Surfactant medication for acute respiratory distress syndrome

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Introductory article

Aerosolized surfactant in adults with sepsis-induced respiratory distress syndrome

A Anzueto, RP Baughman, KK Guntupalli, JG Weg, HP Wiedemann, AA Raventos, F Lemaire, W Long, for the Exosurf Acute Respiratory Distress Syndrome Sepsis Study Group

Background. Patients with acute respiratory distress syndrome (ARDS) have a deficiency of surfactant. Surfactant replacement improves physiologic function in such patients, and preliminary data suggest that it may improve survival. Methods. We conducted a prospective, multicenter, double-blind, randomized, placebo-controlled trial involving 725 patients with sepsis-induced ARDS. Patients were stratified according to the risk of death at baseline (indicated by their score on the Acute Physiologic and Chronic Health Evaluation [APACHE III] index) and randomly assigned to receive either continuously administered synthetic surfactant (13.5 mg of dipalmitoylphosphatidylcholine per millilitre; 364 patients) or placebo (0.45 percent saline; 361 patients) in aerosolized form for up to five days. Results. The demographic and physiologic characteristics of the two treatment groups were similar at baseline. The mean (±SD) age was 50±17 years in the surfactant group and 53±18 years in the placebo group, and the mean APACHE III scores at randomization were 70.4±25 and 70.5±25, respectively. Hemodynamic measures, measures of oxygenation, duration of mechanical ventilation, and length of stay in the intensive care unit did not differ significantly in the two groups. Survival at 30 days was 60 percent for both groups. Survival was similar in the groups when analyzed according to APACHE III score, cause of death, time of onset and severity of ARDS, presence or absence of documented sepsis, underlying disease, whether or not there was a do-not-resuscitate order, and medical center. Increased secretions were significantly more frequent in the surfactant group; the rates of other complications were similar in the two groups. Conclusions. The continuous administration of aerosolized synthetic surfactant to patients with sepsis induced ARDS had no significant effect on 30 day survival, length of stay in the intensive care unit, duration of mechanical ventilation, or physiologic function. (N Engl J Med 1996; 334:1417±21)

The acute respiratory distress syndrome (ARDS) is characterised by a severe impairment in pulmonary gas exchange that occurs in critically ill patients following a variety of local and systemic insults. Although the list of potential causes is long, three conditions ± severe multiple trauma, large volume emergency blood transfusions, and the severe sepsis syndrome/septic shock ± are responsible for many of the cases seen in general intensive care units. Estimates of incidence have varied widely, particularly due to previous differences in definition, and values between 3.5 and 75 cases per year per 100,000 population have been frequently quoted. These figures translate into 10-15 cases of ARDS each year being seen in an average size district general hospital in the United Kingdom. This order of magnitude estimate immediately demonstrates the difficulty of conducting any effective research into the condition within a single treatment centre.

Although relatively uncommon, ARDS has attracted considerable research effort. This reflects the high mortality associated with the condition, which is often in excess of 50%, and the fact that patients with ARDS and the related multi-organ dysfunction syndrome occupy a disproportionate number of bed days in intensive care units and consume a considerable amount of their resources. Successful treatments for ARDS would therefore have important economic as well as individual patient benefits.

One approach that appeared promising in experimental trials and early pilot studies in man was the use of artificial surfactant replacement therapy. Natural surfactant is a complex mixture of surfactant proteins (SP-A, B and C), neutral lipids, and phospholipids released by type II alveolar cells. Surfactant has a vital role in the preservation of normal lung mechanics. It both reduces absolute surface tension at the alveolar
and allows surface tension to vary continuously with the size of the alveolus. These actions maintain lung fluid balance and reduce the work of breathing. Surfactant also has additional anti-inflammatory actions with some evidence for anti-cytokine and neutrophil stabilising roles in the lung.\(^7\)

The trial by Anzueto and co-workers\(^4\) was a logical extension of studies in both neonates with the respiratory distress syndrome (RDS) and patients with ARDS. Artificial surfactants are now routinely used in neonatal RDS with clinical trials showing significant reductions in mortality. In ARDS there is evidence for both a reduction in the quantity and function of surfactant. Type II alveolar cells may be damaged, reducing the synthesis and release of surfactant, the high concentrations of plasma proteins entering the alveolus may inhibit surfactant function, and protease and reactive oxygen species may also inhibit function. In theory therefore the addition of artificial surfactant in ARDS should improve outcome by reinfating collapsed lung units and reducing pulmonary shunt. Barotrauma should also be decreased by the postulated improvement in the distribution of ventilation.

Disappointingly, 30 day survival in the surfactant study was identical in both groups. The most obvious explanation is that the hypothesis tested was incorrect and surfactant function is irrelevant to outcome in ARDS. However, the study can be criticised on a number of technical issues. The artificial surfactant used, Exosurf, is protein free and does not contain surfactant proteins. These may be important in promoting surfactant function and preventing breakdown in the lung. Nebulisation was used as the method of delivery to the lung. This has been shown to result in less than 5% deposition of surfactant in the alveolus and to result in deposition predominantly in ventilated lung units only. In addition, the method of ventilation used and the level of PEEP significantly alter deposition. Finally, the patients were predominantly medical rather than postoperative with Gram positive organisms being the most common pathogens. The results of the study may not be applicable to different patient groups and, in particular, patients with trauma related ARDS may have a different response to surfactant.

Researchers in the field of ARDS (and the pharmaceutical companies) have developed a tradition of well conducted, large, multicentre, randomised, controlled clinical trials. The introductory article on surfactant treatment is a recent example of a long line of such studies in ARDS. Initial investigators focused on the mechanisms producing low pressure pulmonary oedema due to the often dramatic presentation of the syndrome with severe hypoxaemia and diffuse bilateral infiltrates on plain chest radiographs. This research continues to yield new insights into pathophysiology with recent evidence that the resolution of oedema involves an active cellular pumping process. However, within the last decade there has been a change in the direction of research with the discovery of a major acute inflammatory component to the lung injury that occurs in ARDS.\(^5\) This has coincided with the explosive growth in the basic science of acute inflammation driven by the range of new techniques available in the field of cellular and molecular biology. This work has generated a number of new hypotheses about the origins of acute lung injury and suggested novel approaches to treatment.

Single centre trials (unless they are major tertiary referral units) are unlikely to test new treatments for ARDS successfully because of the relatively low incidence of the condition. The need for well conducted, large scale, double blind clinical trials has not been neglected by the critical care community. This was highlighted in a recent editorial aptly entitled “An anecdote is an anecdote . . . but a clinical trial is data”.\(^6\) One of the main concerns of the editorial was the potential problems with the uncritical introduction and subsequent standard adoption of expensive and unproved technology; the case in point was adult extracorporeal membrane oxygenation (ECMO) in the intensive care environment. More recent reports of the use of haemofiltration in septic shock show that the grey area that exists between generation of hypotheses and established treatment in intensive care has not disappeared.

Clinical trials in ARDS

 Investigators in the field of ARDS have taken two basic approaches to treatment trials (figs 1 and 2). The first group have concentrated primarily on the lung alone while the second have viewed the lung injury as part of a systemic process and have targeted treatment in a more global manner.

The studies were identified by Medline accompanied by hand searching review articles and major critical care journals (table 1). Some studies on patients with severe sepsis (septic shock) are also included because of the large overlap between this syndrome and ARDS. It is likely that any treatment that would reduce mortality in septic shock would also reduce the incidence of ARDS and other organ dysfunction.

**Mechanical treatments aimed at improving lung function**

The intensive treating the lung in ARDS is faced with a basic dilemma summarised by the question of lung rest versus lung recruitment\(^2\) in the early stages of ARDS the process of alveolar flooding is not uniform. Functionally the lung in patients with ARDS consists of a systemic process and have targeted treatment in a more global manner.

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**Mechanical treatments aimed at improving lung function**

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of a distinct population of lung units, a reduced number of normal gas exchanging units, and an increased number of abnormal, flooded and collapsed units. The collapsed units are responsible for the large physiological shunt that is one of the characteristics of the illness. In addition there is a third population of partially collapsed and potentially recruitable lung units. Studies of lung mechanics and computerised tomographic scanning indicate that these partially collapsed units are in a dynamic state and can open and close during the respiratory cycle. If these units can initially be expanded and then stabilised gas exchange should improve and ultimate survival could increase. It was recognised at an early stage in A R D S research that the application of positive end expiratory pressure (P E E P) would often improve gas exchange and the serial examination of lung compliance curves suggested that the recruitment of collapsed lung units was a major mechanism for the improvement with P E E P.

There was also early recognition of the adverse effects of positive airway pressures, whether in the form of P E E P or produced by ventilation with high mean airway pressures. Cardiac output is reduced and barotrauma, in the form of recurrent pneumothoraces, occurs. Recently it has been recognised that even modest levels of positive airway pressure can cause lung damage, at least experimentally, and there is growing concern that the levels of P E E P and airway pressure that are so effective in improving gas exchange in the short term may worsen the acute lung injury process. These views have prompted the development of low pressure low volume ventilation strategies. The two conflicting views of lung management - recruitment versus rest - have been partially tested in controlled trials. The philosophy behind adult extracorporeal membrane oxygenation (E C M O) trials has been to reduce ventilatory support by using an external gas exchanging system. Outcome should be improved by reducing barotrauma and "allowing the lungs to heal". This hypothesis was tested in the N at ional H eart, L ung and B lood Institute in the late 1970s using arteriovenous bypass. Mortality in both control and treatment groups was extremely high (88% and 90%, respectively) with no significant improvement in outcome in the treatment group. A number of problems were apparent in the study including an atypical population with a high incidence of bacterial and viral pneumonia and significant coagulation problems associated with the prolonged bypass technique. Following the study enthusiasm for this approach fell in North America but a number of European groups continued with a modified technique of venovenous E C M O. Uncontrolled studies reported a significant improvement in outcome with survival in the region of 40%. This prompted a further controlled trial in North America of the modified E C M O technique. The study had a number of interesting features including the use of pressure controlled inverse ratio ventilation in the control group and the inclusion of a strict protocol driven treatment in both groups. Overall survival in both groups was similar to the uncontrolled European studies and significantly better than that in the original N ational A merican E C M O study. The very high mortality of the original E C M O study can probably be explained by the unusual case mix of the population and the complications of prolonged arteriovenous bypass. The second study emphasised the importance of using current controlled groups rather than historical ones when evaluating new intensive care technology. The alternative approach of recruiting collapsed lung units has also been investigated in randomised controlled trials. In one study P E E P was applied to patients at high risk of developing A R D S but did not affect the incidence of subsequent lung injury or related complications. M odern microprocessor technology has led to the development of large numbers of mechanical ventilators and ventilator modes, many of which have been used in A R D S. Some of these have been shown to be effective in the short term improvement of gas exchange but very few randomised controlled trials have studied longer term outcome in terms of survival. This is at least partly due to the less stringent requirements that new ventilator technologies have to meet in terms of proven efficacy compared with new drug treatments. High frequency jet ventilation has been compared with volume cycled ventilation in a randomised controlled study in adult patients with acute lung injury. No difference in outcome was found and treatment failures and crossovers occurred in both directions. The physiology of jet ventilation is complex and not completely understood and "improved" jet ventilators have been developed since the original studies. In addition, the success of other types of high frequency ventilation in the neonatal and paediatric population makes the re-evaluation of the technology in adults likely.

<table>
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NS = not significant; S = significant; NA = not applicable; ECMO = extracorporeal membrane oxygenation; P E E P = positive end expiratory pressure; P O E = prostaglandin E.
Pharmacological approaches to improving lung function

A number of studies have examined the effect of surfactant therapy in adult ARDS. In adults with ARDS, two relatively small initial studies reported significant benefits, but a large (n = 725) multicentre trial found no difference in outcome compared with placebo. The overall mortality of 40% in both groups was within expected limits for ARDS and there was also no significant difference in other primary endpoints including duration of mechanical ventilation, length of stay in the intensive care unit, or physiological function.

Another agent with local actions on the lung and a unique delivery system is nitric oxide (NO). It is a powerful gaseous vasodilator with additional anti-inflammatory properties and it can be delivered to the lung during mechanical ventilation. The selective vasodilation of ventilated lung units can result in improved pulmonary gas exchange in acute lung injury and the agent is currently the subject of randomised clinical trials in ARDS.

Local versus systemic treatment in ARDS

The above treatment strategies are linked by the idea that improving respiratory function and/or pulmonary gas exchange will improve outcome in ARDS. The fact that they have been unsuccessful challenges the view that agents and treatments that only act on the lung will be successful in treating ARDS. There is a large body of evidence that ARDS is often only one part of a fibrosing process occurring within the lungs of patients with ARDS and more subtle signs of multi-organ dysfunction occur in almost all cases.

Following an initial inciting stimulus a state of systemic inflammation occurs which is known as the systemic inflammatory response syndrome (SIRS). The immunological basis for the syndrome remains unclear but there is evidence of widespread acute inflammation in a variety of organs including the lung. This is confirmed by the presence in the air spaces of large numbers of neutrophils and other soluble inflammatory mediators including cytokines, proteases, and oxygen free radicals. Some inflammatory mediators may be locally produced in the lung but there is also evidence of early systemic inflammation with high circulating levels of acute phase proteins, cytokines, complement factors, and soluble adhesion molecules. The inflammatory response also precedes clinical evidence of acute lung injury with reports of both systemic and local (lung) inflammatory mediator production occurring before and, to some degree, predicting the onset of organ damage and failure.

Treatment in ARDS that is only focused on the lung may therefore not result in improvement in overall outcome.

Systemic anti-inflammatory agents in ARDS

**Corticosteroids**

The use of steroid treatment in a wide variety of inflammatory disorders has led a number of investigators to study their actions in ARDS. Three randomised placebo controlled studies have been performed, all with similar negative outcomes. High dose methyl prednisolone was given to 50 of 99 patients with established ARDS from a variety of causes. Treatment was started at a relatively early stage in the illness but, despite this, there was no difference in 45 day mortality (60% in the methyl prednisolone group, 35% in the placebo limb), reversal of ARDS, or infectious complications.

Sepsis and septic shock are major risk factors for the development of ARDS and other investigators have examined the possibility of preventing ARDS by the early use of steroid therapy. This approach is supported by a large body of experimental evidence indicating that steroid therapy given before a systemic insult may reduce or even prevent the development of organ injury. One study examined the effect of high dose methyl prednisolone on the subsequent development of ARDS in patients with septic shock. A total of 87 patients entered the study of whom 13 in the treatment group and 14 in the placebo group subsequently developed ARDS. Overall mortality was also similar with 22 deaths in the treatment arm and 20 in the placebo group.

A larger multicentre trial of the early use of methyl prednisolone in the prevention of ARDS in patients with septic shock enrolled 304 patients over a three year period. No difference in the subsequent development of ARDS was found (methyl prednisolone 32%, placebo 25%) but 14 day mortality in patients who developed ARDS was significantly higher (52%) than in the placebo group (22%). Despite these clearly negative results, research into the possible use of high dose steroids in ARDS continues. One major area of interest is the use of steroids in patients with the so-called fibroproliferative stage of ARDS. Serial studies of inflammatory markers in lung lavage fluid as well as lung biopsy tissue have shown that the process of lung injury in ARDS can evolve from an initial inflammatory and cellular stage to a more chronic, organising and fibrosing process. In many respects this is similar to the situation that occurs in more chronic interstitial lung disease. A subgroup of patients has been reported who remain ventilator dependent following the acute stage of their illness. A number of these patients have evidence of a continuing inflammatory process within their lungs as demonstrated by persistent elevation of neutrophils and cytokines in bronchoalveolar lavage fluid. Lung biopsy specimens showed a fibrosing process occurring in the lungs with no evidence of infection. High dose steroid therapy was reported to result in considerable improvements in gas exchange but, as yet, there are no data from a placebo controlled trial.

**Antioxidant therapy**

A large number of inflammatory mediators are released during the early stages of ARDS. One group of mediators which has attracted research interest are the oxygen free radicals. These are highly reactive species with unpaired electrons produced by both white blood cells and the endothelium. They cause oxidant related damage to a variety of cell structures including lipid peroxidation of cell membranes. Naturally occurring antioxidant systems exist to prevent this damage but these can be overwhelmed in times of high oxidant stress. The po-
tential importance of lung oxidant damage was shown in a study which found very low circulating levels of antioxidants in a group of high risk patients who later developed ARDS. N-acetylcysteine has an important antioxidant and free radical scavenger action and a number of uncontrolled studies have suggested that it might be effective in ARDS. However, a placebo controlled randomised study on 66 patients with ARDS found no difference in terms of overall outcome, lung compliance, or gas exchange.

**The Arachidonic Acid Cascade**

Eicosanoids are known as an antifungal agent but it is also a potent inhibitor of thromboxane A2 production. Thromboxane A2 is both a pulmonary vasoconstrictor and has pro-aggregation effects on platelets and white cells. An uncontrolled study reported that it might prevent the development of ARDS in high risk patients and this hypothesis was then tested in a randomised placebo controlled trial in 54 surgical patients admitted to a single intensive care unit. The study showed a reduction in ARDS (64%) in the placebo group, 15% in the ketoconazole group as well as a significant reduction in overall mortality. Although the study was relatively small and based on a single centre, the magnitude of the changes are impressive and the results of larger multicentre studies are awaited with great interest.

The potential anti-inflammatory benefits of arachidonic acid metabolites have also been investigated. Prostaglandin E1 (PGE$_1$) can prevent platelet aggregation, reduce neutrophil mediated inflammatory responses, and cause systemic pulmonary vasodilation. One hundred patients with established ARDS were randomised to receive either PGE$_1$ or placebo. Mortality in both groups was similar with a trend to higher mortality in the treatment group.

The neutrophil is a potential therapeutic target in acute lung injury and is currently great interest in the way in which the neutrophil interacts with the vascular endothelium. A series of adhesive steps are involved where binding occurs between complementary surface molecules on the neutrophil and endothelium resulting in neutrophil rolling, arrest, and transmigration into the tissues. One important group of adhesion molecules are the integrins and the integrin CD11b/CD18 plays a role in establishing firm adhesion between neutrophils and the endothelium.

Lipsosomal PGE$_1$ has significant anti-adhesive actions, probably as a result of binding and downregulating integrin molecules. The compound improved oxygenation and decreased ventilator dependency in a small multicentre study of patients with early ARDS and a trend towards decreased mortality was also reported.

**Conclusions**

These controlled trials of treatment in ARDS are important despite the mostly negative results. The studies were very difficult to perform and the ability of the coordinators of the most recent studies to recruit more than 700 patients into their trials is proof of the fact that intensive care medicine has established itself in the last decade as a mature discipline throughout Europe and North America. The studies also allow intensivists to begin to practise evidence based medicine and to avoid treatments that are of no use or may even be harmful.

It cannot, however, be denied that the trial results have been disappointing and require careful examination.
LEARNING POINTS

- A significant number of large, placebo controlled, randomised, controlled clinical trials of treatment have been performed in ARDS.
- These can be broadly divided into those that attempted to improve lung function/gas exchange and those that were targeted at systemic inflammatory or circulatory changes.
- The majority of interventions, including a recent large multicentre study on surfactant replacement, have been ineffective or even harmful.
- To date no large scale multicentre, randomised, controlled clinical trial has been able to demonstrate a definite benefit of a specific treatment in ARDS.
Surfactant medication for ARDS


