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Original article

Exogenous surfactant, a role in the adult acute respiratory distress syndrome?

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Abstract. Adult ARDS still represents a high mortality disease. Exogenous surfactant trials in adults with ARDS failed to prove benefit on survival; anyway limitations of these studies were strongly debated. An Italian group of intensive care doctors, proceeding from trials observations, shared an exogenous surfactant protocol for the treatment of ARDS in adult patients. (www.actabiomedica.it)

Key words: exogenous surfactant, ARDS, hypoxia, mechanical ventilation

Introduction

Adult acute respiratory distress syndrome (ARDS) is one of the most challenging clinical frames for intensive care doctors. ARDS is caused by a variety of lung insults that result in a pro-inflammatory process involving alveoli, interstitium and lung endothelial vessels. This inflammatory state results in decreased lung mechanics and gas exchange. In 1994 an American-European Consensus Conference (1) standardized the definition of ARDS as diagnostic tool for better patient identification and studies stratification. From then on ARDS was still a syndrome with high mortality, a recent review (2) defined an approximately 40% mortality in adult patients, at the same time functional disability was still a major problem after recovery from lung disease (3). Despite great advances in ventilation, monitoring and treatments, many clinical trials on ARDS failed to prove benefit on survival. The only evidence based treatment was mechanical ventilation with the use of low tidal volumes with plateau pressure < 30 cmH_2O (4). Other strategies were investigated in the last 20 years such as: optimal PEEP level (*5*), recruitment manoeuvres (6), high frequency oscillatory ventilation (ongoing OSCAR and OSCILLATE trials will help to define its role in ARDS), prone positioning (*7*), extracorporeal membrane oxygenation (*8*) and several different pharmacological therapies (*9*). Thus far none of these enlisted techniques was considered to be lifesaving in adult patients with ARDS.

Exogenous surfactant trials in adult ards

In late nineties, pulmonary researchers focused on surfactant replacement in adult ARDS; this idea arose from neonatal experience where exogenous surfactant administration demonstrated a mortality reduction in preterm infant with RDS (10) and meconium aspiration syndrome (11). Early clinical phase II trials on adults were encouraging (12, 13), and so phase III trials with larger enrolment were performed with great expectation by the investigators, anyway all these randomized control trials (RCTs) failed to demonstrate beneficial effects on mortality (14-16).

A great debate developed on these RCTs design limitations. Composition of surfactant was one of the main objections addressed, synthetic surfactant with recombinant surfactant protein C as used by Spragg et al. (14, 16) contained only one protein compared with "modified" natural surfactants that are made up of two

surfactant proteins (SP-B and SP-C). The role of highest protein content was assumed to be the determinant factor in the beneficial effects of exogenous surfactant (17) not only for spreading and absorption but also for immunologic and anti-inflammatory properties (18, 19). The only natural surfactant used in an adult RCT was porcine surfactant HL 10 (15), the conclusion of this study was that natural surfactant HL 10 did not improve outcome and showed a trend toward increased mortality and adverse effects, anyway surfactant HL 10 is not actually on market and its safety profile is still uncertain.

Another key issue in exogenous surfactant administration was the dosage. It was recently reported that concentration of SP-B and disaturatedphosphatidylcholine (DSPC) in ARDS aspirates is definitely lower than in healthy subjects and that their turnover is very different with DSPC fractional synthesis rate 3-folds higher in adult ARDS patients (20). Despite these recent kinetic data it is not defined yet the dosage and the timing of re-administration of exogenous surfactant to reduce the surface tension in ARDS adult lungs. Lung mechanics after surfactant administration was studied only by Tsangaris I et al. (21) on 16 adults with thoracic trauma. Maybe before drawing a protocol for the next RCT, could be interesting to investigate what surfactant dosage is needed to better improve lung mechanics in adult patients with ARDS.

In addition, as postulated by Schmidt et al. (22), time of surfactant administration is crucial because surfactant degradation begins at very early stage of ARDS disease, on the other hand all RCTs were designed with exogenous surfactant administration when lung injury was established and relatively advanced. In addition, surfactant administration technique was stressed (23), an ideal way of administration has to instil surfactant in the most affected part of the lung selectively, to be safe and preferentially to clean the airway before the instillation.

The birth of an italian protocol for adults with ARDS

In March 2007 a group of Italian Intensive Care doctors, those have had practice in exogenous surfactant administration, joined up in a meeting that took place in Modena debating on literature evidences. A second meeting was performed on May 2008, where we decided to share an operative treatment protocol in order to standardize the treatment and to share results obtained. Protocol drew his inspiration from a previous experience reported in children by Marraro et al. (24) that performed a bronco-alveolar lavage (BAL) containing surfactant followed by surfactant instillation. The rationale of protocol was therefore based on the hypothesis that simple surfactant instillation was not sufficient because it could be inactivated by inflammatory mediators (*25*), these mediators can be in part removed by a previous BAL containing surfactant as detergent. Theoretically BAL procedure could allow a reduction of the amount of surfactant to be instilled afterwards.

BAL procedure

A preparation of 240 mg phospholipids (PHLs) in 100 mL of saline was used for BAL. The total volume was then divided in 5 aliquots to be separately administered to each pulmonary lobe. BAL was performed with a flexible bronchoscope. Twenty millilitres of diluted surfactant were applied for each lobe containing approximately 48 mg PHLs, left in place for about 5 seconds and gently withdrawn.

Supplementation procedure

After 30 minutes from the BAL procedure, a solution of 240 mg PHLs in 10 mL of saline was prepared for each lobe and administered by means of a flexible bronchoscope. If the patient, after 12 hours from the first treatment, showed a PaO_2/FiO_2>20%, a second BAL and the following supplementation were performed with the same procedure after 24 hours from the first administration.

The typical feature of our 2-step protocol consisted in the use of a low fixed dose for each patient, the early exogenous surfactant administration within 24 hours from patient's intubation and the administration of a porcine surfactant poractant alpha (Curosurf®, Chiesi Pharmaceuticals, Parma, Italy).

Table 1. ALI score in patients treated before the application of a surfactant Italian shared protocol and after the protocol implementation

Time-points	Basal	6 h	12 h	24 h	48 h	72 h
ALI score before protocol (Mean ± SD)	3,1±0,5	2,8±0,5	2,8±0,5	2,7±0,6	2,6±0,6	2,5±0,7
ALI score after protocol (MEAN± SD)	3,0±0,5	2,6±0,5	2,4±0,6	2,0±0,5*	1,9±0,5*	1,5±1,0*

*=p<0.05

A small retrospective experience

We retrospectively reported 10 adult patients with ARDS underwent exogenous surfactant, 5 patients treated before the protocol application and 5 patients treated after the protocol sharing. Patients treated before protocol application received with bronchoscope exogenous surfactant within 72 hours from ARDS diagnosis and supplementation was selectively performed without BAL; the dosage of PHLs administered was the same. After patient's intubation ventilator settings were adjusted as ARDSnet indications (*26*) and patients were treated for *compassionate use* only when severe hypoxia persisted. We tested the progression of the disease by means of an acute lung injury (ALI) score in both groups according to Murray et al. (27) which evaluated radiographic consolidation, hypoxemia, level of PEEP and static lung compliance (Tab. 1). Despite the small sample of this study, improvement of ALI score was statistically significant (p<0.05) in the 5 patients treated with the protocol, comparing 24, 48, 72 hours time-points with the basal value, while in no-protocol group ALI improvement was lower and no significant. No patients developed adverse events ascribable to exogenous surfactant administration.

Conclusions

Clinical trials reported negative outcomes and maybe after these evidences (*28*) no further studies will be performed on adult ARDS in the next future, anyway a final sentence on the role of exogenous surfactant on adult ARDS is not written yet. As we assumed with our protocol, a revised approach will be advisable learning from the limitations of the previous RCTs, early administration, natural tested surfactant and BAL may help to reach positive results. Moreover, a patho-physiological method have to be implemented as suggested by Dushianthan et al. (29); pulmonary surfactant during the acute phase of ARDS is reduced in production, degraded by alveolar plasma proteins and inactivated by hydrolyses or oxidation processes (20, 22, 30). Patients stratification must be targeted on these 3 dysfunction categories maybe with nonradioactive isotope surfactant precursors (20, 31) or other biomarkers, in order to identify adult patients with low production that will get real benefits from natural surfactant or patients with higher inactivation that will need novel synthetic formulations with phospholipase-resistant lipid analogs.

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