Early Extubation and Nasal Continuous Positive Airway Pressure After Surfactant Treatment for Respiratory Distress Syndrome Among Preterm Infants <30 Weeks’ Gestation

Carlo Dani, MD; Giovanna Bertini, MD; Marco Pezzati, MD; Alessandra Cecchi, MD; Cosimo Caviglioli, MD; and Firmino F. Rubaltelli, MD

ABSTRACT. Objective. To test the hypothesis that preterm infants with infant respiratory distress syndrome who are treated with nasal continuous positive airway pressure (NCPAP) and surfactant administration followed by immediate extubation and NCPAP application (SURF-NCPAP group) demonstrate less need for mechanical ventilation (MV), compared with infants who receive MV after surfactant administration (SURF-MV group).

Methods. A prospective randomized study was conducted, in which infants <30 weeks’ gestation were randomized to the SURF-NCPAP group or the SURF-MV group.

Results. At 7 days of life, no patient in the SURF-NCPAP group but 6 patients (43%) in the SURF-MV group still were undergoing MV. The duration of oxygen therapy, NCPAP, and MV, the need for a second dose of surfactant, and the length of stay in the intensive care unit were significantly greater in the SURF-MV group.

Conclusions. The immediate reintroduction of NCPAP after surfactant administration for infants with infant respiratory distress syndrome is safe and beneficial, as indicated by the lesser need for MV and the briefer requirement for respiratory supports, compared with the institution of MV after surfactant treatment. Moreover, this strategy contributed to reducing the need for surfactant treatment and reducing the time and costs involved in keeping the infants in the neonatal intensive care unit. Pediatrics 2004;113:e560–e563. URL: http://www.pediatrics.org/cgi/content/full/113/6/e560; continuous positive airway pressure, mechanical ventilation, surfactant, respiratory distress syndrome, infant.

ABBREVIATIONS. a/APO2, arterial/alveolar oxygen tension ratio; iRDS, infant respiratory distress syndrome; MV, mechanical ventilation; NCPAP, nasal continuous positive airway pressure; SURF-MV, mechanical ventilation after surfactant treatment; SURF-NCPAP, nasal continuous positive airway pressure after surfactant treatment; FIO2, fraction of inspired oxygen; IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; PDA, patent ductus arteriosus.

The cornerstones of treatment of infant respiratory distress syndrome (iRDS) are artificial respiratory support and surfactant treatment. Among respiratory support techniques, nasal continuous positive airway pressure (NCPAP) and mechanical ventilation (MV) are known for their effectiveness in reducing the mortality and morbidity rates associated with iRDS. Moreover, early application of NCPAP and early treatment with surfactant are effective in decreasing the need for MV, with its related adverse effects. Unfortunately, these results are not always taken into account in neonatal intensive care units, and MV is often initiated after endotracheal intubation for surfactant administration, without consideration of the fact that many infants who are able to breathe spontaneously could be supported with NCPAP only.

The present study was planned to test the hypothesis that preterm infants (<30 weeks’ gestation) with iRDS who were treated with NCPAP and surfactant administration followed by immediate reintroduction of NCPAP could fare better than those who received MV after surfactant administration and who were weaned progressively from MV. In particular, our aim was to determine whether the first strategy could reduce the need for MV during the subsequent clinical course of our patients.

METHODS

Study Design

The study was conducted in the neonatal intensive care unit of the University Hospital of Florence, after approval by the local ethics committee, between June 2001 and May 2003. Because of the impossibility of masking the different postextubation strategies to the operators, a nonblinded study was performed. After parental consent was obtained (either prenatally or early postnatally), infants born of 0 to 6 hours of age and <30 weeks’ gestation with iRDS who were enrolled consecutively in the study if they required NCPAP (4–7 cm H2O) and a fraction of inspired oxygen (FIO2) of ≥30% to maintain arterial hemoglobin oxygen saturation of ≥88% and Po2 of ≥50 mm Hg. The iRDS diagnosis was based on the occurrence of classic symptoms, such as the need for oxygen supplementation, tachypnea, intercostal retractions, and grunting, and the exclusion of other causes of respiratory failure and was confirmed by a typical radiologic pattern with reduced air content and a reticulogranular pattern of lung and air bronchograms.

Infants with major congenital malformations, intraventricular hemorrhage (IVH) of more than grade 2 (identified with transfontanellar cerebral ultrasonography performed within the first 6 hours of life), or the requirement for MV within the first 6 hours of life were excluded.

Two of the main principles for the treatment of infants in our intensive care unit were the early initiation of NCPAP (Infant
Flow System; Emi Ltd, Brighton, United Kingdom) at signs of respiratory distress and the institution of MV (patient-triggered ventilation: Babylgo 8000 plus; Drager, Lübeck, Germany; high-frequency oscillatory ventilation: Sensormedics 3100A; Sensor Medics Corp, Yorba Linda, CA) when pH was < 7.20, P$_{O_2}$ was < 50 mm Hg with F$_{O_2}$ of > 0.50, and P$_{CO_2}$ was > 65 mm Hg. All enrolled patients were intubated for surfactant treatment (Curosurf, 200 mg/kg; Chiesi, Parma, Italy), which was administered in 2 bolus fractions of 100 mg/kg each, instilled through a tracheal tube, with an interval of a few minutes. Manual ventilation was administered for 1 minute after each dose. The patients then randomly received the reinstition of NCPAP (SURF-NCPAP group) or MV (SURF-MV group). The randomization was performed at the time of enrollment by opening sealed envelopes. Operators were allowed to administer an additional dose of surfactant (100 mg/kg) 12 hours later if the infant still required a F$_{O_2}$ of > 0.50.

Infants in the SURF-NCPAP group were extubated as soon as the respiratory rate, heart rate, and arterial hemoglobin oxygen saturation were satisfactory (usually within 5 minutes), whereas infants in the SURF-MV group were extubated after a loading dose of caffeine (20 mg/kg), when the F$_{O_2}$ was ≤ 0.40, mean arterial pressure was ≤ 6 cm H$_2$O, and P$_{O_2}$ and P$_{CO_2}$ were ≥ 50 and < 65 mm Hg, respectively. The extubation of infants undergoing MV was mandatory within 2 hours after they reached extubation criteria; moreover, after extubation, decisions regarding whether to begin new NCPAP to avoid the necessity of reintubation, to offer oxygen supplementation only, or to place the patient directly in room air were completely up to the neonatologist on duty. The criteria for discontinuing NCPAP were the same for both groups, i.e., F$_{O_2}$ of ≤ 0.40, positive end expiratory pressure of ≤ 5 cm H$_2$O, P$_{O_2}$ of ≥ 50 mm Hg, and P$_{CO_2}$ of ≥ 65 mm Hg. For each infant, gestational age, birth weight, gender, type of delivery, Apgar score at 5 minutes, Clinical Risk Index for Babies score, arterial/alveolar oxygen tension ratio (a/A$P_{O_2}$)$^{18}$ before and 6 hours after surfactant treatment, need for a second dose of surfactant, main maternal pregnancy diseases, and prenatal corticosteroid treatment were recorded.

**Primary End Point**

The primary end point was the need for MV at 7 days of life. The indications for MV were respiratory acidosis with pH of < 7.20 and P$_{CO_2}$ of > 65 mm Hg, hypoxemia with P$_{O_2}$ of < 50 mm Hg at F$_{O_2}$ of > 0.50, or a severe apnea attack. Severe apnea was defined as > 4 episodes per hour or the need for mask ventilation > 2 times per hour.

**Secondary End Points**

Secondary end points were the a/A$P_{O_2}$, 6 hours after surfactant administration, the need for MV, death before discharge, the duration of oxygen treatment, NCPAP, and MV, the need for a second dose of surfactant, the incidences of pneumothorax, patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), IVH, periventricular leukomalacia, retinopathy of prematurity (ROP), and necrotizing enterocolitis, and the length of stay in the intensive care unit and in hospital. BPD was defined as an oxygen requirement at a postconceptual age of 36 weeks.$^{14}$ IVH was classified according to the method described by Papile et al,$^{15}$ and ROP was graded according to the international classification of ROP.$^{13}$ Our patients were discharged from the intensive care unit and transferred to a special care unit when they did not require assisted ventilation and central vessel catheterization.

**Statistical Analyses**

In planning our study, on the basis of data collected for infants of < 30 weeks’ gestation who were born in our center between June 1999 and May 2001, we calculated that a sample size of at least 24 infants in each group was required for detection of a difference of 50% in the occurrence of MV at 7 days of life in the SURF-NCPAP group, compared with the SURF-MV group, with 80% power at a 0.05 level. However, when interim analysis (which was not preplanned but was performed because of clear evidence of lower respiratory support levels in the SURF-NCPAP group) demonstrated that the difference between the groups with respect to the primary end point was significant with the study of only 27 infants, our consulting statisticians and 2 independent observers informed us of the opportunity to stop the study and to limit the study duration.

Clinical characteristics of the 2 groups were described with mean and SD values and with rates and percentages. Statistical analyses were performed by using Student’s $t$ test for continuous variables and Fisher’s exact test for categorical variables. $P < 0.05$ was considered statistically significant.

**RESULTS**

During the study period, 40 infants were considered eligible, but only 27 of those infants constituted the study group; 7 infants were excluded because of their MV requirement within the first 6 hours of life, 3 because of a lack of parental consent, 2 because of the presence of grade 3 IVH, and 1 because of a major cardiac malformation (tetralogy of Fallot). Of the 27 patients, 13 were enrolled in the SURF-NCPAP group and 14 in the SURF-MV group. The characteristics of the patients in the 2 groups did not demonstrate significant differences (Table 1). In particular, the Clinical Risk Index for Babies scores, F$_{O_2}$ values at study entry, and a/A$P_{O_2}$ values before surfactant treatment indicated that the IRDS severity was similar for the 2 groups.

NCPAP began 1 to 150 minutes after birth, at the mean age of 35 minutes. The SURF-NCPAP group received surfactant at 2.7 ± 1.4 hours, whereas the

<table>
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<tr>
<th>TABLE 1. Characteristics of Study Groups*</th>
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<tr>
<td>SURF-NCPAP (n = 13)</td>
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<tr>
<td>Birth weight, g</td>
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<tr>
<td>Gestational age, wk</td>
</tr>
<tr>
<td>Male gender</td>
</tr>
<tr>
<td>Cesarean section</td>
</tr>
<tr>
<td>Apgar score at 5 min</td>
</tr>
<tr>
<td>Pre-natal steroid treatment</td>
</tr>
<tr>
<td>CRIB score</td>
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<tr>
<td>F$_{O_2}$ at study entry</td>
</tr>
<tr>
<td>a/A$P_{O_2}$ before surfactant</td>
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<tr>
<td>Main maternal pregnancy disease</td>
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<tr>
<td>Gestosis</td>
</tr>
<tr>
<td>PPROM</td>
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<tr>
<td>Abruptal placenta</td>
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<td>Idiopathic preterm delivery</td>
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</table>

CRIB indicates Clinical Risk Index for Babies; PPROM, preterm premature rupture of membranes. Values are mean ± SD or rate (%).
SURF-MV group received surfactant at 3.5 ± 1.6 hours (P = .180). Infants in the SURF-NCPAP group were extubated 2.8 ± 0.8 minutes after the surfactant treatment, and only 2 patients (15%) subsequently required MV because of the worsening of iRDS (1 patient required patient-triggered ventilation for 24 hours beginning 2 hours after surfactant treatment and 1 patient required patient-triggered ventilation for 3 days beginning at 3 days of life).

At 7 days of life, no patient in the SURF-NCPAP group but 6 patients (43%) in the SURF-MV group still were intubated and undergoing ventilation (P = .027). Six hours after surfactant administration, the a/ArO₂ values were similar for the 2 groups (0.49 ± 0.17 vs 0.48 ± 0.13; P = .864). After surfactant treatment, 12 patients (92%) in the SURF-NCPAP group were treated with oxygen therapy for 7.0 ± 2.9 days, 12 patients (92%) were treated with NCPAP for 3.2 ± 2.4 days, 2 patients (15%) required MV for 2.0 ± 1.4 days, and none received additional surfactant doses. After surfactant treatment, all patients in the SURF-MV group received oxygen therapy for 11.3 ± 5.6 days, 9 patients (64%) received NCPAP for 6.2 ± 3.0 days, 14 patients (100%) received MV (patient-triggered ventilation, 11 patients; high-frequency oscillatory ventilation, 5 patients) for 5.6 ± 3.1 days, 2 patients (14%) required a second intubation after the first extubation, and 7 patients (50%) received a second dose of surfactant. The duration of oxygen therapy (P = .025), NCPAP (P = .009), and MV (P = .031) and the incidence of administration of a second dose of surfactant (P = .006) were significantly greater in the SURF-MV group (Table 2).

The incidences of PDA, pneumothorax, BPD, IVH, periventricular leukomalacia, ROP, and necrotizing enterocolitis and the lengths of stay in the hospital were similar for the SURF-NCPAP and SURF-MV groups, whereas the length of stay in the intensive care unit was shorter for the SURF-NCPAP group (21.7 ± 10.1 vs 29.9 ± 8.0 days; P = .027) (Table 3). Among the 10 patients with PDA, only 1 in the SURF-MV group required surgical ligation. All observed ROP and IVH cases were grade 1.

**DISCUSSION**

A widely held opinion is that very low birth weight infants usually require MV soon after the development of iRDS and that the use of early NCPAP for such infants cannot be of great benefit. Therefore, ~70% of very low birth weight infants undergo MV during their clinical course.14 However, many articles seem to confirm what Avery et al15 found in the 1980s by comparing the different methods of treatment and outcomes among very low birth weight infants at 8 major centers, ie, the highest survival rates and the lowest incidences of BPD were associated with a respiratory support policy of early NCPAP and tolerance of high Pco₂. In 1994, Verder et al4 in a Danish-Swedish multicenter study, randomized a cohort of preterm infants who were being treated with NCPAP for iRDS to receive surfactant or to continue receiving NCPAP alone. Those authors4 found that infants treated with NCPAP and surfactant exhibited reduced needs for subsequent MV. Some years later, the same authors5 randomized an additional cohort of infants of <30 weeks’ gestation who were being treated with NCPAP for iRDS to receive a single dose of surfactant either early (at the mean age of 5.2 hours) or late (at the mean age of 9.9 hours) after iRDS worsening. That study demonstrated that early treatment with NCPAP and surfactant reduced the subsequent need for MV.5 Moreover, Blennow et al16 reported that immediate extubation after surfactant treatment was effective in improving the clinical course of iRDS and in decreasing the need for MV, and NCPAP has been found to be effective in preventing the failure of extubation and the resumption of MV among preterm infants.17

For these various reasons, we investigated the outcomes of 2 different strategies of iRDS treatment among preterm infants. All of our patients were treated early (and not prophylactically) with NCPAP and surfactant, but newborns in the SURF-NCPAP group were extubated quickly and then retreated with NCPAP, whereas newborns in the SURF-MV group were treated with MV after surfactant administration and then were weaned gradually from MV. We found that the iRDS clinical course among infants in the SURF-NCPAP group was better than that among infants in the SURF-MV group, as evidenced by lower incidences of MV and administration of a second dose of surfactant, shorter durations of oxygen therapy, NCPAP, and MV, and shorter lengths of stay in the intensive care unit. These results were obtained without inducing acute worsening of iRDS, as demonstrated by the similar a/ArO₂ values at 6 hours after surfactant treatment, and without inducing additional differences in outcomes between the groups, as demonstrated by the similar incidences of BPD, pneumothorax, PDA, IVH, periventricular leukomalacia, ROP, and death and the similar length of stay in the hospital.

These results are in agreement with the reported benefits of NCPAP4,5,16,17 in iRDS treatment and are

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**TABLE 2.** Data on Study End Points

<table>
<thead>
<tr>
<th></th>
<th>SURF-NCPAP (n = 13)</th>
<th>SURF-MV (n = 14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV at 7 d</td>
<td>0/13</td>
<td>6/14 (43)</td>
<td>.026</td>
</tr>
<tr>
<td>a/ArO₂ after 6 h</td>
<td>0.47 ± 0.17</td>
<td>0.48 ± 0.13</td>
<td>.864</td>
</tr>
<tr>
<td>O₂ therapy duration, d</td>
<td>7.0 ± 2.9</td>
<td>11.3 ± 5.6</td>
<td>.026</td>
</tr>
<tr>
<td>NCPAP duration, d</td>
<td>3.2 ± 2.4</td>
<td>6.2 ± 3.0</td>
<td>.009</td>
</tr>
<tr>
<td>MV duration, d</td>
<td>2.0 ± 1.4*</td>
<td>5.6 ± 3.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Second dose of surfactant</td>
<td>0/13</td>
<td>7/14 (50)</td>
<td>.006</td>
</tr>
</tbody>
</table>

Values are mean ± SD or rate (%). *These data are for the only 2 patients in this group who received MV.
well explained by the mechanisms of action of continuous positive airway pressure; creating a constant airway-opening pressure is important to decrease the work of breathing, to establish and maintain an adequate functional residual capacity, to stabilize air space, and to promote the release of surfactant stores. Moreover, avoiding endotracheal intubation is of benefit for mucociliary transport and humidification of inspired air, as well as decreasing the risk of airway damage and secondary infection and the occurrence of lung barotrauma and volutrauma secondary to MV.

CONCLUSIONS

We found that, among infants being treated with NCPAP for iRDS, the immediate reinstitution of NCPAP after surfactant administration was safe and beneficial, as evidenced by the decreased need for MV and the shorter requirement for respiratory support, compared with infants who received MV after surfactant treatment. This strategy contributed to reducing the need for surfactant treatment and decreasing the stays of our patients in the intensive care unit, thus decreasing neonatal intensive care unit costs.

REFERENCES

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