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Review

Surfactant therapy for acute respiratory distress in infants

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Abstract

Acute respiratory distress syndrome (ARDS) remains the primary indication for admission to paediatric intensive care units and accounts for significant mortality, morbidity and resource utilization. Respiratory infections, in particular pneumonia and severe bronchiolitis, are the most common causes of respiratory failure requiring mechanical ventilation in infants and children. This paper reviews the pathophysiology of ARDS and the management of paediatric patients with acute lung injury. Data indicate that adoption of a lung protective ventilation with low tidal volumes and of an open-lung ventilation strategy, characterized by sufficient positive end-expiratory pressure (PEEP) to avoid atelectasis, provides the greatest likelihood of survival and minimizes lung injury. The relative benefits of strategies such as high frequency oscillatory ventilation (HFOV), inhaled nitric oxide (iNO), recruiting manoeuvres and prone position are also considered.

Moreover this article examines exogenous lung surfactant replacement therapy and its efficacy in the treatment of paediatric ARDS. In infants and children with acute lung injury the endogenous surfactant system is not only deficient, as observed in preterm infants, but altered *via* a variety of other mechanisms like inhibition and dysfunction. All factors contribute to the altered physiology seen in ARDS. The role of exogenous surfactant in lung injury beyond the neonatal period is therefore more complex and its limited efficacy may be related to a number of factors, among them inadequacy of pharmaceutical surfactants, insufficient dosing or drug delivery, poor drug distribution or, simply, an inability of the drug to counteract the underlying pathophysiology of ARDS. Several trials have found no clinical benefit from

various surfactant supplementation methods in adult patients with ARDS, however some studies have shown that this therapy can improve oxygenation and decrease mortality in some specific clinical conditions of paediatric ARDS. Further studies in the paediatric field are therefore needed to clarify aspects of drug composition, dosage, dilution and timing of delivery and new researches must be carried out on development of more robust pharmaceutical surfactants.

Keywords

Acute respiratory distress syndrome, infants, lung protective ventilation, surfactant, recruiting maneuvers, prone position.

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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 at birth, due to a lack of mature alveolar type II epithelial cells. There is also evidence of surfactant dysfunction in many forms of acute respiratory distress syndrome (ARDS) in paediatric age, 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. ARDS in infants and children develops, indeed, mainly from the impaired production and inactivation of surfactant and it is a many-sided pathology that also includes prominent aspects of inflammation, vascular dysfunction, oxidant injury, cellular injury and oedema. Moreover, unlike with premature infants for whom 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 ARDS paediatric patients due to inflammation leading to increased pulmonary vascular permeability and loss of aerated lung tissue.

Definition of ARDS

ARDS is a disease syndrome caused primarily by increased permeability to proteins across the pulmonary endothelial and epithelial barriers and is characterized as a restrictive disease with reduced lung compliance caused by loss of surfactant function, atelectatic lung regions and accumulation of interstitial/alveolar plasma leakage [1]. Patients usually develop acute respiratory failure rapidly because of arterial hypoxaemia, as well as impaired carbon dioxide excretion and elevated work of breathing.

Recently ARDS was given a new definition, the so-called Berlin Definition [2], and has been classified into three categories on the basis of the degree of hypoxaemia in order to provide better grading of prognosis and treatment selection:

- mild: 200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg;
- moderate: 100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg;
- severe: PaO_2/FiO_2 ≤ 100 mmHg.

Four other variables are considered for the diagnosis of ARDS:

- timing: within 1 week of a known clinical insult or new or worsening symptoms;
- chest radiograph: bilateral opacities consistent with pulmonary oedema not fully explained by effusions, lobar/lung collapse or nodules/masses;
- origin of oedema: respiratory failure not fully explained by cardiac failure or fluid overload;
- positive end-expiratory pressure (PEEP) level: equal to or greater than 5 cm H_2O, which may be delivered noninvasively in the mild ARDS group.

The common underlying diseases that may originate ARDS in infants and children can be divided into two main groups:

- direct lung injury, that include pulmonary viral or bacterial infections, aspiration (e.g. gastric aspiration, meconium aspiration in infants) or more rarely other conditions such as near-drowning, inhalation of smoke or other toxicants and thoracic trauma;
- systemic or indirect causes of lung injury, that comprise septic shock or less frequently hypovolemic shock, generalized trauma, burn injury and other primary extra-pulmonary injuries. Indirect forms of ARDS have

a substantial multi-organ pathology that significantly affects long term patient outcomes, frequently reducing the impact and effectiveness of pulmonary-based therapies like exogenous surfactant administration [3, 4].

Although the incidence of ARDS is relatively low from a population-based perspective, the severity of the illness, as demonstrated by mortality rate (~11-25%), is quite high [5]. The diverse underlying conditions and triggering diseases across the ages explain why paediatric ARDS shows a remarkable variability in epidemiology, prognosis, and management.

Pathophysiology of acute respiratory distress syndrome

ARDS is characterized by an initial injury that triggers cell-mediated mechanisms releasing a cascade of a variety of mediators, which alter the integrity and function of the cellular linings of the alveolar-capillary unit. Hyaline membranes, flooded alveoli with protein-rich oedema fluid, infiltrates of polymorphnuclear neutrophils, macrophages and erythrocytes are the leading histological hallmarks of ARDS [1, 6, 7]. The net effect at cellular level is massive cell damage, alveolar denudation and sloughing of cell debris into the lumen of the alveolus. Surfactant function is inactivated by leakage of plasma proteins and its production is further diminished by damage to type II pneumocysts [8]. The degree of inflammation depends on the imbalance between pro- and anti-inflammatory cytokines and a close interrelationship exists between inflammatory mediators and the coagulation cascade [9, 10]. Activation of pro-coagulative factors and inhibition of fibrinolysis have been identified to produce platelet-fibrin thrombi in small pulmonary vessels [11, 12].

On the clinical level, work of breathing increases secondary to surfactant depletion, alveolar filling, cellular debris within the alveoli and increased airway resistance. Surfactant loss leads to alveolar collapse because of increased surface tension. The remaining viable lung may be considered as being smaller rather than stiff and as little as 25% of its volume may be participating in gas exchange. During mechanical ventilation, lung inhomogeneity due to the presence of regions of collapse (reversible lung closure) or consolidation (irreversible lung closure) results in much of the inspired tidal volume being directed toward the remaining and largely reduced open lung regions. Uninjured portions of the lung may then become over-distended if exposed to excessive inflating pressures (volutrauma) and are thus subject to potential complications from air leaks. Alveolar instability also results in repetitive opening and closure of the collapsed areas during the respiratory cycle, which may cause shear forces that in addition worsen lung injury (atelectrauma).

Moreover a widened interstitial space between the alveolus and the vascular endothelium decreases oxygen-diffusing capacity and collapsed alveoli result in low ventilation-perfusion units or in right-to-left pulmonary shunt: the net effect is severe impairment of oxygenation. Severe pulmonary hypertension may also develop from hypoxia, hypercarbia, and small-vessel thrombosis and can result in increased right ventricular work, right ventricular dilatation and, eventually, in left ventricular outflow tract obstruction secondary to intraventricular septal shifting toward the left ventricle. These changes, in turn, may decrease cardiac output and further reduce oxygen delivery to vital organs.

For resolution, the dynamic interaction between inflammation, coagulation, restoration of water transport and cell function needs to be rebalanced and surfactant production restarted. Unfortunately, in some patients resolution is hampered: histologically, these patients show alveolar fibrosis along with persistence of inflammatory cells and only partial resolution of pulmonary oedema. In the long term, permanent abnormalities in respiratory function and reduced health-related quality of life may be observed.

Surfactant dysfunction in acute respiratory distress syndrome

The pathogenesis of lung surfactant alterations in ARDS is complex and the pathways by which its activity can be compromised during acute pulmonary injury are many and not yet fully understood. These include reduced surfactant synthesis by injured type II cells, dilution of surfactant material by oedema fluid, surfactant functional inhibition by plasma constituents and increased breakdown by activated oxidative and hydrolytic pathways. Each of these mechanisms may contribute to surfactant dysfunction to varying degrees in individual patients. 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 may compromise surfactant function [13-15].

Albumin and other plasma proteins impair surface activity primarily by competitive adsorption, which reduces the entry of active surfactant components into the alveolar air-water interface with resultant dysfunctional film formation [16]. By contrast, cell membrane lipids or fatty acids act in part by mixing into the surface film thus compromising its ability to reach low surface tension during dynamic compression, whereas proteases, phospholipases and reactive oxygen-nitrogen species act by an oxidative disruption of surfactant lipids and proteins essential to its function [13, 16, 17]. Another mechanism of surfactant dysfunction is the depletion or impairment of activity of the 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 broncho-alveolar lavage (BAL) of patients with ARDS. However, it is 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 ARDS [19, 20].

All these data support the theoretical utility of exogenous surfactant supplementation, but it seems unlikely that its use in infancy and childhood could follow the same strategy employed in premature infants characterized by administration of high doses by bolus, as the aetiology of surfactant deficiency differs between these age groups.

Mechanical ventilation: treatment strategies

Positive pressure mechanical ventilation with supplemental oxygen is the cornerstone of treatment of severe hypoxaemia, but careful attention must also be given to nutrition, sedation, analgesia, cardiopulmonary interactions and fluid balance. Over the past decades patho-anatomical and computerized tomographic studies have demonstrated the uneven distribution of aerated areas and dense consolidated regions of the lung affected by ARDS: the remaining alveolar surface for gas exchange was found to be largely reduced in adult patients and Gattinoni introduced the term "baby lung" to represent this condition [21]. The use of large tidal volumes (10 ml/kg) may cause a remarkable overdistention of the "baby lung" resulting in loss of compliance. Based on these observations the concept of ventilator induced lung injury (VILI) evolved during the 1990s and VILI is now considered to initiate and to sustain lung injury (secondary lung injury) following a similar histological and inflammatory pattern to that of the original ARDS. Current opinion is that secondary lung injury may be reduced using a lung protective strategy [1, 4, 22] characterized by:

- low tidal volumes < 8 ml/kg of predicted body weight in order to avoid overdistension;
- sufficient PEEP in order to maintain functional residual capacity (FRC) above closing volumes and to minimize repeated alveolar collapse and re-expansion. Unfortunately definitive data do not exist to guide PEEP management for paediatric ARDS patients. The right strategy is to balance the cardiorespiratory effects of higher PEEP by determining the optimal relationship between increased pulmonary compliance, reduced dead-space ventilation and satisfactory haemodynamics, while maintaining adequate oxygenation. Optimal oxygen delivery may not occur at the point of maximal arterial oxygen content, because this may correspond to excessive mean intrathoracic pressure and, thus, lower cardiac output. It is likely that individual patients respond differently to diverse PEEP levels: infants with recruitable lung may benefit from a more aggressive PEEP strategy whereas in patients with non-recruitable lung a more aggressive PEEP strategy might worsen outcomes;
- plateau pressure limited to 30 cm H_2O or less.

If achievement of a normal pH and normal $PaCO_2$ requires respiratory support strategies that are potentially damaging to the lung, lower pH and higher $PaCO_2$, compared to normal levels, should be tolerated to minimize this risk. Permissive hypercapnia is therefore acceptable to reduce tidal volumes or plateau pressure, but $PaCO_2$ should remain ≤ 50-55 mmHg and balanced by serum bicarbonate levels to determine a pH above 7.20. Adult data have demonstrated a significant improvement in mortality with this approach, which has also gained widespread acceptance in the paediatric field although no large-scale randomized controlled trials (RCTs) have been performed to date. If adequate oxygenation and ventilation cannot be met with the lung protective strategy, the following therapeutic tools should be considered: exogenous surfactant, inhaled nitric oxide (iNO), high frequency oscillatory ventilation (HFOV), recruitment manoeuvres and prone position.

Surfactant treatment of paediatric acute respiratory distress syndrome

Respiratory infections, in particular pneumonia and severe RSV bronchiolitis, are the most common causes of respiratory failure requiring mechanical ventilation 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 [23]. 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 RCTs of surfactant in intubated and mechanically ventilated children with acute respiratory failure (trials enrolling neonates or patients with asthma were excluded), Duffett et al. [24] showed that surfactant was associated with significantly lower mortality and positive effects on several other secondary outcome measures, such as more ventilator-free days to day 28, significantly shorter duration of mechanical ventilation, shortened duration of intensive care unit stay and lower use of rescue therapy. Transient hypotension and transient hypoxia were the most commonly reported adverse events. Observational studies conducted in mechanically ventilated infants with viral pulmonary infection have demonstrated lower concentrations of surfactant lipids in BAL fluids or endotracheal aspirates [25, 26], which could be explained by viral invasion of type II pneumocytes and altered regulation of the production of surfactant lipids. The observation of lower levels of surfactant phospholipids during viral pulmonary infections leads to the hypothesis that exogenous surfactant might improve the clinical outcome of affected infants. A recent meta-analysis [27], which included three small RCTs enrolling 79 participants, suggested that the use of surfactant for critically ill infants and children with bronchiolitis may decrease the duration of mechanical ventilation 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 and the small cohorts 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.

Many of the published works have evaluated surfactant delivery in paediatric age *via* intratracheal instillation: a large quantity of surfactant is generally delivered by this route, which may be of benefit in counteracting the effect of surfactant inhibition. However, this large quantity delivery can also result in flooding of the central airways and lead to increased airway resistance and worsening of hypoxaemia. Moreover, uniform delivery of surfactant to both collapsed and expanded parts of the lung might improve atelectasis in affected regions but may be harmful in unaffected areas. An alternative is bronchoscopic segmental administration [28, 29], however this technique is not always easy to perform in clinical practice. BAL with diluted surfactant is another modality of supplementation that could have greater efficacy as surfactant is supplied simultaneously with removal of inhibitors from the alveoli [30, 31].

Therefore, surfactant supplementation remains a great challenge for ARDS treatment in infants and children but larger trials are necessary to test different modalities of dosage, dilution and supplementation not only for different lung diseases but also for different paediatric ages. Moreover, the inherent costs of surfactant preparations and the risk of inactivation urge the search for new synthetic and less expensive surfactant preparations with properly designed analogues of SP-B and SP-C [32]. Probably this strategy will allow an early and no more compassionate use of surfactant supplementation.

Inhaled nitric oxide

Hypoxaemia in ARDS is mainly caused by ventilation/perfusion mismatch with increased intrapulmonary shunting and pulmonary hypertension. Inhaled nitric oxide has been shown to be an ideal selective pulmonary vasodilator improving oxygenation and decreasing pulmonary artery pressure. In a multicentre RCT, iNO improved oxygenation at 12 and 24 h, however by 72 h there was no difference between the treatment and the placebo group [33]. Subgroup analysis suggests that iNO was more efficacious than placebo in patients with severe hypoxaemia, but

despite these effects mortality was not reduced. These data suggest that iNO may be effective in specific clinical conditions and perhaps this is the reason why its use persists despite no clear evidence of efficacy.

High frequency oscillatory ventilation

With HFOV it is possible to ventilate the patients in the so-called "safe zone of the pressure/volume curve" preventing volutrauma and atelectrauma: consequently, the main goals of lung protective ventilation may theoretically be achieved with this technique. For the treatment of paediatric ARDS, only one prospective RCT on HFOV has been conducted: it was found that physiological parameters, oxygenation and lung recruitment improved, but the duration of mechanical ventilation and 30-day mortality did not differ between the HFOV and the control group [34]. Moreover, in the conventional group large tidal volumes were employed and this factor could have favoured the HFOV group. A recent multicentre RCT compared the outcomes of adult patients affected by ARDS and treated with the open-lung approach or HFOV [35]. The trial demonstrated that early application of HFOV does not reduce, and may increase, in-hospital mortality. Thus the use of HFOV in paediatric patients should be carefully considered on an individual basis.

Recruiting manoeuvres

Lung recruitment is considered an addition to lung protective strategy and in part it counteracts the chronic derecruitment that occurs secondary to low tidal volume ventilation. This chronic derecruitment, coupled with the acute derecruitment that occurs with each circuit disconnection and the application of suction to the airways, contributes to the incidence of VILI. Lung recruitment is a strategy to increase transpulmonary pressure and to maximize the number of alveoli participating in gas exchange, particularly in distal and dependant regions of the lung and it can be achieved by either a sustained inflation (SI), ranging from 25-40 cm H_2O and held for a period of 10-30 seconds in the paediatric field, or by briefly increasing PEEP, or by an incremental increase in both peak inspiratory pressure (PIP) and PEEP [36]. These methods aim to overcome alveolar threshold opening pressures and/or to overcome alveolar threshold closing pressures. This may improve oxygenation, gas exchange and end-expiratory levels. Restoration of end expiratory levels and stabilization of the alveoli may reduce the incidence of VILI. These interventions should be considered in children with early ARDS and severe hypoxaemia, although their effects may be transitory in a subset of patients. But there is also the potential risk that some children will be non-responders to lung recruitment and that this manoeuver may in fact simply overdistend already recruited alveoli, particularly in proximal regions. Moreover, the increase of the intrathoracic pressure during the recruitment manoeuvre provokes an unavoidable reduction in venous return and therefore of cardiac output. Additionally, overdistension of alveoli will increase the regional pulmonary vascular resistance and will subsequently decrease regional perfusion. The current evidence does not allow a consensus to be reached on which method is most effective, nor on which patients are most appropriate to lung recruitment manoeuvres: for these reasons their clinical use is still controversial. Nevertheless, bedside monitoring of alveolar recruitment by transthoracic lung ultrasound is increasing in clinical practice and in the near future it should became a powerful tool for monitoring and estimating the effects of recruitment manoeuvres on lung expansion in real time.

Prone positioning

Decreased lung compliance in patients with ARDS is the result of uneven distribution of transpulmonary pressure with hyperinflation of nondependent (sternal) zones and collapse and/or consolidation of dependent (dorsal) ones, in which there is also an increased interstitial fluid retention. Prone positioning determines, under the influence of gravity and reducing the compression of the lungs by the heart, changes in the distribution of transpulmonary pressure and pulmonary perfusion in the dependent lung regions and may be helpful in reducing the amount of collapsed areas and in facilitating the drainage of secretions. In the prone position the application of PEEP or alveolar recruitment manoeuvres can distribute the pressures more homogeneously, leading to more uniform lung expansion [37].

Two recent papers have shown that early and prolonged application of the prone position reduces mortality among adult patients with severe ARDS receiving protective lung ventilation [38, 39]. The failure of this technique may be due to the late start of its application, when the dependant areas of the

lung are already consolidated, or to an excessively short duration of the treatment. However the prone position is not without problems: the patients are at increased risk of pressure ulcers, obstruction of the endotracheal tube, dislodgement of the thoracostomy tube and they may have an increased need of sedation and difficulties with enteral feeding, but these adverse events probably occur above all in centres with personnel who use prone positioning infrequently [39].

Also if a recent meta-analysis concluded that in hospitalized infants and children affected by acute respiratory distress the prone position is significantly superior to the supine position in terms of oxygenation [40], currently there is not enough evidence to recommend its use routinely in the paediatric field, but its employment must be considered in infants affected by severe ARDS.

Conclusions

The cornerstone of ARDS management is the early and correct intensive care treatment of the primary cause (e.g. pneumonia, sepsis) and prevention of its side effects and complications as VILI and multiple organ failure: this strategy may improve outcomes and increase survival. It has already been shown that surfactant therapy is beneficial in several lung-injury applications in 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 ARDS is not a single disease but the end result of many different types of acute pulmonary injuries. However, it is likely that this therapy will find a significant place in the treatment of paediatric ARDS when some important problems have been resolved, such as the strategy for surfactant administration and the capacity of new synthetic surfactants to resist inhibition by substances that leak into the alveolar space.

Declaration of interest

The Authors declare that there is no conflict of interest.

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