injury, cellular injury and oedema. This article examines the pathophysiology of acute lung injury and surfactant use for treatment of acute respiratory failure in infants and children. (www.actabiomedica.it)

Key words: surfactant, children, acute lung injury, respiratory distress

Introduction

Surfactant therapy is currently a mainstay in neonatal care, where its use has been associated with a significant reduction in the morbidity and mortality of preterm infants who have a primary deficiency of surfactant due to a lack of mature alveolar type II epithelial cells at birth. There is also evidence of surfactant dysfunction in many forms of acute pulmonary injury in term infants, children and adults, but the evidence of therapeutic efficacy for exogenous surfactant outside the neonatal period is more limited. In this case the acute pulmonary injury is much more complicated than simple surfactant deficiency of prematurity because it has a many-sided pathology that includes also prominent aspects of inflammation, vascular dysfunction, oxidant injury, cellular injury and oedema. Moreover, unlike with premature infants in which surfactant is given in the immediate post-natal period when pulmonary oedema and inflammation is minimal, delivery and distribution of exogenous surfactant to the alveoli is more difficult in these patients due to oedema inflammation which characterizes their lung injury.

Definition and epidemiology of ALI/ARDS

Acute lung injury and acute respiratory distress (ALI/ARDS) is a clinical syndrome caused primarily by increased permeability to proteins across the endothelial and epithelial barriers of the lungs and is characterized as restrictive disease with reduced lung compliance caused by loss of surfactant function, atelectatic lung regions and accumulation of interstitial/alveolar plasma leakage. Patients usually develop acute respiratory failure rapidly because of arterial hypoxemia as well as impaired carbon dioxide excretion and elevated work of breathing. The American-European Consensus Conference (AECC) in 1994 defined ARDS as respiratory failure of acute onset with a PaO_2/FiO_2 ratio ≤200 mmHg (regardless of the level of positive end expiratory pressure, PEEP) and bilateral infiltrates on a frontal chest radiograph. ALI is defined identically except for a higher PaO_2/FiO_2 limit of <300 mmHg (1). Among the mechanically ventilated children the incidence of ALI is about 9%, and 80% of this group develops ARDS resulting in an incidence of 7-8%. Overall mortality in children suffering from ALI/ARDS ranges from 18-27%, but increases to 29-50% when considering only the ARDS group and is only 3-11% in those who do not develop ARDS (2, 3). It is essential, however, to distinguish between ALI/ARDS

associated with direct pulmonary causes compared to systemic (indirect, extra-pulmonary) causes. Direct pulmonary causes of ALI/ARDS include pulmonary viral or bacterial infections, aspiration (e.g., gastric aspiration, meconium aspiration in infants), thoracic trauma with lung contusion, near-drowning and the inhalation of oxygen, smoke or other toxicants. Indirect (systemic) causes of ALI/ARDS include sepsis, burn injury, hypovolemic shock, generalized trauma with long bone fracture, multiple transfusions, pancreatitis, and other primary extra-pulmonary injuries. Indirect forms of ALI/ARDS have substantial multi-organ pathology that significantly affects long term patient outcomes, reducing the impact and effectiveness of pulmonary-based therapies like exogenous surfactant administration (4, 5).

Pathophysiology of ALI/ARDS

ALI is characterized by an initial injury, which triggers cell-mediated mechanisms releasing a cascade of a variety of mediators that disturb the integrity and function of the cellular linings of the alveolar-capillary unit. Hyaline membranes, flooded alveoli with protein-rich oedema fluid, infiltrates of polymorphonuclear neutrophils, macrophages and erythrocytes are the leading histological hallmarks of ALI (6, 7). The degree of inflammation depends on the biological activity and the imbalance between pro- and anti-inflammatory cytokines and, similar to bacterial sepsis, a close interrelationship exists between inflammatory mediators and the coagulation cascade (8, 9). Activation of pro-coagulative factors (tissue factor) and inhibition of fibrinolysis (plasminogen activator inhibitor) have been identified to produce platelet–fibrin thrombi in small pulmonary vessels (10, 11). This interplay occurs both in the alveolar compartment and in intra- and extravascular space: unresolved fibrin depositions and alveolar hyaline membranes are the net result. Surfactant function is inactivated by leakage of plasma proteins and its production is further diminished by damage of type II pneumocytes (12). For resolution the dynamic interaction between inflammation, coagulation, restoration of water transport and cell function need to be rebalanced and surfactant production restarted.

Surfactant dysfunction in ALI/ARDS

There are a number of pathways by which lung surfactant activity can be compromised during acute pulmonary injury. Extensive studies have documented that such as plasma and blood proteins, meconium, cell membrane lipids, fluid free fatty acids, reactive oxidants, and lytic enzymes including proteases and phospholipases (13-15). Albumin and other blood proteins impair surface activity primarily by competitive adsorption that reduces the entry of active surfactant components into the alveolar air-water interface (16). In contrast, cell membrane lipids, lysophospholipids, or fatty acids act in part by mixing into the surface film and compromising its ability to reach low surface tension during dynamic compression (13, 16, 17). Another type of surfactant dysfunction is the depletion or impairment of activity of large surfactant aggregates that are distributed in the alveolar hypophase (18); the percentage of large aggregates and their content of SP-A and SP-B have also been shown to be reduced in Bronchoalveolar lavage (BAL) from patients with ARDS. It is, however, well documented that surface activity deficits from all these mechanisms can be mitigated in vitro by increasing the concentration of active surfactant (19) and that, in vivo, exogenous surfactant therapy has the capacity to improve acute respiratory pathology in animal models of ALI/ARDS (19, 20). All these data support the theoretical utility of exogenous surfactant supplementation strategies.

Surfactant treatment of paediatric ALI/ARDS

Respiratory infections, in particular pneumonia and severe RSV bronchiolitis, are the most common causes of respiratory failure requiring MV in children and the efficacy of exogenous surfactant is expected to be greater than in adults due to a higher proportion of cases of primary pulmonary disease (21). Despite this, there are few studies that have analysed the efficacy of surfactant in paediatric lung injury. Several authors suggest that studies are hampered by the lack of appropriate surfactant preparations able to resist local inactivation. In a systematic review including six

prospective, randomized, controlled trials of surfactant in intubated and mechanically ventilated children with acute respiratory failure (trials enrolling neonates or patients with asthma were excluded), Duffett et al. (22) showed that surfactant was associated with significantly lower mortality (relative risk=0.7, 95% confidence interval=0.4–0.97, p=0.04) and positive effects on several other secondary outcome measures: ventilator-free days, shorter duration of Mechanical Ventilation (MV), shortened duration of PICU stay and lower use of rescue therapy.

Observational studies conducted in mechanically ventilated infants with viral pulmonary infection have demonstrated lower concentrations of surfactant lipids in BAL fluids or endotracheal aspirates (23), which could be explained with viral invasion of type II pneumocytes and altered regulation of the production of surfactant lipids. This observation has led to the hypothesis that exogenous surfactant might improve the clinical outcome of affected infants. A recent meta-analysis (24), which included three small randomized controlled trials enrolling 79 participants, suggested that the use of surfactant for critically ill infants and children with bronchiolitis may decrease the duration of MV and the duration of intensive care unit stay without any side effects. Moreover use of surfactant had favourable effects on oxygenation and CO_2 elimination. These data suggest a beneficial role for exogenous surfactant in the treatment of viral respiratory infection when there are oxygenation disturbances. The limited number of studies with small numbers of participants were the limitations of this review.

Surfactant therapy has been tried also for respiratory failure secondary to hydrocarbon aspiration, near-drowning, severe inhalation injury and burns, idiopathic pulmonary haemorrhage, and aspiration pneumonia. In all cases exogenous surfactant improved the oxygenation index and clinical outcome.

Conclusions

It has already been shown that surfactant therapy is beneficial in several lung-injury applications in term infants and children. The insufficiency of some clinical results on surfactant therapy in paediatric lung injury is due to many factors and among these the fact that ALI/ARDS is not a single disease, but the end result of many different types of acute pulmonary injury. However, it is likely that this therapy will find an significant place in the treatment of paediatric ALI/ARDS when some important problems are resolved, such as the capacity of new synthetic surfactant to resist inhibition by substances that leak into alveolar space and the strategy of surfactant administration.

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