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THE EFFECT OF EXOGENOUS SURFACTANT REPLACEMENT THERAPY ON LUNG FUNCTION*

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SUMMARY: Yüksel B, Greenough A. (Department of Child Health, King's College Hospital, London, England). The effect of exogenous surfactant replacement therapy on lung function. Turk J Pediatr 35: 53-57, 1993.

Exogenous surfactant replacement therapy, regardless of type, reduces mortality and morbidity. We have reviewed the existing data to determine the effect this form of treatment has on lung function. Several studies have demonstrated that surfactant replacement therapy improves compliance, but the timing and magnitude of the effect is variable. The effect is dependent firstly on the type of surfactant used, natural surfactant being associated with a more rapid effect than artificial surfactant; secondly whether the surfactant is given as rescue or therapy as prophylaxis and thirdly the gestational age of the infant treated. Preliminary evidence also suggests that surfactant replacement therapy may influence lung function in the long term, since infants treated with surfactant rather than a placebo have lower airways resistance and higher specific conductance at follow-up. These preliminary reports are encouraging because they suggest that exogenous surfactant replacement therapy may have the additional benefit of reducing chronic respiratory morbidity associated with premature birth. *Key words: lung function, premature birth, respiratory distress syndrome, surfactant.*

Surfactant deficiency was recognized as the cause of respiratory distress syndrome many years ago[1]. Unfortunately, early studies of surfactant replacement therapy yielded disappointing results[2, 3]. In the early 1980s, however, both a natural[4] and a artificial surfactant[5] were used apparently with good clinical effect. Over the last decade there has been an explosion in the number of surfactants available[4-10]. Their efficacy has been assessed in a large number of trials, which have demonstrated that exogenous surfactant replacement therapy, regardless of type, reduces mortality[11-14] and morbidity[9, 14-16]. We have reviewed the existing data on the effect of surfactant replacement therapy on lung function. Our aims were firstly to determine factors influencing the acute effects of exogenous surfactant on lung function and secondly to assess if this therapy was likely to affect the long term respiratory morbidity frequently associated with premature birth[17].

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Lung function abnormalities in surfactant deficient infants

Surfactant is a surface tension lowering agent which promotes alveolar stability[18] and protects epithelial surfaces[19]. As a consequence, the presence of an adequate surfactant monolayer reduces the work of breathing[19]. In surfactant deficiency, the lungs become atelectatic, with a decrease in lung compliance[19]. Lung function measurements reveal affected infants to have both a low compliance and low functional residual capacity (FRC)[20]. Thus surfactant replacement therapy would be predicted to improve both these lung function abnormalities.

Acute changes in lung function following surfactant replacement therapy

A variety of studies have demonstrated that surfactant replacement therapy is associated with an improvement in compliance, but that the timing and magnitude of the effect is variable[21-24]. Natural surfactant has an immediate effect on lung function, with the improvement in compliance occurring at the same time as the reduction in requirement for respiratory support[22]. These rapid effects may occur as a consequence of natural surfactant being recruited into the existing alveolar monolayer and thus immediately "functional". In contrast, artificial surfactants have a slower onset of action[5, 9, 21, 25]. No significant difference was noted between infants given an artificial lung expanding compound (ALEC) or placebo in the resuscitation period[26] or one hour after treatment[27]. The administration of ALEC was associated with an improvement in lung compliance only six hours after the initial therapy had been given. The improvement in lung function became more significant at 24 hours[21]. Artificial surfactants, rather than being recruited into the monolayer, may instead be taken up into the Type II pneumocytes where they are utilized to produce the infant's own surfactant which subsequently affects lung function. This sequence is likely to explain the apparent delay in effect of the artifical surfactant; as endogenous surfactant is recycled with a "cycle-time"[28] which is similar to the duration of the delay of action of ALEC on lung compliance.

Whether surfactant is given as prophylaxis or as rescue therapy, it also influences its effect on lung function. The administration of ALEC is only associated with an improvement in compliance when given as prophylaxis[21], but not as rescue therapy[29]. The latter trial, however, was small and the possibility of a type II error cannot be ignored. The effect of exogenous surfactant on lung function is also influenced by gestational age. A significant improvement in compliance following ALEC was only noted in infants of less than 30 weeks of gestation, but not in those greater than that level of maturity[9].

More recently, the effect of surfactant on FRC has been assessed. One study demonstrated, in response to human surfactant, an immediate increase in FRC

but, surprisingly, a reduction in respiratory compliance[30]. This combination of changes in lung function was explained by the possible alteration in the shape of the static recoil pressure characteristics of the diseased lungs which could occur as a result of treatment[31]. The FRC of the surfactant-deficient ventilated infant, however, would be predicted to be low. Thus, it is surprising that any single treatment could increase the FRC to such a level that the position on the pressure/volume curve would be so shifted as to be associated with a reduction in compliance.

Longer term effects of surfactant replacement therapy on lung function

Measurements of compliance at 7 and 28 days after treatment have suggested that the effect of surfactant on lung function may be short-lived[24, 32]. No significant differences in compliance were noted at 7 days following administration of ALEC or placebo[21]. Similarly, pulmonary resistance was significantly decreased at 2, 3 and 14 days following surfactant, but there was no difference at 28 days, compared to controls[24]. In contrast, a recent study has found that lung function measured by plethysmography at 7 months of age was better in infants given Exosurf than those administered placebo. The former group had significantly lower airways resistance and higher specific conductance[33]. These apparently conflicting results may be explained by the known effects of surfactant. The lower survival rate of the placebo groups may suggest that the "control" infants with severe lung function abnormalities die during the perinatal period. Thus, this would bias the lung function data obtained immediately outside the perinatal period in favour of the controls. Surfactant replacement therapy also, however, reduces acute respiratory complications, such as air leak, an important determinant of the degree of abnormality of lung function in the first year of life[34]. Thus it is not surprising that Exosurf-treated infants were found to have significantly better lung function at 7 months of age[33]. Abnormal lung function at 6 months of age is a highly specific predictor of chronic respiratory morbidity persisting into the second year of life[34]. Thus, these preliminary reports[33] are extremely encouraging because they suggest that exogenous surfactant replacement therapy may reduce the chronic respiratory morbidity associated with premature birth[17].

REFERENCES

1. Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. *Am J Dis Child* 97:517, 1959.
2. Robillard E, Alaire Y, Dagenais-Prerusse P, et al. Microaerosol administration of synthetic beta-gamma-dipalmitoyl-L-alpha-lecithin in the respiratory distress syndrome: a preliminary report. *Can Med Assoc J* 90:55, 1964.
3. Chu J, Clements JA, Cotton EK, et al. Neonatal pulmonary ischemia. Part I: Clinical and physiological studies. *Pediatrics* 40:709, 1967.

4. Fujiwara T, Maeta H, Chida S, et al. Artificial surfactant therapy in hyaline membrane disease. *Lancet* 1:55, 1980.
5. Morley CJ, Bangham AD, Miller N, Davis JA. Dry artificial lung surfactant and its effect on very premature babies. *Lancet* 1:64, 1981.
6. Shapiro DL, Notter RH, Morin FC 3d, et al. Double-blind, randomized trial of a calf lung surfactant extract administered at birth to very premature infants for prevention of respiratory distress syndrome. *Pediatrics* 76:593, 1985.
7. Speer CP, Robertson B, Curstedt T, et al. Randomized European multicentre trial of surfactant replacement therapy for severe neonatal respiratory distress syndrome: single versus multiple doses of Curosurf. *Pediatrics* 89:13, 1992.
8. Hallman M, Merritt TA, Schneider H, et al. Isolation of human surfactant from amniotic fluid and a pilot study of its efficacy in respiratory distress syndrome. *Pediatrics* 71:473, 1983.
9. Morley CJ, Greenough A, Miller NG, et al. Randomized trial of artificial surfactant (ALEC) given at birth to babies from 23 to 34 weeks gestation. *Early Hum Dev* 17:41, 1988.
10. Stevenson D, Walther F, Long W, et al. The American Exosurf Neonatal Study Group I. *J Pediatr* 120:53, 1992.
11. Ten Centre Study Group Ten centre trial of artificial surfactant (artificial lung expanding compound) in very premature babies. *Br Med J* 294:961, 1987.
12. Soll RF, Hoekstra RE, Fangman JJ, et al. Multicenter trial of single-dose modified bovine surfactant extract (Survanta) for prevention of respiratory distress syndrome. Ross Collaborative Surfactant Prevention Study Group. *Pediatrics* 85:1092, 1990.
13. Dunn MS, Shennan AT, Hoskins EM, et al. Two-year follow-up of infants enrolled in a randomized trial of surfactant replacement therapy for prevention of neonatal respiratory distress syndrome. *Pediatrics* 82:543, 1988.
14. Collaborative European Multicentre Study Group Surfactant replacement therapy for severe neonatal respiratory distress syndrome: An international randomized clinical trial. *Pediatrics* 82:683, 1988.
15. Merritt TA, Hallman M, Bloom BT, et al. Prophylactic treatment of very premature infants with human surfactant. *N Engl J Med* 315:785, 1986.
16. Konishi M, Fujiwara T, Naito T, et al. Surfactant replacement therapy in neonatal respiratory distress syndrome. A multi-centre, randomized clinical trial: comparison of high-versus low-dose of surfactant TA. *Eur J Pediatr* 147:20, 1988.
17. Greenough A, Maconochie I, Yüksel B. Recurrent respiratory symptoms in the first year of life following pretern delivery. *J Perinat Med* 18:489, 1990.
18. Jobe A, Ikegami M. Surfactant for the treatment of respiratory distress syndrome. *Am Rev Respir Dis* 136:1256, 1987.
19. Van Golde LM, Batenburg JJ, Robertson B. The pulmonary surfactant system: biochemical aspects and functional significance. *Physiol Rev* 68:374, 1988.
20. Hjalmarson O. Mechanics of breathing in respiratory distress syndrome. In Raivio KO, Hallman M, Kouvalainen K, Volimoki I (eds). *Respiratory Distress Syndrome.* London: Academic Press, 1984, pp 171-185.
21. Morley CJ, Greenough A. Respiratory compliance in premature babies treated with artificial surfactant (ALEC) *Arch Dis Child* 66:467, 1991.
22. Davis JM, Veness-Meehan K, Notter RH, et al. Changes in pulmonary mechanics after the administration of surfactant to infants with respiratory distress syndrome. *N Engl J Med* 319:476, 1988.
23. Couser RJ, Ferrara TB, Ebert J, et al. Effects of exogenous surfactant therapy on dynamic compliance during mechanical breathing in preterm infants with hyaline membrane disease. *J Pediatr* 116:119, 1990.

24. Bhutani V, Abbasi S, Long WA, Gerdes JS. Pulmonary mechanics and energetics in preterm infants who had respiratory distress syndrome treated with synthetic surfactant. *J Pediatr* 120:S18, 1992.

25. Morley CJ. On behalf of the trial collaborators. Ten centre trial of artificial surfactant (ALEC) in very premature babies. *Br Med J* 294:991, 1987.

26. Milner AD, Vyas H, Hopkin IE. Effect of exogenous surfactant on total respiratory system compliance. *Arch Dis Child* 59:369, 1984.

27. Milner AD, Vyas H, Hopkin IE. Effects of artificial surfactant on lung function and blood gases in idiopathic respiratory distress syndrome. *Arch Dis Child* 58:458. 1983.

28. Jacobs H, Jobe A, Ikegami M, Jones S. Surfactant phosphatidylcholine source, fluxes, and turnover times in 3-day-old, 10-day-old, and adult rabbits. *J Biol Chem* 257:1805, 1982.

29. Greenough A, Morley CJ, Wood S, et al. Effect of surfactant on lung function in preterm neonates. *Second International Surfactant Symposium.* Basel: Karger, 1984.

30. Edberg KE, Ekström-Jodal B, Hallman M, et al. Immediate effects on lung function of instilled human surfactant in mechanically ventilated newborn infants with IRDS. *Acta Paediatr Scand* 79:750, 1990.

31. Goldsmith LS, Greenspan JS, Rubenstein SD, et al. Immediate improvement in lung volume after exogenous surfactant: alveolar recruitment versus increase distention. *J Pediatr* 119:424, 1991.

32. Goldman SL, Bosque E, McCann E, Lewis K. Pulmonary mechanics in premature infants one month after treatment with synthetic surfactant. *J Pediatr* 120:S25, 1992.

33. Yüksel B, Greenough A, Gamsu HR. Respiratory function at follow-up after neonatal surfactant replacement therapy. *Early Hum Dev* 1992, (in press).

34. Yüksel B, Greenough A. Persistence of respiratory symptoms into the second year of life: predictive factors in infants born preterm. *Acta Paediatr Scand* 1992, (in press).