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 reinstitution 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.

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.
Flow System; Eme Ltd, Brighton, United Kingdom) at signs of respiratory distress and the institution of MV (patient-triggered ventilation: Babylog 8000 plus; Drager, Lübeck, Germany; high-frequency oscillatory ventilation: Sensormedics 3100A; Sensor Medics Corp, Yorba Linda, CA) when pH was <7.20, Po2 was <50 mm Hg with FiO2 of >0.50, and Pco2 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 reinstatement 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 FiO2 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 FiO2 was ≤0.40, mean arterial pressure was ≤6 cm H2O, and Po2 and Pco2 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., FiO2 of ≤0.40, positive end expiratory pressure of ≤5 cm H2O, Po2 of ≥50 mm Hg, and Pco2 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/APO2), 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 Pco2 of >65 mm Hg, hypoxemia with Po2 of <50 mm Hg at FiO2 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/APO2, 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 postconceptional age of at least 36 weeks. IVH was classified according to the method described by Papile et al.25 and ROP was graded according to the international classification of ROP. 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 < .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, FiO2 values at study entry, and a/APO2 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 1. Characteristics of Study Groups

<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>Birth weight, g</td>
<td>1078 ± 321</td>
<td>1126 ± 170</td>
<td>.628</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>29.0 ± 2.2</td>
<td>28.3 ± 1.32</td>
<td>.322</td>
</tr>
<tr>
<td>Male gender</td>
<td>5/13 (38)</td>
<td>6/14 (43)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>11/13 (85)</td>
<td>11/14 (76)</td>
<td>1.000</td>
</tr>
<tr>
<td>Apgar score at 5 min</td>
<td>8.2 ± 0.7</td>
<td>7.4 ± 0.9</td>
<td>.346</td>
</tr>
<tr>
<td>Pre-natal steroid treatment</td>
<td>8/13 (62)</td>
<td>13/14 (93)</td>
<td>.077</td>
</tr>
<tr>
<td>CRIB score</td>
<td>1.9 ± 1.7</td>
<td>2.6 ± 1.8</td>
<td>.310</td>
</tr>
<tr>
<td>FiO2 at study entry</td>
<td>0.33 ± 0.13</td>
<td>0.35 ± 0.09</td>
<td>.644</td>
</tr>
<tr>
<td>a/APO2 before surfactant</td>
<td>0.28 ± 0.13</td>
<td>0.21 ± 0.14</td>
<td>.191</td>
</tr>
<tr>
<td>Main maternal pregnancy disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestosis</td>
<td>6/13 (46)</td>
<td>7/14 (50)</td>
<td>1.000</td>
</tr>
<tr>
<td>PPROM</td>
<td>1/13 (7.7)</td>
<td>2/14 (14)</td>
<td>1.000</td>
</tr>
<tr>
<td>Abruptal placenta</td>
<td>1/13 (7.7)</td>
<td>1/14 (7.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Idiopathic preterm delivery</td>
<td>5/13 (38)</td>
<td>5/14 (38)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

CRIB indicates Clinical Risk Index for Babies; PPROM, preterm premature rupture of membranes. Values are mean ± SD or rate (%).
SURF-MV group required surgical ligation. All ob-

Among the 10 patients with PDA, only 1 in the

groups, whereas the length of stay in the intensive
care unit was shorter for the SURF-NCPAP group
among infants in the SURF-MV group, as evidenced
by lower incidences of MV and administration of a
second dose of surfactant. The duration of oxygen ther-
dapy (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
tenterocolitis 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 ob-
served 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 NC-
PAP for such infants cannot be of great benefit. Therefore, ~70% of very low birth weight infants
undergo MV during their clinical course. However,
many articles seem to confirm what Avery et al found in the 1980s by comparing the different meth-
ods 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 al,4 in a Danish-Swedish multicenter study, ran-
domized 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 surfac-
tant 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 demonstrat-
ed that early treatment with NCPAP and surfac-
tant reduced the subsequent need for MV.5 More-
ever, Blennow et al16 reported that immediate
exhuabation after surfactant treatment was effective in
improving the clinical course of iRDS and in decreas-
ing 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 out-
comes 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 admin-
istration and then were weaned gradually from MV.
We found that the iRDS clinical course among in-
fants 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 oxy-
gen 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/Apo2 values at 6
hours after surfactant treatment, and without induc-
ing additional differences in outcomes between the
groups, as demonstrated by the similar incidences of
BPD, pneumothorax, PDA, IVH, periventricular leu-
komalacia, 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

<table>
<thead>
<tr>
<th>TABLE 2. Data on Study End Points</th>
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<tr>
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<tr>
<td></td>
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<tr>
<td>MV at 7 d</td>
</tr>
<tr>
<td>a/Apo2 after 6 h</td>
</tr>
<tr>
<td>O2 therapy duration, d</td>
</tr>
<tr>
<td>NCPAP duration, d</td>
</tr>
<tr>
<td>MV duration, d</td>
</tr>
<tr>
<td>Second dose of surfactant</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 reinstition of NC-PAP 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 stays of our patients in the intensive care unit, thus decreasing neonatal intensive care unit stays.

**REFERENCES**


3. Stevens TP, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for RDS. Cochrane Database Syst Rev. 2002;CD003063.


21. Tarnow-Mordi WO, Sutton P, Wilkinson AR. Inadequate 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.


**TABLE 3. Secondary Outcome Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SURF-NCPAP (n = 13)</th>
<th>SURF-MV (n = 14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0/13</td>
<td>1/14 (7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>PDA</td>
<td>4/13 (31%)</td>
<td>6/14 (43%)</td>
<td>0.694</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>0/13</td>
<td>1/14 (7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen at day 28</td>
<td>3/13 (23%)</td>
<td>7/14 (50%)</td>
<td>0.236</td>
</tr>
<tr>
<td>Oxygen at postconceptional week 36</td>
<td>0/13</td>
<td>3/14 (21%)</td>
<td>0.222</td>
</tr>
<tr>
<td>IVH</td>
<td>1/13 (8%)</td>
<td>1/14 (7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Periventricular leukomalacia</td>
<td>0/13</td>
<td>0/14</td>
<td></td>
</tr>
<tr>
<td>ROP</td>
<td>1/13 (8%)</td>
<td>3/14 (21%)</td>
<td>0.595</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>0/13</td>
<td>0/14</td>
<td>1.000</td>
</tr>
<tr>
<td>Length of stay in intensive care unit, d</td>
<td>21.7 ± 10.1</td>
<td>29.9 ± 8.0</td>
<td>0.027</td>
</tr>
<tr>
<td>Length of stay in hospital, d</td>
<td>58.3 ± 21.5</td>
<td>68.8 ± 17.6</td>
<td>0.176</td>
</tr>
</tbody>
</table>

Values are mean ± SD or rate (%).
Early Extubation and Nasal Continuous Positive Airway Pressure After Surfactant Treatment for Respiratory Distress Syndrome Among Preterm Infants <30 Weeks’ Gestation

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