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Original article

Surfactant therapy in pediatric ALI and ARDS: are we there yet?

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Abstract. Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) are serious life-threatening disorders in the pediatric population, arising from direct or indirect lung damage, leading ultimately to overwhelming lung inflammation and severe hypoxia. In this inflammatory setting, endogenous surfactant is likely to be either lacking or inactivated by plasma proteins, proteases and reactive oxygen species flooding the injured alveoli. Besides supportive treatment (mechanical ventilation with low tidal volumes, positive end-expiratory pressure to open collapsed alveoli, supplemental oxygen, and supportive care of other organs' failure), exogenous surfactant has been advocates as a possible therapy. However, apart from case reports and small clinical trials, review of the recent literature failed to confirm striking benefit from exogenous replacement therapy. Further studies are needed to confirm a possible role of surfactant in pediatric acute respiratory failure as well as to clarify issues related to this promising therapy.. (www.actabiomedica.it)

Key words: exogenous surfactant, pediatric acute lung injury, pediatric acute respiratory distress syndrome

Abbreviations: ALI: Acute Lung Injury; ARDS: Acute Respiratory Distress Syndrome; PaO2/FiO2: ratio of arterial oxygen tension and fraction of inspired oxygen

Introduction

Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) constitute major clinical problems in pediatric intensive care, due to their high morbidity and mortality.

These life-threatening conditions typically arise from underlying critical illness causing direct (i.e. pneumonia, aspiration, near-drowning) or indirect (i.e. sepsis, pancreatitis, trauma…) lung damage. Distinctive features of both ALI and ARDS include increased lung vascular permeability leading to non-cardiogenic protein-rich lung edema, release of cytokines and pro-inflammatory molecules by neutrophils and macrophages and sloughing off of both alveolar endothelium and epithelium. As a result, reduced lung compliance, overwhelming lung inflammation and profound hypoxemia occur.

Independently of age, ALI and ARDS are defined by the American European Consensus Conference (AECC) criteria (1), namely: I) Acute onset; II) Evidence of bilateral infiltrates on frontal chest radiograph; III) Severe hypoxemia, defined by PaO2/FiO2<300 (for ALI) or PaO2/FiO2<200 (for ARDS); IV) A pulmonary artery wedge pressure less than 18 mmHg or, if unavailable, no clinical evidence of left atrial hypertension.

ALI and ARDS are characterized by an initial insult, which triggers cell-mediated mechanisms releasing a cascade of various mediators. They disarrange the lining integrity and function of the alveolar-capillary unit, both directly causing death of endothelial and epithelial cells or increasing the permeability of the lung microvasculature, leading to plasma-protein leakage into the alveoli and the interstitial space, hyaline membrane formation, infiltration of neutrophils

and macrophages, ultimately leading to severe hypoxemia and impaired carbon dioxide excretion.

In this inflammatory milieu, pulmonary surfactant inhibition and degradation has been postulated and demonstrated in several studies (2-4); surfactant in ALI and ARDS may either be lacking, due to the death of type II pneumocytes or inactivated by the plasma proteins, proteases and reactive oxygen species flooding the alveolar spaces; thus, overcoming a dysfunctional or lacking endogenous surfactant seems a promising therapy for these life-threatening conditions.

Pathophysiology, diagnosis and management of ALI and ARDS are nowadays subject of extensive research; however, clinical research on ALI and ARDS is dominated by studies performed in adult patients. For example, a Medline search utilizing MeSH database including the terms "Acute Lung Injury" OR "Respiratory Distress Syndrome, Adult" retrieved 12198 results (as of 05/23/2012); however, when limited to children only 2019 clinical investigations remained. Highlighting the differences between children and adults in epidemiology, diagnosis and management of ALI and ARDS seems therefore essential.

Epidemiology

ALI and ARDS occur with less frequency in children than in adults; in studies performed in a PICU, among mechanically ventilated children, 7% to 8% developed ARDS; in relation to PICU admissions the incidence of ARDS was calculated to be 3% to 4% (5-7); the only European population-based study (conducted in Germany) reported an incidence of pediatric ARDS of 3.2 cases per year/100.000 inhabitants (8); a population incidence of 2.9 cases per year/100.000 inhabitants was described in a multicentre observational study conducted in Australia and New Zealand (5). By contrast, a much higher incidence was found in adults, ranging from 18 to 86 cases per year/100.000 inhabitants (9-11). Mortality in pediatric patients with ARDS ranged between 8% and 35% (6, 12), while in adult patients even case fatality up to 60% have been described (13).

Diagnosis

Characteristic pathological findings in the lungs of patients with ARDS (14) are of little help in diagnosing ARDS in children, since lung biopsies are uncommon in the pediatric population. Therefore AECC criteria, mentioned above, are the common method to diagnose ALI and ARDS in pediatric patients.

Treatment

Treatment of children with ALI and ARDS is largely supportive, and includes mechanical ventilation with low tidal volumes, positive end-expiratory pressure to open collapsed alveoli, supplemental oxygen, and supportive care of other organs' failure.

A review on the ventilatory management of ALI and ARDS in children is beyond the objectives of this brief comment; however, using lung protective ventilation strategies aiming to prevent atelectasis as well as overdistention, re-open atelectatic regions and avoid high-pressure ventilation is undoubtedly beneficial, since ventilator-induced-lung-injury (VILI) is a great contributor to multi-organ failure and death (15).

Potential role of exogenous surfactant treatment in pediatric ALI and ARDS

As mentioned above, administration of exogenous pulmonary surfactant has been considered a possible treatment option in children with ALI and ARDS, since surfactant recovered from bronchoalveolar lavage fluid from children with ALI showed alterations of the phosphatidylcholine and surfactant proteins profile, and had impaired surface-tension-lowering properties (16).

In contrast to neonatal RDS, in pediatric ALI and ARDS there is secondary surfactant depletion and inactivation (17); nonetheless, a potential role of exogenous surfactant administered with the aim of replenishing endogenous surfactant pool and restoring near-normal surface tension in critically injured lungs had been greeted with enthusiasm, as it had been for

the "surfactant revolution" for neonatal RDS in the last two decades of the twentieth century. Unfortunately, unlikely the dramatic improvement in morbidity and mortality among premature infants with RDS, exogenous surfactant therapy hasn't still demonstrated an equivalent potential in pediatric ALI and ARDS.

A great amount of the scientific production on surfactant therapy in children with ALI or ARDS consists of case reports or small (mostly unblinded) clinical trials. Surfactant has been evaluated in the treatment of pediatric ARDS due to near-drowning (18-19), RSV infection (20-22), cardiopulmonary bypass (23), severe aspiration (either of gastric content or toxic compounds, i.e. hydrocarbon) (24-26). In all these studies, exogenous surfactant overall was found to determine at least a transient clinical improvement in the patient treated, and this was more considerable in conditions whose pathophysiology is based on the extreme dilution of the surfactant endogenous pool (i.e. fresh water near-drowning). However, the extreme heterogeneity of the conditions treated and the lack of uniformity on the criteria used to evaluate any lung recovery (i.e. improvement of gas exchange, reduction in ventilatory requirement or oxygen supply, possibility of weaning from the ventilator, increased lung compliance…) make this amount of literature noteworthy but lacking any evidence-based support.

A meta-analysis of six trials of exogenous surfactant replacement therapy in children with acute respiratory failure showed decreased mortality and decreased duration of mechanical ventilation (27). However, the large heterogeneity between patients enrolled in those studies somewhat reduces the strength of inferences that can be made regarding the effect of surfactant on the secondary outcomes of ventilator-free days and duration of PICU stay, as authors question about the reproducibility of treatment effects generated from relatively small unblinded clinical trials (21, 22, 28-30).

Very few trials in pediatric critical care suggest a favourable impact on mortality (31).

In summary, review of the recent literature on the potential role of surfactant replacement therapy in pediatric ALI and ARDS fail to confirm any striking benefit, although it is undisputable that surfactant could be an adjunct at least in selected cases of pediatric respiratory failure. Nonetheless, many issues still remain about the optimal dosage (is in older children a pro kg dosage feasible?), timing of administration (rescue treatment or prophylactic treatment, before the lungs had been exposed to the noxious effects of mechanical ventilation for long periods?), delivery strategy (intratracheal bolus versus bronchoalveolar lavage) and patient selection (is surfactant efficacy higher in patients with direct lung injury?). Thus large, prospective, randomized clinical trials to clarify these issues are needed.

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