SURFACTANT THERAPY AND NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE FOR NEWBORNS WITH RESPIRATORY DISTRESS SYNDROME

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Abstract *Background.* In southern Scandinavia most babies with respiratory distress syndrome are initially treated with nasal continuous positive airway pressure. We performed a multicenter trial to investigate whether the addition of a single dose of porcine surfactant administered during a short intubation before the occurrence of serious deterioration could reduce the subsequent need for mechanical ventilation.

Methods. We randomly assigned 35 infants with moderate-to-severe respiratory distress syndrome to surfactant therapy (Curosurf, 200 mg per kilogram of body weight) plus nasal continuous positive airway pressure and 33 infants to nasal continuous positive airway pressure alone. The study was not blinded. The indications for mechanical ventilation were a ratio of arterial to alveolar oxygen tension of less than 0.15, severe apneic attacks, or both.

Results. Six hours after randomization, when the median age of the babies was 18 hours, the mean ratio of arterial to alveolar oxygen tension was 0.37 in the surfactant-treated babies, as compared with 0.25 in the controls ($P<0.001$). The need for subsequent mechanical ventilation was reduced with surfactant therapy (to 43 percent of the surfactant-treated babies, as compared with 85 percent of the controls; $P = 0.003$). When 17 infants with ratios of arterial-to-alveolar oxygen tension of less than 0.15 at randomization were excluded, the need for mechanical ventilation was still significantly reduced in the surfactant-treated group (to 33 percent [9 of 27 babies], as compared with 83 percent [20 of 24 babies] in the control group; $P<0.001$). After 28 days, two of the surfactant-treated babies had died, as compared with five of the control babies.

Conclusions. In babies with moderate-to-severe respiratory distress syndrome treated with nasal continuous positive airway pressure, a single dose of surfactant reduced the need for subsequent mechanical ventilation. (N Engl J Med 1994;331:1051-5.)

THE introduction of continuous positive airway pressure in 1971[1] improved the treatment of neonatal respiratory distress syndrome. With the early application of continuous positive airway pressure delivered nasally or by a face mask, the progression of this syndrome can be delayed or arrested. Some babies can avoid mechanical ventilation,[2-5] and in those who require it later, ventilation can be given at lower pressures.[5] These promising results seem to have been forgotten at many centers.

The combination of surfactant replacement and mechanical ventilation was introduced in 1980.[6] Currently, this combination is used as both prophylactic and rescue therapy for respiratory distress syndrome, with a reduction in mortality.[7] When surfactant is given prophylactically at birth, some infants who do not need the medication are treated. On the other hand, waiting until respiratory distress syndrome has developed may mean that the treatment is given too late to benefit some babies. Furthermore, mechanical ventilation may have complications. Suction of the trachea may cause hypoxia,[8] and suboptimal ventilatory settings may cause leakage of air and depletion of surfactant.[9,10]

After conducting two pilot studies,[11,12] we investigated whether nasal continuous positive airway pressure initiated early (i.e., at the first sign of respiratory distress) in combination with a fast-acting surfactant administered during a short intubation could halt the progression of respiratory distress syndrome, reduce the need for mechanical ventilation, and improve outcomes in newborns.

METHODS

Surfactant

Curosurf (Chiesi Farmaceutici, Parma, Italy), the surfactant used, is isolated from minced pig lungs by a combination of washing, centrifugation, extraction with chloroform–methanol, and liquid-gel chromatography.[13] It contains approximately 99 percent lipids, mainly phospholipids, and 1 percent apoproteins (surfactant proteins B and C).[13] The efficacy of this product has been documented in previous trials.[14,15]

Continuous Positive Airway Pressure

For continuous positive airway pressure, the lightweight system based on Benveniste's pediatric gas-jet valve (Dameca, Copenhagen, Denmark), originally developed for artificial ventilation, was used.[16,17] This system eliminates the risk that accidental kinking of the tubes in the ventilation system will produce excessive pressure in the airways and the risk that ambient air will be mixed with the inhaled gases.[18,19] The Benveniste valve generates positive pressures of 4 to 10 cm of water by creating a narrow stream of humidified air mixed with oxygen at a rate of flow of 10 to 16 liters per minute. The mixture is delivered through nasal prongs.

Study Design

Seventy-three infants with moderate-to-severe respiratory distress syndrome treated early with nasal continuous positive airway pressure were randomly assigned either to receive surfactant or to

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*The members of the Danish–Swedish Multicenter Study Group are listed in the Appendix.

continue receiving nasal continuous positive airway pressure. The study was organized as a multicenter trial involving 11 neonatal intensive care units in Denmark and Sweden. The indication for mechanical ventilation was standardized, and all infants undergoing ventilation could receive surfactant as rescue therapy. The trial was conducted from September 1991 to October 1992.

The primary end point was the percentage of patients requiring mechanical ventilation. On the basis of data from one of the pilot studies,[12] we set a goal of reducing this percentage from 80 percent in the controls to 40 percent in the surfactant-treated babies. Assuming a power of 90 percent and a significance level of 5 percent (two-tailed), we estimated that 108 infants would have to be randomized.

The secondary end point was the ratio of arterial to alveolar oxygen tension[20] six hours after randomization. Our hypothesis was that the mean ratio in the babies treated with surfactant would be 50 percent higher than the mean ratio in the controls. The protocol called for an interim analysis after half the infants had been randomized. The criterion for stopping the study was a P value of 0.01 for the primary end point.

The criteria for entry into the study were as follows: clinical and radiologic findings of respiratory distress syndrome; gestational age of 25 to 35 weeks; age of 2 to 72 hours; a requirement for nasal continuous positive airway pressure $\geq$6 cm of water; and a ratio of arterial to alveolar oxygen tension of less than 0.22. Neonates with Apgar scores below 3 five minutes after birth, those whose mothers had had rupture of the membranes for more than 14 days, and those with severe malformations, pneumonia, or pneumothorax were not enrolled. If twins were born, only the first twin to fulfill the criteria was enrolled. Randomization was performed by opening sealed envelopes that were numbered sequentially and kept at each hospital. It was performed in blocks of four so that a similar number of babies would be enrolled in each treatment group at each center.

Prophylaxis with theophylline was optional (5 mg per kilogram of body weight intravenously or orally, followed by 2.5 mg per kilogram twice daily). Transcutaneous partial pressure of oxygen and partial pressure of carbon dioxide were monitored continually (Radiometer, Copenhagen, Denmark, or Hellige, Freiburg, Germany), and these measurements were used to calculate the ratio of arterial to alveolar oxygen tension.[20]

Infants randomly assigned to treatment with surfactant were treated with morphine (0.1 mg per kilogram intravenously) and atropine (10 μg per kilogram intravenously) before intubation. Treatment with naloxone (10 μg per kilogram intravenously) before extubation was optional. Surfactant (200 mg [2.5 ml] per kilogram) was given in two bolus doses a few minutes apart. After each dose, the infants underwent manual ventilation, usually for two to five minutes. As soon as respiration was judged satisfactory, the infants were extubated. Treatment was considered to have failed in infants who were not extubated within one hour or who were reintubated for ventilator therapy within five days. The study was not blinded.

The indications for mechanical ventilation were a decrease in the oxygen-tension ratio to less than 0.15, severe attacks of apnea, or both. Babies who had oxygen-tension ratios of less than 0.15 at randomization had their transcutaneous gas values monitored for at least 10 minutes before mechanical ventilation was initiated. If the oxygen-tension ratio was improving after the 10-minute period, the decision to administer ventilation was postponed for 20 more minutes — i.e., until 30 minutes had elapsed after randomization. Babies whose oxygen-tension ratios were still less than 0.15 were then intubated for mechanical ventilation.

Infants treated with mechanical ventilation were permitted to receive surfactant at a dose of 200 mg per kilogram if they required a concentration of inspired oxygen greater than 60 percent.[12] Additional doses of surfactant could be given 12 and 24 hours later if an infant still required a concentration of inspired oxygen greater than 60 percent. (None of the babies in fact required more than one such rescue dose of surfactant.) Pressure-limited, time-cycled, continuous-flow ventilators were used (Dräger, Lübeck, Germany).

Chest films were obtained for all patients at randomization and were assessed retrospectively in a blinded fashion by two of the investigators. The chest films were classified as normal or as indicating mild, moderate, or severe respiratory distress syndrome.[21] All babies who survived underwent cerebral ultrasonography seven days after birth. Intracerebral hemorrhage was diagnosed and classified according to the method of Papile et al.[22] Periventricular leukomalacia was diagnosed by ultrasonography.[23] Patent ductus arteriosus was diagnosed by clinical signs, by echocardiography, or both.

The trial was approved by the research ethics committee at each institution. Written informed consent was obtained from the parents of the newborns before randomization.

Statistical Analysis

Base-line differences between the groups at randomization were evaluated by the Mann–Whitney test or Fisher's exact test (two-tailed). Logistic-regression analysis[24] was used to investigate possible associations between the need for mechanical ventilation and the following variables: gestational age, birth weight, sex, antenatal steroid treatment, birth in the hospital or outside the hospital, cesarean section, perinatal asphyxia (Apgar score, $\leq$6 at five minutes), theophylline treatment, age at randomization, transcutaneous partial pressure of carbon dioxide at randomization, chest-film findings at randomization, treatment center, and treatment with surfactant.

We sought to determine the effect of surfactant treatment when the other variables were controlled for. By including interaction terms in the regression model,[24] we investigated how the effect of treatment changed as the variables changed — for example, whether the effect of treatment was the same for boys as for girls. When we used the oxygen-tension ratio at six hours as the dependent variable, ordinary multiple regression analysis was used.[24] P values of less than 0.05 were considered to indicate statistical significance.

Results

An interim analysis performed after 54 infants had been randomized showed a statistically significant benefit for those treated with surfactant. The trial was stopped as soon as this analysis was completed. At that time, 73 infants had been randomized (36 treated with surfactant and 37 controls), including 5 who did not meet the entry criteria (2 with gestational ages of 36 weeks, 2 with oxygen-tension ratios of 0.22 and 0.23 at randomization, and 1 with pneumonia at randomization). Therefore, data for 68 patients (35 treated with surfactant and 33 controls) were analyzed. The characteristics of the patients in each group were similar (Table 1). Nasal continuous positive airway pressure was begun at a median age of 19 minutes, and the babies were randomly assigned to the treatment groups at a median age of 12 hours.

Thirty-three of the 35 babies who were intubated for treatment with surfactant were extubated within 5 to 60 minutes. Thirteen of the babies who were intubated (37 percent) were reintubated for mechanical ventilation a median of nine hours after the instillation of surfactant. In the control group, 28 babies (85 percent) were intubated for mechanical ventilation a median of three hours after randomization ($P = 0.017$ for the difference in the time to mechanical ventilation; $P = 0.003$ for the difference in the proportion of ba-

Table 1. Characteristics of the Patients at Randomization, According to Study Group.*

Characteristic	Surfactant Group (N = 35)	Control Group (N = 33)
Gestational age (wk) — median (range)	30 (25–35)	29 (25–35)
Birth weight (g) — median (range)	1380 (740–2915)	1303 (740–2860)
Age at entry (hr) — median (range)	13 (4–70)	10 (3–66)
Male sex — no. (%)	22 (63)	19 (58)
Cesarean section — no. (%)	25 (71)	22 (67)
Antenatal steroids — no. (%)	14 (40)	20 (61)
2 Doses	8 (23)	10 (30)
Born in hospital — no. (%)	27 (77)	25 (76)
Theophylline — no. (%)	19 (54)	20 (61)
Oxygen-tension ratio — mean ±SD	0.17±0.04	0.16±0.04
Transcutaneous PCO_2 (mm Hg) — mean ±SD	52.5±12	51.0±14
Respiratory distress syndrome† — no. (%)		
Severe	11 (33)	12 (36)
Moderate	17 (52)	12 (36)
Mild	5 (15)	9 (27)

*Differences between groups were not significant. PCO_2 denotes partial pressure of carbon dioxide.

†Severity was determined by chest radiography. Data are missing for two patients in the surfactant group.

bies requiring mechanical ventilation). Data on the requirement for mechanical ventilation are shown in Table 2. Most babies responded to surfactant with a rapid increase in the transcutaneous partial pressure of oxygen and a slow decrease in the transcutaneous partial pressure of carbon dioxide, as in our pilot study.[12] Six hours after randomization, the mean oxygen-tension ratio in the surfactant group was 0.37, as compared with 0.25 in the control group (P<0.001) (Table 2). The predominant reasons for the use of mechanical ventilation were an oxygen-tension ratio of less than 0.15 in the control babies (21 of 28) and apnea in the surfactant-treated babies (10 of 15) (P = 0.02 for the difference).

Babies with Oxygen-Tension Ratios below 0.15 at Randomization

Eight babies with oxygen-tension ratios below 0.15 who were randomly assigned to surfactant therapy responded to treatment with increases in the ratio to more than 0.15. Seven were extubated without having undergone ventilation; the eighth had apnea and required continued ventilation. Five of the seven babies who were extubated required mechanical ventilation 2 to 24 hours after randomization, three because of apnea and two because of oxygen-tension ratios below 0.15. Eight of the control babies with oxygen-tension ratios below 0.15 at randomization were intubated for mechanical ventilation 10 minutes to 7 hours later; the other baby's oxygen-tension ratio increased to more than 0.15, and nasal continuous positive airway pressure was continued. When the 17 infants with oxygen-tension ratios of less than 0.15 at randomization were excluded from the analysis, the need for subsequent mechanical ventilation was still significantly reduced by treatment with surfactant (mechanical ventilation was required by 33 percent of the babies [9 of 27] in the treatment group vs. 83 percent [20 of 24] in the control group; P<0.001).

Total Dose of Surfactant

Three of the 15 infants who were randomly assigned to surfactant treatment and later required mechanical ventilation received an extra dose of surfactant (200 mg per kilogram). Among the control babies who required mechanical ventilation, 19 received one dose of surfactant (200 mg per kilogram). Thus, the 35 babies initially treated with surfactant received a total of 38 doses (35 of which were part of the initial treatment), and the 33 controls received a total of 19 doses. None of the babies undergoing mechanical ventilation required multiple-dose treatment for rescue.

Multiple Regression Analysis

In a logistic-regression model that used the requirement for mechanical ventilation as the dependent variable with no interaction terms, only surfactant treatment was significant in reducing the need for mechanical ventilation (P = 0.003) (Table 2). When interaction terms were included, the effects of treatment with surfactant on the need for mechanical ventilation was greater for boys than for girls (P = 0.008). No other interaction term was statistically significant. There was a trend, however, toward better outcomes in babies with higher birth weights and babies randomized earlier (data not shown). When the oxygen-tension ratio at six hours was used as the dependent variable, treatment with surfactant was associated with a higher mean ratio (P<0.001). In this analysis, the effect of surfactant treatment was also significantly greater for boys than for girls (P = 0.006).

Secondary Outcome Measures

The 15 surfactant-treated and 28 control babies who required mechanical ventilation received it for a median of 2.5 days (the same value for both groups). The median duration of treatment with supplemental oxygen was also similar in both groups.

The outcomes at 28 days of life are summarized in

Table 2. Data on Study End Points in the Two Study Groups.

End Point	Surfactant Group (N = 35)	Control Group (N = 33)	P Value
Need for mechanical ventilation — no. (%)	15 (43)	28 (85)	0.003
Male infants	6	18	<0.001
Female infants	9	10	0.90
Mean (±SD) oxygen-tension ratio after 6 hr	0.37±0.15	0.25±0.10	<0.001
Days of oxygen treatment — median (range)	6 (1–75)	6 (1–76)	0.60

Table 3. No significant differences between the groups were found.

Discussion

Respiratory distress syndrome is a progressive condition with deterioration during the first hours and days of life. Early treatment with continuous positive airway pressure can prevent or temporarily compensate for the increased alveolar-retraction forces that are a consequence of high surface tension caused by deficiency of surfactant.[9] Our study indicates that the combination of early nasal continuous positive airway pressure and surfactant therapy further retards the progression of this syndrome by improving lung function, as indicated by an increased oxygen-tension ratio, a decreased transcutaneous partial pressure of carbon dioxide, and a reduced need for mechanical ventilation. The babies in our pilot study[12] had severe respiratory distress, with an average oxygen-tension ratio of 0.12 when they were treated with surfactant at a mean age of 19 hours. Many of those babies had increasing apnea and required mechanical ventilation despite a good response to surfactant. Therefore, we decided to treat babies at an earlier stage of the disease — i.e., when they had higher oxygen-tension ratios — before severe respiratory distress developed.

Few pulmonary and extrapulmonary complications occurred in either the surfactant-treated babies or the controls. This probably reflected both the selection of patients and the treatment strategy. About 6 percent of babies with birth weights below 1500 g who are treated early with nasal continuous positive airway pressure need mechanical ventilation within the first two hours of life[4]; this represents the approximate proportion of babies with very severe respiratory distress syndrome who were not included in our trial. The frequent use of steroids before birth to mature the lungs may also have reduced the incidence of complications. Nasal continuous positive airway pressure probably mitigated respiratory distress syndrome in both groups of newborns, as in earlier studies in which survival was improved[25] and the incidence of bronchopulmonary dysplasia reduced[5,25] with the early use of this therapy. The overall incidence of pulmonary complications and mortality was lower in the present study than in the OSIRIS and Curosurf 4 trials[26,27]; in both these studies, mechanical ventilation and treatment with surfactant were combined in babies with oxygen-tension ratios of less than 0.22. Direct comparison of data from these three trials is not possible, however, because of differences in treatment strategies in the first hours of life.

Table 3. Outcomes of the Study Patients at 28 Days of Life.*

Outcome	Surfactant Group (N = 35)	Control Group (N = 33)
	no. (%)	
Death	2 (6)	5 (15)
Intracerebral hemorrhage at day 7		
Grade 1 or 2	5 (14)	3 (9)
Grade 3 or 4	3 (9)	5 (15)
Death or survival with intracerebral hemorrhage grade 3 or 4	4 (11)	9 (27)
Periventricular leukomalacia	0	1 (3)
Pneumothorax	1 (3)	2 (6)
Pulmonary hemorrhage	0	2 (6)
Oxygen required at 28 days	3 (9)	3 (9)
Patent ductus arteriosus†	13 (37)	6 (18)
Necrotizing enterocolitis	0	0
Retinopathy of prematurity‡	1 (3)	1 (3)

*Differences between groups were not significant.
†Treated.
‡Treated with cryotherapy.

It is possible that the brief period of intermittent positive-pressure ventilation at the time of treatment with surfactant could have contributed to the improved outcome in the surfactant group. On the basis of previous experience,[28] we believe that this is unlikely. In babies who receive early nasal continuous positive airway pressure, any possible positive effects of such ventilation are probably outweighed by the negative effects of handling, intubation, and extubation. For these reasons, we did not consider it ethical to subject the babies in the control group to sham maneuvers that mimicked the administration of surfactant.

The lack of blinding is another potential problem. This factor might have influenced the decision to intubate the babies for mechanical ventilation. Complete blinding, however, would have required using separate dosing teams (medical personnel not otherwise involved in the treatment of the baby) to administer surfactant at all 11 neonatal intensive care units. This was not possible, given budgetary constraints. Furthermore, it would have been difficult to be unaware of the rapid improvement in oxygenation that characteristically occurs very soon after the administration of surfactant.[12] The typical indications for intubation and mechanical ventilation differed between the groups: an oxygen-tension ratio of less than 0.15 in the controls, and apnea in the babies receiving surfactant.

Substantially more boys than girls responded favorably to early treatment with nasal continuous positive airway pressure and surfactant. In another study, a reduction in the severity of respiratory distress syndrome was reported in boys but not girls after combined treatment with antenatal steroids and prophylactic calf-lung surfactant.[29] We did not find a similar additive effect of these treatments.

Babies with respiratory distress syndrome who require mechanical ventilation and receive surfactant early in their disease do better than those who are treated late.[30] Several studies have documented a beneficial effect of prophylactic treatment with surfactant in very-low-birth-weight infants,[7] and the administration of surfactant at birth may be superior to

treatment when decompensation occurs.[31] However, prophylactic treatment of all infants under a certain gestational age (e.g., 29 weeks) implies that surfactant would be given to some infants with mature lungs who do not need it. This is an issue of both ethics and economy. Our findings suggest an intermediate approach: the use of surfactant when the diagnosis of respiratory distress syndrome is established, but before serious deterioration has occurred.

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Appendix

In addition to the authors, the following persons and institutions participated in the Danish–Swedish Multicenter Study Group.

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References

1. Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory-distress syndrome with continuous positive airway pressure. N Engl J Med 1971;284:1333-40.
2. Kamper J, Wulff K, Larsen C, Lindequist S. Early treatment with nasal continuous positive airway pressure in very low-birth-weight infants. Acta Paediatr 1993;82:193-7.
3. Jacobsen T, Grønvall J, Petersen S, Andersen GE. "Minitouch" treatment of very low-birth-weight infants. Acta Paediatr 1993;82:934-8.
4. Lundstrøm KE, Greisen G. Early treatment with nasal-CPAP. Acta Paediatr 1993;82:856.
5. Allen LP, Reynolds ER, Rivers RPA, LeSouëf PN, Wimberley PD. Controlled trial of continuous positive airway pressure given by face mask for hyaline membrane disease. Arch Dis Child 1977;52:373-8.
6. Fujiwara T, Maeta H, Chida S, Morita T, Watabe Y, Abe T. Artificial surfactant therapy in hyaline-membrane disease. Lancet 1980;1:55-9.
7. Jobe AH. Pulmonary surfactant therapy. N Engl J Med 1993;328:861-8.
8. Tarnow-Mordi W. Is routine endotracheal suction justified? Arch Dis Child 1991;66:374-5.
9. Bos J, Lachmann B. Surfactant function: is it influenced by artificial ventilation? In: Cosmi EV, Di Renzo GC, Anceschi MM, eds. The surfactant system of the lung: prevention and treatment of neonatal and adult respiratory distress syndrome. London: Macmillan Academic and Professional, 1991:96-106.
10. Lachmann B. Open up the lung and keep the lung open. Intensive Care Med 1992;18:319-21.
11. Victorin LH, Deverajan LV, Curstedt T, Robertson B. Surfactant replacement in spontaneously breathing babies with hyaline membrane disease — a pilot study. Biol Neonate 1990;58:121-6.
12. Verder H, Agertoft L, Albertsen P, et al. Surfaktantbehandling af nyfødte med respiratorisk distress-syndrom primært behandlet med nasalt kontinuerligt positivt luftvejstryk: en pilotundersøgelse. Ugeskr Laeger 1992;154: 2136-9.
13. Robertson B, Curstedt T, Johansson J, Jörnvall H, Kobayashi T. Structural and functional characterization of porcine surfactant isolated by liquid-gel chromatography. Prog Respir Res 1990;25:237-46.
14. Collaborative European Multicenter Study Group. Surfactant replacement therapy for severe neonatal respiratory distress syndrome: an international randomized clinical trial. Pediatrics 1988;82:683-91.
15. Speer CP, Robertson B, Curstedt T, et al. Randomized European multicenter trial of surfactant replacement therapy for severe neonatal respiratory distress syndrome: single versus multiple doses of Curosurf. Pediatrics 1992;89:13-20.
16. Benveniste D, Pedersen J-EP. A valve substitute with no moving parts, for artificial ventilation in newborn and small infants. Br J Anaesth 1968;40: 464-70.
17. Benveniste D, Berg O, Pedersen J-EP. A technique for delivery of continuous positive airway pressure to the neonate. J Pediatr 1976;88:1015-9.
18. Brendstrup A, Benveniste D, Pedersen J-EP. The magnitude of air admixture with a jet device in paediatric anaesthesia. Br J Anaesth 1975;47:1335-7.
19. Kamper J, Brendstrup A. Treatment of respiratory insufficiency in infants using nasal CPAP and a gas jet. Acta Anaesthesiol Scand 1978;22:367-70.
20. Gilbert R, Keighley JF. The arterial-alveolar oxygen tension ratio: an index of gas exchange applicable to varying inspired oxygen concentrations. Am Rev Respir Dis 1974;109:142-5.
21. Mortensson W, Noack G, Curstedt T, Herin P, Robertson B. Radiologic observations in severe neonatal respiratory distress syndrome treated with the isolated phospholipid fraction of natural surfactant. Acta Radiol 1987; 28:389-94.
22. Papile L-A, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529-34.
23. Hill A, Melson GL, Clark HB, Volpe JJ. Hemorrhagic periventricular leukomalacia: diagnosis by real time ultrasound and correlation with autopsy findings. Pediatrics 1982;69:282-4.
24. Altman DG. Practical statistics for medical research. London: Chapman & Hall, 1991.
25. Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics 1987;79: 26-30.
26. The OSIRIS Collaborative Group. Early versus delayed neonatal administration of a synthetic surfactant — the judgment of OSIRIS. Lancet 1992;340:1363-9.
27. Halliday HL, Tarnow-Mordi WO, Corcoran JD, Patterson CC. Multicentre randomised trial comparing high and low dose surfactant regimens for the treatment of respiratory distress syndrome (the Curosurf 4 trial). Arch Dis Child 1993;69:276-80.
28. Svenningsen N, Robertson B, Andreason B, Berggren P, Jonson B, Lindroth M. Endotracheal administration of surfactant in very low birth weight infants with respiratory distress syndrome. Crit Care Med 1987;15:918-22.
29. Farrell EE, Silver RK, Kimberlin LV, Wolf ES, Dusik JM. Impact of antenatal dexamethasone administration on respiratory distress syndrome in surfactant-treated infants. Am J Obstet Gynecol 1989;161:628-33.
30. Bevilacqua G, Halliday H, Parmigiani S, Robertson B. Randomized multicentre trial of treatment with porcine natural surfactant for moderately severe neonatal respiratory distress syndrome. J Perinat Med 1993;21:329-40.
31. Kendig JW, Notter RH, Cox C, et al. A comparison of surfactant as immediate prophylaxis and as rescue therapy in newborns of less than 30 weeks' gestation. N Engl J Med 1991;324:865-71.