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European Multicenter Trials of Curosurf for Treatment of Neonatal Respiratory Distress Syndrome

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Abstract. Curosurf, a preparation of polar lipids and hydrophobic proteins isolated from porcine lungs by liquid-gel chromatography, is currently used in European multicenter trials for prevention and treatment of neonatal respiratory distress syndrome (RDS). In babies requiring artificial ventilation with 60–100% oxygen, tracheal instillation of a single dose of Curosurf (200 mg/kg) leads to a dramatic improvement of gas exchange and reduced mortality, without increasing the incidence of neurodevelopmental handicap among survivors. Several factors, including high ventilator pressure and oxygen requirements, have a negative impact on the therapeutic response, suggesting that the patients should be treated at a comparatively early stage of the disease. Clinical trials testing this hypothesis, as well as the effect of multiple treatment doses, are in progress.

Key words: Neonatal respiratory distress syndrome—Curosurf—Polar lipids—Porcine lungs—Multicenter trials.

Introduction

Treatment with exogenous surfactant improves the odds for survival and reduces the incidence of air-leak complications in babies ventilated mechanically for severe respiratory distress syndrome (RDS). Similar therapeutic effects have been obtained with human surfactant isolated from amniotic fluid [1] and with bovine surfactant extract fortified with synthetic lipids [2–5]. Yet another clearly effective surfactant substitute, Curosurf [6], is isolated from minced porcine lungs by a combination of washing, centrifugation, chloroform : methanol extraction and liquid-gel chromatography [7]. All these preparations

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contain, besides a bulk of surface active lipids, the specific hydrophobic surfactant-associated polypeptides, SP-B and SP-C; human surfactant isolated from amniotic fluid by sucrose-gradient centrifugation contains, in addition, the hydrophilic surfactant-associated protein, SP-A. This latter protein is probably involved in the transformation of secreted lamellar bodies into tubular myelin, but may not be an essential component of surfactant preparations designed for replacement therapy.

For reasons not well understood, some babies with RDS respond only transiently to surfactant replacement. Furthermore, a large number of surfactant-treated patients suffer from a left-to-right shunt through a patent ductus arteriosus which may require pharmacological or surgical intervention, and bronchopulmonary dysplasia (BPD) remains an important problem among survivors [1–6]. We have analyzed data from a large consecutive series of babies receiving Curosurf for severe neonatal RDS to identify factors influencing the clinical response and to provide guidelines for new treatment protocols. The complete data from this study will be reported elsewhere (Collaborative European Multicenter Study Group, submitted for publication).

Patients and Statistical Methods

A total of 164 babies with severe RDS were treated with Curosurf at neonatal intensive care units in Amsterdam, Belfast, Groningen, Göttingen, Lund, Paris, Parma-Pavia-Mantua, and Stockholm. The first 77 patients were enrolled during 1985–87 in a randomized multicenter trial [6], and the new series of 87 consecutive patients were treated during the following one year period at the same units. Since there was, in the first trial, a striking improvement in the clinical outcome among surfactant-treated babies [6], a nontreated control group was no longer used. Criteria for entry included birth weight 700–2,000 g, age at treatment 2–15 h, clinical and radiological findings typical of RDS [8], and requirement of artificial ventilation with at least 60% oxygen. All babies were treated with a single large dose of Curosurf (200 mg/kg), instilled into the central airways via a feeding tube as previously described [6].

Clinical data from these patients were subjected to multiple regression and logistic analysis. The independent variables were birth weight, gestational age, sex, asphyxia as reflected by the Apgar score at 5 min, inborn (yes/no), maternal steroid treatment (yes/no), hospital allocation (Amsterdam, Belfast, etc., as listed above), and the following data recorded at entry: age, FiO_2, PaO_2/FiO_2, a/APO_2, pH, peak insufflation pressure, and mean airway pressure. Dependent variables were a/APO_2 6 and 24 h after treatment, time in ventilator, time in >21% oxygen, and mortality.

Results

In general, the clinical response in the new series of treated patients was similar to that in the previous, randomized trial. The mean (SD) values for a/APO_2 24 h after treatment were 0.29 (0.14) and 0.30 (0.16), respectively, which represents, approximately, a twofold improvement in comparison with the corresponding control level in the randomized trial, 0.15 (0.09) ($p < 0.001$). The incidence of pulmonary interstitial emphysema was even lower in the new series (11%) than

among surfactant-treated babies in the controlled trial (23%) ($p < 0.05$); each of these figures is significantly lower than the incidence of interstitial emphysema among the randomized controls in the 1985–87 series, 39% ($p < 0.001$). Early neonatal mortality was reduced from 31% in babies randomized to surfactant treatment in the first series [6] to 15% in the new series of treated patients ($p < 0.05$). This represents a significant improvement in comparison with the mortality rate in the randomized control group, 51% (p vs each of the treated groups < 0.05 and < 0.001, respectively). However, the number of surfactant-treated babies surviving without evidence of BPD was the same in the new series as in the previous one, 55%.

Asphyxia and high FiO_2 requirement at entry both had a negative impact on a/APO_2 after treatment. The duration of artificial ventilation and total time in >21% oxygen were lower in babies with high birth weight, who also had a lower mortality. Male babies and outborn patients tended to have a higher mortality. Hospital allocation had a significant influence on all dependent variables. For a/APO_2 after 6 h, this varied from a negative impact twice as high as that for asphyxia to a positive impact of even larger magnitude.

One year follow-up of patients from the first, randomized trial [6] revealed no difference in growth parameters between treated babies and the control group. However, the number of babies surviving without any handicap was significantly larger in the surfactant-treated group (56% vs 35%; $p = 0.02$) [9].

Discussion

The data summarized in this condensed report confirm the beneficial effect of surfactant replacement in babies with severe RDS. In the new series of treated patients, there is a trend toward a further reduced incidence of air-leak problems and lower mortality than among babies randomized to surfactant treatment in the controlled trial. This may represent a "learning curve," improving the skills of the hospital staff responsible for the management of the surfactant-treated patients. The trend toward higher incidence of BPD in the new series of treated patients (balancing the reduced mortality), constitutes an important challenge for future trials of alternative treatment protocols for surfactant replacement in neonatal RDS.

The unfavorable influence of high FiO_2 and high insufflation pressure at entry suggests that better results may be obtained by treating the babies at an earlier stage of the disease. We are currently testing this hypothesis in a new multicenter trial, in which babies ventilated for RDS are randomized at 40% instead of 60% oxygen requirement. Other ongoing clinical trials, organized within the framework of the European Multicenter Study Group, evaluate the use of multiple surfactant doses in patients with a transient response to a single dose, and investigate the effects of surfactant replacement on cerebral blood flow and oxygenation.

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References

1. Hallman M, Merritt TA, Jarvenpaa A-L, Boynton B, Mannino F, Gluck L, Moore T, Edwards D (1985) Exogenous human surfactant for treatment of severe respiratory distress syndrome: a randomized prospective clinical trial. J Pediatr 106:963–969
2. Gitlin JD, Soll RF, Parad RB, Horbar JD, Feldman HA, Lucey JF, Taeusch HW (1987) Randomized controlled trial of exogenous surfactant for the treatment of hyaline membrane disease. Pediatrics 79:31–37
3. Raju TNK, Vidyasagar D, Bhat R, Sobel D, McCulloch KM, Anderson M, Maeta H, Levy PS, Furner S (1987) Double-blind controlled trial of single-dose treatment with bovine surfactant in severe hyaline membrane disease. Lancet 1:651–656
4. Fujiwara T, Konishi M, Nanbu H, Ogawa Y, Niitsu N, Naito T, Akamatsu H, Tada H, Okuyama K, Nishida H, Imura S, Takeuchi Y, Goto A, Shimura K, Kito H, Kuroyanazi M, Ogino T, Fujimura M, Nakamura H, Takemine H, Nakata E, Hashimoto T (1987) Surfactant replacement for respiratory distress syndrome (RDS)—a multicenter clinical trial. Jpn J Pediatr 40:549–568 (in Japanese)
5. Horbar JD, Soll RF, Sutherland JM, Kotagal U, Philip AGS, Kessler DL, Little GA, Edwards WH, Vidyasagar D, Raju TNK, Jobe AH, Ikegami M, Mullett MD, Myerberg DZ, McAuliffe TL, Lucey JF (1989) A multicenter randomized, placebo-controlled trial of surfactant therapy for respiratory distress syndrome. N Eng J Med 15:959–965
6. Collaborative European Multicenter Study Group (1988) Surfactant replacement therapy for severe neonatal respiratory distress syndrome: an international randomized clinical trial. Pediatrics 82:683–691
7. Robertson B, Curstedt T, Johansson J, Jörnvall H, Kobayashi T (1990) Structural and functional characterization of porcine surfactant isolated by liquid-gel chromatography. Prog Respir Res 25:237–246
8. Hjalmarson O (1981) Epidemiology and classification of acute, neonatal respiratory disorders. Acta Paediatr Scand 70:773–783
9. Tubman TRJ, Halliday HL (1989) Surfactant replacement in severe respiratory distress syndrome (RDS): follow-up at one year (Abstract). Ir J Med Sci 158:283