The Turkish Journal of Pediatrics 1996; 38: 45-50

EXOGENOUS SURFACTANT THERAPY IN NON-RESPIRATORY DISTRESS SYNDROME*

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SUMMARY: Greenough A. (Department of Child Health, King's College School of Medicine and Dentistry, London, United Kingdom). Exogenous surfactant therapy in non-respiratory distress syndrome. Turk J Pediatr 1996; 38: 45-50.

There is clinical evidence of the benefit of exogenous surfactant therapy to certain neonates with severe respiratory failure, diaphragmatic hernia, pneumonia and meconium aspiration syndrome. There still remain, however, important unanswered questions regarding, for example, optimum dosage and method of administration; appropriate randomized trials must be undertaken. *Key words: surfactant replacement therapy, neonatal respiratory disorders.*

Exogenous surfactant replacement therapy (SRT) has a well-established place in the treatment of respiratory distress syndrome. Data, however, are becoming available that SRT may also have a role in the management of other neonatal respiratory disorders[1]. The aim of this review is to examine the evidence for surfactant dysfunction/deficiency in such disorders and the efficacy of SRT in animal models and infants.

Severe Respiratory Failure

Bronchoalveolar lavage (BAL) studies[2] have demonstrated that in adult respiratory distress syndrome (ARDS) there is reduction in dipalmityl phosphatidylcholine and increasing accumulation of proteinaceous edema fluid which interferes with the alveolar surfactant monolayer. Studies involving animal models, however, have suggested that the response to SRT will depend on the mechanism by which ARDS has been produced; SRT is only effective in restoring the pressure-volume characteristics of an ARDS model created by serial lavage resulting in progressive surfactant depletion, but not in those involving hypoxia resulting in proteinaceous edema or administration of an antibody to surfactant protein B (SP-B).

In clinical use, surfactant replacement therapy has been particularly useful in infants who are described as having respiratory distress syndrome (RDS) at term. Infants, all greater than 37 weeks of gestational age with an a/A ratio ≤ 0.23, were given Survanta (100 mg/kg in up to four doses)[3]. Twenty-three of the 29 patients had a clinically significant response, that is greater than a 25 percent reduction in the oxygen index. Prior to surfactant the mean oxygen index was

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30, and SRT significantly reduced this to 12 ($p < 0.01$)[3]. In contrast, in seven infants with severe respiratory failure due to either pneumonia, aspiration of blood or hemorrhagic pulmonary edema, all of whom required a mean peak pressure of 30 cmH_2O and at least 90 percent inspired oxygen concentration, the response to Curosurf was variable. A rapid improvement in two patients, show improvement in four and no improvement in one patient occurred, although there were no side effects.

Surfactant "deficiency" has also been demonstrated in infants whose respiratory failure was so severe they needed axtracorporeal membrane oxygenation (ECMO). In a group of such patients[4], 18 with meconium aspiration syndrome and four with pneumonia, serial sampling of tracheal aspirates for phospholipid and surfactant protein A (SP-A) content demonstrated a mean increase of 200 percent in the levels in the 72 hours prior to weaning from ECMO. Those infants with the greatest improvement in surfactant status had the fastest weaning from ECMO. The results suggested that SRT could have a role in shortening the duration of ECMO. That hypothesis was tested by administering Survanta (up to four doses) to infants requiring ECMO for meconium aspiration syndrome, group B streptococcal sepsis with pneumonia, respiratory distress syndrome and pulmonary hypertension of the newborn[5]. On days 2 and 3, the compliance of the infants who had received surfactant was significantly greater than that of the placebo group. There was also a trend in the surfactant group towards a shorter time to extubation and duration of oxygen therapy, as well as a younger age at discharge. The only statistically significant difference, however, was the duration of ECMO, being a mean of 107 hours in the surfactant group and 139 hours in the control group (5).

Congenital Diaphragmatic Hernia (CDH)

Biochemical immaturity of the surfactant system has been demonstrated in several animal models. Comparison of neonatal rats with or without diaphragmatic hernia (CDH) demonstrated, not surprisingly, that the rats with CDH had lower lung weights, DNA and protein contents as well as lower amounts of disaturated phosphatidylcholine. Similarly, in a lamb model in which a diaphragmatic hernia was created surgically at 80 days of gestation, the lambs with CDH compared to the controls not only had smaller lungs, lower total lung capacity and reduced compliance, but also a reduction in the percentage of phosphatidylcholine and an increase in lavage protein and surface tension. SRT in such a lamb model resulted, therefore, in predictable improvements. Fifty mg/kg of Infrasurf in "CDH" lambs was associated with a significant improvement in oxygenation, compliance and lung volume when compared to controls.

In humans, there is also evidence for surfactant abnormalities in CDH-affected patients[6]. The lung compliance and pressure-volume loops of such patients are

similar to surfactant-deficient infants. Hyaline lung membrane formation, immature amniotic fluid lecithin: sphingomyelin (L:S) ratios and absence of phosphatidyl glycerol in the amniotic fluid are found postmortem. There is a differential effect between the lungs, with the ipsilateral lung being more affected than the contralateral lung, as evidenced by a decrease in the phospholipid fraction. To date in the literature, however, there is very little evidence to suggest that SRT is efficacious in infants with CDH. Three infants who received 100 mg/kg of Infrasurf prior to the first breath have been reported. The patients survived despite a predicted mortality of 80 percent[7]. This mortality was estimated as the infants all had prenatal diagnosis, polyhydramnios, dilated stomach in the chest, a patch closure of the defect and a ventilation index greater than 1000.

Pneumonia

In all types of animal models, in "infective" pneumonia there is evidence of surfactant dysfunction and some evidence of SRT efficacy. For example, influenza virus adversely affects the type II pneumocytes, reducing the phospholipid content. In such a model, SRT improved survival from zero to 75 percent Mycoplasma pneumonia is associated with reduction in lung compliance, abnormal lung pressure-volume curves, a decrease in sphingomyelin and an increase of palmitic acid. In humans, BAL studies have shown that in bacterial pneumonia there is reduced surface tension, SP-A and lung lavage phospholipids. In an animal model of bacterial pneumonia, SRT improved lung compliance to normal levels. There is some evidence to suggest that gram-negative rather than gram-positive bacterial pneumonia may be more deleterious to the surfactant system and that this may be an endotoxin effect. The endotoxin may cause injury to the type II cells, producing an abnormal quantity and composition of surfactant, with a reduced L:S ratio, phosphatidyl glycerol and amount of palmitic acid in the phosphatidyl choline. Functional changes also occur as evidenced by a reduction in total lung capacity, static compliance and diffusing capacity, with an increase in pulmonary arterial pressure. There is also evidence to suggest that aspiration pneumonia, involving acid aspiration and pulmonary edema, is associated with a reduction in surfactant function and hyaline membrane formation. In a rabbit model of aspiration, SRT improved lung recoil.

One study has suggested that surfactant treatment of congenital pneumonia may improve respiratory status[8]. Fourteen infants, with either meconium aspiration syndrome or pneumonia and requiring an inspired oxygen concentration of 1.0 and a mean airway pressure of 13-15 cmH_2O with a pre-treatment a/A ratio of 0.09, were given 90 mg/kg of calf lung surfactant extract (CLSE). A further three doses were administered if they still required an inspired oxygen concentration greater than 0.5 and a mean airway pressure of at least 7 cmH_2O. The first dose

of SRT was associated with an immediate improvement in the a/A oxygen ratio. None of the infants required ECMO, died or was oxygen-dependent for more than 14 days.

Our own experience using a synthetic surfactant (Exosurf) has been more mixed; certain infants have showed a rapid improvement in oxygenation as shown by a decline in $AaDO_2$, others have shown no improvement and some have subsequently had a pulmonary hemorrhage. There has been reported a similar mixed response to Alveofact; 15 infants who reguired an inspired oxygen greater than 0.5 and peak inspiratory pressure greater than 22 cmH_2O were given 50 mg/kg of Alveofact eight hours after birth. They received three further doses of Alveofact if necessary, but unfortunately they required the same inspired oxygen concentration 12 hours after treatment as pre-treatment. Ten of the infants died, four of respiratory failure, four of sepsis and two of intracranial hemorrhage[9].

Meconium Aspiration Syndrome (MAS)

Meconium has been shown to displace surfactant from the alveolar surfaces and inhibit surfactant's surface tension lowering function. This, however, can be overcome if a high enough concentration of surfactant is given[10]. The effect of human meconium is dose-dependent. In an experimental newborn rabbit, 65 mg/ml of human meconium resulted in a 27 percent reduction in lung thorax compliance, whereas 130 mg/ml brought about a 38 percent reduction. Separation of human meconium into the water methanol soluble phase (protein and bilirubin) and the chloroform soluble phase (fatty acids, triglyceral and cholesterol) demonstrated the latter to have the highest activity against surfactant, as measured in a pulsating bubble[11].

Studies in animal models of MAS have demonstrated some efficacy of SRT. Animals given 3 mg/kg of human meconium showed a 30 percent improvement in oxygenation following administration of CLSE immediately and 67 percent at one hour. This was also associated with no change in compliance, and a 44 percent increase in resistance[12]. In a piglet model, lavage with Survanta was more efficacious than saline lavage or suction only. Although there were no radiographic or pathological differences between the groups, immediate improvement in oxygenation, as shown by a decrease in the oxygen index, was demonstrated in the surfactant lavage group[13].

Experience in human infants has been variable. In infants greater than 37 weeks gestation with a/A ratios less than 0.23, Survanta (100 mg/kg up to six doses) resulted in 14 of 20 infants having a clinically significant response, that is a greater than 25 percent reduction in the oxygen index. Only one infant deteriorated. The mean oxygen index pre-surfactant was 36 and at one hour post-surfactant

was 24[3]. Our own experience with Exosurf has been mixed; some infants had a modest improvement in oxygenation, but certain infants went on to require high frequency oscillation (HFO), one infant died and another ultimately had to be rescued by ECMO. Similarly, with Alveofact (50 mg/kg, one to four doses) begun at four to eight hours, there was a varied response: six of 10 infants did not respond, and although no infant deteriorated and all survived, two infants required HFO and one ECMO.

Conclusion

Preliminary evidence from clinical studies suggests that SRT may be useful in a variety of neonatal respiratory disorders. Key issues still, however, need to be addressed before this therapy can be used optimally in non-RDS respiratory failure. For example, the characteristics of those patients most likely to benefit should be identified. Pilot data suggests natural rather than artifical surfactant to be most useful, but there are no comparative studies. Dosage should be carefully determined, although in meconium aspiration syndrome, existing results suggest that a dose regimen higher than that used in RDS should be employed. The method of administration may also influence efficacy; lavage or nebulization could offer advantages.

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