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REVIEW

# Exogenous Surfactant Treatment in Children with ARDS

**LUCA TORTOROLO • ORAZIO GENOVESE • ENZO PICCONI • MARCO PIASTRA • GIORGIO CONTI**

LUCA TORTOROLO ( ✉ )
ORAZIO GENOVESE •
ENZO PICCONI •
MARCO PIASTRA •
GIORGIO CONTI
Paediatric Intensive Care
University Hospital A. Gemelli
Rome, Italy
Phone:+39- 0630155203
Fax: +39-06-30155283
E-mail: luca.tortorolo@gmail.com

## ABSTRACT

*Since the Food and Drug Administration (FDA) approved exogenous surfactant in the early 90s for the treatment of neonates with Hyaline Membrane Disease (HMD), many studies have focused on enlarging its indications for others types of lung injuries and for other age groups. Although in the past 20 years no studies have shown clear results about the efficacy of exogenous surfactant treatment in paediatric Acute Respiratory Distress Syndrome (ARDS), many of them were able to point out and better define very important aspects of this treatment like dosage, timing, ways of administration and usage of different types of surfactant (natural and synthetic). In this review we retrace the development of studies looking at the role of exogenous surfactant treatment in paediatric ARDS.*

**Key words: surfactant, ARDS, bronchoalveolar lavage.**

## Introduction

Despite the development of many different therapeutic strategies (High Frequency Oscillatory Ventilation - HFOV, Nitric Oxygen - NO, Non Invasive Mechanical Ventilation, surfactant and corticosteroids) for the management of Acute Respiratory Distress Syndrome (ARDS), none of them achieved statistically significant results in terms of beneficial effects on primary outcomes (1) and in paediatric patients, with ARDS mortality remaining high (>40%) in the last 10 years. (1-4) Among the various strategies used to fight ARDS, treatment with exogenous surfactant is supported by the strongest experimental evidence: in many animal models of ARDS, (5-9) and in children with ARDS, (1,4,10-12) it is clearly evident that synthesis of surfactant is decreased while surfactant inactivation and consumption is increased. The alveoli of ARDS children show a lack of surfactant active forms (large aggregates) and an increase in small aggregates that are the catabolic products of surfactant and are functionally inactive. (4) This impairment in surfactant function is closely associated with alterations in pulmonary function that characterize children with ARDS. (4) Although in animal models the administration of exogenous surfactant is able to change the course of ARDS, when it is studied in children its beneficial effect is weak or totally absent. (4-12) We would like to analyze the reasons for this, focusing our attention on dosage, modality of administration and type of surfactant used. ARDS is different from HMD and treatment differs.

## ARDS Pathophysiology

Acute respiratory distress syndrome is a lung pathology induced by diverse injuries, including trauma, sepsis, liquid aspiration, inhaled gases, radiation, pneumonitis and many others. ARDS is characterised by damage to the arteriolar-capillary endothelium and alveolar epithelium, including type I and type II pneumocytes. (3) Damage to the latter results in surfactant deficiency and atelectasis. Even though surfactant abnormalities in ARDS are not the primary pathogenic factor, surfactant deficiency, either in the presence or absence of type II pneumocyte alterations, may result from primary or secondary inhibition or inactivation of pulmonary surfactant in the alveolar space. (3-13) Surfactant deficiency and inactivation will further induce alveolar collapse and pulmonary oedema, leading to the characteristic pathophysiology of ARDS. (3-13)

ARDS was first described in 1967. (14) It is characterized by fast, acute development of clinically significant hypoxemia, with the appearance of diffuse pulmonary infiltrates, such as seen in the case of lung edema. Edema results from increased vascular permeability, which does not appear due to left-side cardiac impairment or increased pressure in the left atrium (pulmonary wedge pressure is lower than 18 mmHg). With regard to the level of hypoxemia, we distinguish between the milder form, where the ratio between the partial oxygen pressure in arterial blood and inspired

oxygen concentration ($PaO_2/FiO_2$) is between 300 and 200, and the severe form, named ARDS, where the $PaO_2/FiO_2$ ratio is lower than 200. (15) This definition has been recently revised as the 'Berlin Definition' and was published in JAMA. An important factor in ARDS development is probably also genetic predisposition, which contributes to the response of the organism to direct or indirect triggers of lung impairment. Observed direct triggers include pneumonia, drowning, aspiration of stomach contents, inhalation of smoke or irritant gases, fat embolism, thoracic bruise and alveolar hemorrhage, while indirect causes include, among others, sepsis, transfusion, shock, pancreatitis and overdose of salicylates or narcotics. ARDS can affect patients of all ages. (15) Therapy is primarily oriented toward the treatment of hypoxemia, and identification and treatment of the direct cause of respiratory distress. (16)

In the case of newborns and babies, severe forms of respiratory failure (ARDS) can be treated by high-frequency oscillatory ventilation, and when severe pulmonary hypertension is present, we add a selective dilator of pulmonary vessels, NO gas in doses of 20 to 40 parts per million (ppm). Exogenous surfactant is also used for newborns and babies, as ARDS involves secondary deficiency of the natural surfactant, which results in lung collapse. (17)

In the last 10 years, the use of exogenous surfactant in the treatment of respiratory disorder of newborns has significantly reduced the mortality of premature babies; nevertheless, it remains the main cause of death of such infants. Respiratory distress suffered by a newborn, results from two pathophysiological mechanisms: surfactant deficiency and action of surfactant inhibitors. (4-17) After birth, the lungs of neonates are still full of fluid, and functionally and morphologically immature. They have low functional residual capacity and insufficient amount of surfactant. (4-17)

## Surfactant Treatment

Pulmonary surfactant used as a medicinal product is a natural surface-active substance obtained from animal lungs (e.g. porcine surfactant). It contains almost exclusively phospholipids, especially phosphatidylcholine (approximately 70% of the total content of phospholipids) and around 1% of specific low-molecular hydrophobic proteins SP-B and SP-C. (18) The surface-active substance in the alveoli mostly consists of phospholipids and specific proteins. It covers the inner surface of the alveoli, with its principal task being to reduce surface tension in the lungs. (18) The reduction of surface tension is crucial for the stabilization of the alveoli and prevention of their collapse at the end of an exhale, so that adequate gas exchange is maintained throughout the ventilation cycle. (18)

Regardless of the cause, deficiency of this surface-active agent in the alveoli of premature neonates results in severe respiratory insufficiency, known as respiratory distress syndrome (RDS) or hyaline membrane disease. RDS is the main cause of acute mortality and acute morbidity of newborns, and perhaps also responsible for long-term respiratory and neurological consequences. (18) When administered intratrachealy, the natural surfactant, as an exogenous surface-active substance, compensates for the lack of the endogenous surface-active substance in the alveoli. The properties of a natural surfactant as a surface-active substance enable its even distribution in the lungs and spreading on the surfaces where air and fluid meet in the alveoli. The physiological and therapeutic effects of a natural surfactant in the case of surface-active substance deficiency in the alveoli are extensively documented for various animal models. In all studies published, no safety concerns have been reported. (18) There were no adverse drug reactions (ADRs), namely events that were considered by neonatologists to be related to study treatment. The reported adverse events (AEs) were those typically associated with prematurity. More than three hundred publications can be selected in PubMed using the search term "Curosurf or poractant alfa". Literature confirms that surfactant therapy is the standard of care in the management of preterm neonates with RDS, a specific disease of premature neonates. The benefits of surfactant treatment, including the reduction of mortality and incidence of pulmonary air leaks, especially of pneumothorax, in neonates suffering from RDS, counterpoise any risks.

## Paediatric studies

Compared to neonates, only a few studies or case reports have been published on the use of surfactant in critically ill children or adults with ARDS. No specific risks were described in all these papers. Despite discouraging findings in adults, (19) most of them due to evident bias in term of type of surfactant, (20) dosage and way of administration, (20) the first studies published using surfactant in paediatric ARDS were able to underline some important issues: 1) a trend to improve gas exchange and pulmonary mechanics early after surfactant instillation in the endotracheal tube; 2) a dilution of this effect over time with a return after 12-24 hours to the pre-surfactant treatment situation; 3) no or few effects on primary outcomes, such as duration of mechanical ventilation, Intensive Care Unit (ICU) length of stay (LOS) and mortality. (19) Compared to adults, the weakness of paediatric studies included the small sample size of the enrolled patients and their heterogeneity in age and weight. (19) On the other hand, paediatrics patients were much more homogenous than adults in regard to underlying diseases (primary and secondary lung injuries), way of administration (endotracheal instillation), dosages (range 50- 100 mg/kg) and type of surfactant used (all used natural surfactant with adequate concentration of protein). (19) Willson and Luchetti (21,22) focused their attention on primary lung injured patients and on a restricted group of babies with brochiolitis (those were also more homogenous in terms of age and weight). They were able to show a beneficial effect of exogenous natural surfactant treatment on primary out-

come as days on mechanical ventilation, days of ICU LOS and mortality. The same studies were utilized and analysed by Duffet in his meta-analysis in 2007. (19) He confirmed that in children on mechanical ventilation with primary lung injuries, endotracheal instillation of 50-100 mg/kg of surfactant reduced days of mechanical ventilation, days of ICU LOS and in some way, mortality. These results are much more encouraging compared to the failure of using surfactant in adult ARDS as reported in 1996 by Anzueto in his randomized control trial (RCT). (23) He enrolled more than 400 patients but he used a synthetic surfactant with no proteins and he administered it by aerosolization over 24 hours via the endotracheal tube. Later this strategy resulted in less than 5% of a not very active surfactant reaching the ARDS alveoli. (20) Otherwise Anzueto's study weight in terms of sample size influenced for a long period of time the negative feeling about exogenous surfactant treatment in ARDS out of the neonatal age. After Duffet's meta-analysis, no other randomized controlled trials were published on the topic in paediatric patients except Willson's trial published just last month. Unexpectedly it showed no benefit of using Calfactant in children with direct lung injury, overturning the findings of their previous studies. They concluded it may have occurred due to weak distribution caused by the absence of recruitment manoeuvres, increased concentration and less volume of Calfactant solution used in the study. They also enrolled an extremely heterogeneous group of children aging 2 months to 18 years. This study highlighted all the difficulties associated with arranging a good quality RCT with an adequate sample size. The need for huge, multicentre trials developing over a long period of time and facing heterogeneity in regards to case definition, underlying disease, age, associated strategy of treatment, sets of mechanical ventilation etc. with the high risk of spending a lot of resources and time and having little prospects of getting clear results, restrained researchers from planning such a study. On the other hand, some experimental studies (24-30) speculated that endotracheal instillation could not be the best way of surfactant administration in ARDS lungs, arguing that especially in the latest stage, ARDS lungs are unevenly ventilated with part of the alveoli completely filled of inflammatory proteins, cells and debris. This prevented homogenous distribution of surfactant in all regions of the lungs and moreover, most of these inflammatory factors are strong surfactant inactivators decreasing rapidly over time the efficacy of exogenous surfactant treatment. (4) In different ARDS animal models, (24-29) bronchoalveolar lavage compared to tracheal instillation showed a more powerful and more lasting beneficial impact on gas exchange. The best results were obtained when bronchoalveolar lavage, using a diluted surfactant solution, (24) was followed by a supplementation of exogenous surfactant with regular instillation. This procedure, increasing the volume of solution used until 10-15 cc/kg, was able to: 1) achieve better distribution of exogenous surfactant in all alveoli despite their nonnhomogeneity, 2) reduce the total amount of surfactant utilized and 3) use the detergent proprieties of surfactant as a safe, soft and potent lavage solution. A total volume above 10cc/kg could generate side effects such as hypoxia, bradycardia, impairments of gas exchange and vagal reflex. (29) These animal studies on exogenous surfactant lavages are very impressive but in the literature there are no trials in humans except for a few small studies done in adults and in older children using the bronchoscope. (31-33) The bronchoscope allows reduction of the total volume of lavages to 1-3 cc/kg, decreasing side effects from larger volumes but it requires a lot of expertise in the management of such respiratory unstable patients during this invasive procedure. Nevertheless, in treated subjects most of the studies showed an improvement in gas exchanges.

In smaller infants, the only study using diluted surfactant via bronchoalveolar lavage was done in neonates with Meconium Aspiration Syndrome (MAS). (34) In this model, nonnhomogeneity of aerated versus collapsed areas of lungs, presence of inflammatory factors, inactivation of surfactant and severe lung injury are quite similar to the ARDS situation: MAS neonates suffered more from inactivation of surfactant than from a deficit of its synthesis. This RCT showed that in this category of neonates with severe lung injury, bronchoalveolar lavage with exogenous surfactant was able to reduce the need for extra corporal membrane oxygenation (ECMO) and mortality in hospital without ECMO, in respect to standard of care. Furthermore, we found many case reports describing bronchoalveolar lavage with diluted surfactant in ARDS children using, either bronchoscope manoeuvres (older child) or direct tracheal lavages (smaller child). Despite ARDS, the etiology was very different (sepsis, near drowning, trauma, and aspiration syndrome) and all of them showed a rapid decrease of ventilator settings and improvement of lung mechanics after the treatment. Primary outcomes were not evaluated. (30,32,35,36)

Recently we reported 14 patients with severe ARDS (Oxygen Index $>$ 20) not responding to HFOV, NO or corticosteroids that took advantage of bronchoalveolar lavages with diluted surfactant (8mg/ml) done 3 times in the 3 different classic positions. Gas exchange and pulmonary mechanics improved rapidly after the procedures and in half of the patients a second treatment was needed after a median time of 12 hours. No side effects were reported and these results were presented at ESPR 2007 in Prague. (30)

## Conclusion

Although recent preliminary studies using surfactant bronchoalveolar lavages in paediatric patients with ARDS are encouraging, no definitive results were obtained and a RCT facing questions about time, dosage and way of administration has not yet been done. The major reasons for this are: 1) high cost

of exogenous surfactant; 2) difficulty in planning a suitable trial; 3) no specific therapeutic indication in children with the absence of standardization for timing, dosage and way of administration. All these factors are strictly correlated and the absence of an indication and standardization in children with ARDS has resulted in most paediatric intensivists using it only on an experimental basis in neonates with severe ARDS not responding to all other therapies. This means, to face ARDS in the latest stages when lungs become very inhomogenous, full of inflammatory factors obstructing alveoli and lower airways. In this advanced state, inflammatory factors that fill alveoli inactivate easily most of the endogenous surfactant further worsening lung injury and gas exchange. (13) Late treatment has a high risk of failure due to few substances reaching the alveoli. Moreover, the small amount of exogenous surfactant that reaches the airways peripherally is rapidly inactivated. (4) Surfactant bronchoalveolar lavage seems to act better than simple instillation because it uses a larger volume and has better peripheral distribution especially in severely injured lungs. (37) Bronchoalveolar lavage cleans up inflammatory factors that inactivate surfactant and reduce the dosage of exogenous surfactant left in the lungs after lavage. There is no standardized dose of natural exogenous surfactant either for lavages or for supplementation but most authors used a 10 times diluted solution of surfactant (5 to 10 mg/ml) with a total volume of 3 to 5 cc / kg, leaving in the lungs, at the end of the procedure, 25 mg to 50 mg /kg of natural surfactant as supplementation.

Using exogenous surfactant in the early stage of ARDS could be associated with lower dosage, better distribution and better efficacy. When lungs are less injured, other ways of administration could also be used, such as simple instillation or aerosolization because some new experimental studies (38-40) have shown a good distribution of these less invasive tools especially when lungs have not yet deteriorated.

Other investigations in exogenous surfactant treatment in ARDS examined the possibility of using different types of synthetic surfactant. (41) A recent type of synthetic exogenous surfactant seems to overcome the old problem related to their scares efficacy. This new synthetic surfactant has a synthetic protein which seems to be more resistant to inactivation. We can speculate that in the near future there will be different types of synthetic surfactant available for different types of lung illnesses and for different methods of administration (aerosol vs. instillation vs. lavages). To verify all the possible developments of exogenous surfactant treatments with definitive results and to standardize it according to timing, way of administration, stage of illness, type of surfactant used and ARDS handling associated strategy, will be very difficult. To design a rigorous trial, RCT, with a high risk of generating an extremely long, expensive and uninterpretable study will be challenging. Small experimental studies done with stable isotopes are promising and have already given us important data regarding endogenous and exogenous surfactant turn over and metabolism in premise, neonates and children with and without lung injury. (24-44) Stable isotopes could be very accurate for individualizing the correct timing, route of administration and dosage of different types of surfactant.

There is no magic bullet for managing ARDS in children. This is a multifactorial disease and different strategies have to act at different levels to deal with all the problems associated with ARDS and underlying diseases that often match with this lung injury. Exogenous surfactant could be one of these strategies helping to improve pulmonary mechanics and gas exchange and decreasing the need for mechanical ventilation that in turn consumes surfactant and worsens lung injury in the classical bimodal process of ARDS. Breaking this vicious cycle could be a key element in overcoming ARDS. In 2004 an editorial in the New England Journal of Medicine (45-47) was wondering why surfactant treatment in ARDS is still a matter of discussion despite the majority of trials done in the last 10 years showing no beneficial effects on primary outcome. Now we can affirm that surfactant's special status as "substance under prolonged investigation" suggests a new and interesting aspect extending it usage to different age groups and lung diseases.

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