Surfactant Administration via Thin Catheter During Spontaneous Breathing: Randomized Controlled Trial

WHAT’S KNOWN ON THIS SUBJECT: A policy of intubation, mechanical ventilation, and surfactant administration is commonly used for the treatment of respiratory distress syndrome worldwide; however subsequent development of bronchopulmonary dysplasia remains as risk with this standard approach.

WHAT THIS STUDY ADDS: Noninvasive surfactant administration technique during spontaneous breathing (Take Care) along with nasal continuous positive airway pressure support successfully reduces the need for further respiratory support and bronchopulmonary dysplasia rate in very low birth weight infants.

abstract

BACKGROUND: The primary aim of this randomized study was to describe the feasibility of early administration of surfactant via a thin catheter during spontaneous breathing (Take Care) and compare early mechanical ventilation (MV) requirement with the InSurE (Intubate, Surfactant, Extubate) procedure.

METHODS: Preterm infants, who were <32 weeks and stabilized with nasal continuous positive airway pressure (nCPAP) in the delivery room, were randomized to receive early surfactant treatment either by the Take Care or InSurE technique. Tracheal instillation of 100 mg/kg poractant α via 5-F catheter during spontaneous breathing under nCPAP was performed in the intervention group. In the InSurE procedure, infants were intubated, received positive pressure ventilation for 30 seconds after surfactant instillation, and placed on nCPAP immediately.

RESULTS: One hundred infants in each group were analyzed. The MV requirement in the first 72 hours of life was significantly lower in the Take Care group when compared with the InSurE group (30% vs 45%, P = .02, odds ratio –0.52, 95% confidence interval –0.94 to –0.29). Mean duration of both nCPAP and MV were significantly shorter in the Take Care group (P values .006 and .002, respectively). Bronchopulmonary dysplasia rate was significantly lower among the infants treated with the Take Care technique (relative risk –0.27, 95% confidence interval –0.1 to –0.72).

CONCLUSIONS: The Take Care technique is feasible for the treatment of respiratory distress syndrome in infants with very low birth weight. It significantly reduces both the need and duration of MV, and thus the bronchopulmonary dysplasia rate in preterm infants. Pediatrics 2013;131:e502–e509

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KEY WORDS surfactant, InSurE, bronchopulmonary dysplasia, preterm, spontaneous breathing, mechanical ventilation

ABBREVIATIONS BPD—bronchopulmonary dysplasia
DR—delivery room
FiO2—fraction of inspired oxygen
GA—gestational age
InSurE—intubate, surfactant, extubate
MV—mechanical ventilation
nCPAP—nasal continuous positive airway pressure
PEEP—positive end-expiratory pressure
PPV—positive pressure ventilation
RDS—respiratory distress syndrome
RR—relative risk
SpO2—oxygen saturation

Dr Kanmaz was responsible from the design and the content of the study, and contributed to acquisition and interpretation of data and analysis. Dr Erdeve was responsible for the design and the content of the study, drafting the article, and revising it critically for important intellectual content. Dr Canpolat was responsible for drafting the article and revising it critically for important intellectual content and performing the statistical analysis. Dr Mutlu was responsible for acquisition and interpretation of data. Dr Dilmen was responsible for final approval of the version to be published.

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Respiratory distress syndrome (RDS) is the most important cause of mortality and morbidity in preterm infants. Although surfactant has been used with success in the treatment of RDS, its introduction did not reduce the incidence of bronchopulmonary dysplasia (BPD). There has been a noninvasive trend to use nasal continuous positive airway pressure (nCPAP) more frequently and early to avoid mechanical ventilation (MV)-related adverse effects. A meta-analysis of 6 recent studies indicated that early nCPAP with early surfactant compared with nCPAP with late surfactant significantly reduced BPD, MV need, and air leaks. Therefore, to combine the benefits of both principles, the so-called Intubate, Surfactant, Extubate (InSurE) method was developed. However, surfactant instillation requires intubation and positive pressure ventilation (PPV) for its distribution, and even a short period of vigorous manual ventilation can induce significant lung injury. There is an ongoing discussion on potential hazardous effects of even brief PPV and intubation that are required in the InSurE procedure. There has been a great endeavor to create alternative ways of surfactant administration. Recently, surfactant administration via a thin endotracheal catheter during spontaneous breathing with CPAP has come into clinical use, especially in Germany. A randomized clinical trial demonstrated that this method reduced the need for MV; however, this trial was multicentric without standardized care and enrolled only infants with 26 to 28 weeks of gestational age (GA). Recently, we developed a noninvasive surfactant administration technique modified by the one that Kribs et al described and called it the Take Care procedure, as our primary aim was taking care of these vulnerable preterm infants. The Take Care technique differs from the previously described technique by a shorter duration (30 to 60 seconds) of a single type of surfactant (poractant α) administered by only experienced physicians in the NICU, shorter catheter length, and no need for any forces during application.

The aim of this study was to assess the efficacy and the feasibility of the Take Care technique and to compare its short- and long-term effects with the InSurE procedure, especially on the requirement of intubation and MV in the first 72 hours of life, which are known to be the major contributing factors for BPD.

**METHODS**

**Setting and Participants**

This prospective single-center randomized controlled study was conducted in the NICU of Zekai Tahir Burak Maternity Teaching Hospital between December 2010 and December 2011. The trial was approved by the local ethics committee and written informed parental consent was obtained for each patient. Inborn preterm infants with GA <32 weeks and who suffered from RDS were enrolled in the study. Infants with major congenital anomalies, no parental consent, and who required PPV or intubation in the delivery room (DR) and who were not resuscitated by trial investigators in the DR were excluded. RDS was diagnosed in infants exhibiting the following symptoms: need for supplemental oxygen, tachypnea, grunting, and intercostal retractions, and confirmed by typical x-ray and blood gas findings. Patients with signs of RDS, who were under nCPAP treatment and required fraction of inspired oxygen (FiO2) ≥0.4 in first 2 hours of life to maintain SpO2 levels between 85% to 92%, were randomized to receive surfactant treatment either by the Take Care or InSurE procedure. Sequentially numbered sealed opaque envelopes stratified by GA (≤28 weeks and 29 to 32 weeks) were used for randomization.

**Procedures**

Preterm infants who required respiratory support with supplemental oxygen and had favorable effort of spontaneous breathing were stabilized in the DR and transported to the NICU. In case of a requirement, positive end-expiratory pressure (PEEP) at 5 to 7 cm H2O supplied by T-piece device (Neopuff Infant Resuscitator; Fisher and Paykel, Auckland, New Zealand) was administered in the DR and during transportation. nCPAP was continued by positioning Hudson binasal prongs, connected to an SLE 2000 mechanical ventilator (SLE Ltd, London, United Kingdom) set at PEEP with 5 to 7 cm H2O for patients with respiratory distress in the NICU. FiO2 was set as 0.3 and then adjusted so that oxygen saturation (SpO2) measured by pulse oximetry was 85% to 92%.

Exogenous surfactant administration via the new technique called the Take Care procedure was performed once the infant was in a stable condition. A 5F, flexible, sterile nasogastric tube was used for the procedure. The catheter was prepared by shortening at 33-cm depth from the catheter hub. Desired depths of insertion beyond the vocal cords for preterm infants with 25 to 26, 27 to 28, and 29 to 32 weeks GA were 1.0, 1.5, and 2.0 cm, respectively. After catheter placement, the laryngoscope was removed. Porcine surfactant (Curosurf; Chiesi Farmaceutici, Parma, Italy) at a dose of 100 mg/kg (1.25 mL/kg) was drawn up in a 5-mL syringe, and an additional 1 mL of air was drawn up into the syringe taking account of the dead volume of the instillation catheter. Exogenous surfactant was administered in 1 bolus in 30 to 60 seconds and the tracheal catheter was immediately withdrawn. During the Take Care procedure, direct laryngoscopy was performed by using a standard
laryngoscope and Miller 00 blade, and CPAP support was not disrupted. If visualization of vocal cords and replacement of catheter was not possible within 20 to 30 seconds, a further catheterization attempt was postponed for at least 1 minute. Infants who suffered severe apnea and bradycardia (<100/min), along with desaturation (<80%) lasting longer than 20 seconds got PPV by T-piece device.

Patients who received surfactant via the InSurE technique were first orally intubated with a double-lumen endotracheal tube, and porcine surfactant at a dose of 100 mg/kg (1.25 mL/kg) was instilled to the trachea in 30 seconds. Manual lung inflation by a T-piece device at 20/5-cm H₂O pressure was performed during the surfactant instillation and then the patient was promptly extubated. Right after extubation, nCPAP support was recommended, as described in the Take Care technique. No premedication, such as sedation or atropine, was used during both procedures.

Management after the Take Care or InSurE procedure was as per standard practice at our institution. Control arterial blood gas samples were taken ~2 hours after the procedure. CPAP pressure was titrated according to work of breathing and oxygen requirement, with SpO₂ target of 85% to 92%. If the patient did not respond to treatment or deteriorated after 6 hours of first application (FiO₂ >0.4, partial pressure of carbon dioxide >60 mm Hg), a second dose of surfactant of 100 mg/kg was repeated and the same procedure was used as during the first surfactant instillation. Maximum acceptable settings were sustained CPAP pressure of beyond 7-cm H₂O along with an FiO₂ of 0.6. Infants exceeding these limits were intubated, and a further dose of surfactant was given if clinically indicated. Other indications for intubation were sustained respiratory acidosis (pH <7.2) and apnea requiring repeated episodes of PPV.

**Measures**

To assess the demographic and prenatal risks, standardized data, such as GA, birth weight, gender, Apgar score at 5 minutes, preterm premature rupture of membranes, and antenatal steroid use regardless of the time interval between steroid administration and birth, were collected. Clinical data, along with details of failure of first attempt during catheterizing the trachea, occurrence of coughing or gagging, and need for PPV in the Take Care procedure and surfactant reflux, bradycardia, and desaturation in both procedures were recorded prospectively. The nCPAP, oxygen requirement, and SpO₂ were documented before, during, and at first hour; 24 hours, 48 hours, and 72 hours after the surfactant administration. Partial pressure of carbon dioxide and pH values were compared in paired arterial blood gas samples taken before and 2 hours after surfactant application. The radiographic severity of RDS was graded as normal (grade 1), mild (grade 2), moderate (grade 3), or severe (grade 4) before the procedures. The mode of respiratory management during the first 72 hours of life was noted prospectively. Need for MV during the first 72 hours of life in infants who had initially been managed with nCPAP was classified as failure of nCPAP.

**Outcomes**

The primary outcomes of study were the effects of the Take Care technique on the need for intubation and MV in the first 72 hours (and thereafter) of life in addition to feasibility of the technique. Secondary outcomes were repeated surfactant therapy, duration of respiratory support, rates of pneumothorax, patent ductus arteriosus requiring medical or surgical treatment, intraventricular hemorrhage (grade >2 according to the Papille classification), retinopathy of prematurity greater than stage 2 as defined in the international classification, necrotizing enterocolitis with Bells stage 2 or greater, length of hospitalization, and especially BPD or death. BPD was diagnosed on the basis of the National Institutes of Child Health and Development diagnostic criteria.

**Statistical Analysis**

On the basis of our previous experiences with the InSurE technique, 50% of patients required intubation and MV in first 72 hours of life. To reduce the need for MV treatment with this new Take Care technique from 50% to 30%, we estimated that a sample size 100 for each group will yield >80% power. The statistical evaluation of the data was performed by using SPSS software, version 17.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY). Normally distributed data were given as mean and SD, others were presented as median and range. Demographic percentage and mean outcome measures of the patients were compared between 2 groups with Fisher’s exact test, chi-squared test, and t-test, respectively. Abnormally distributed data were evaluated with the Kolmogorov-Smirnov test; P < .05 was considered statistically significant. The absolute risk reduction and the number needed to treat together with 95% confidence intervals (CIs) and the relative risk (RR) were calculated as the effect measures, multinominal logistic regression used for this calculation.

**RESULTS**

During the study period, 357 infants were assessed for eligibility. A total of 254 infants who were treated with nCPAP immediately after birth were assessed for surfactant treatment; 200 patients who required surfactant were randomized into either the Take Care or
InSurE group, and 100 infants in each group were eligible for the statistical analysis (Fig 1). Baseline characteristics and perinatal risk factors, which are summarized in Table 1, did not show any significant difference between groups.

Arterial blood gas analysis, which was obtained before and 2 hours after surfactant treatment and radiologic scoring of chest x-rays, revealed no significant differences between the 2 groups (Table 2). Alteration in FiO2 and PEEP levels over time in both groups during 24 hours of life, which are demonstrated in Fig 2 and Fig 3, showed similarity.

Coughing and gagging (11%) and bradycardia and desaturation (17%) were recorded as peridosing adverse events in the Take Care group. Failure of the first attempt was recorded in 18% of patients in the Take Care group and 10% in the InSurE group and the difference was not statistically significant ($P = .07$). Bradycardia and desaturation rates were not statistically different between groups (18% vs 17%, $P = .35$). Observed surfactant reflux during the attempt was significantly higher in the Take Care group in contrast to the InSurE group (21% vs 10%, $P = .002$). Twelve percent ($n = 12$) of patients had severe apnea lasting $>20$ seconds and bradycardia ($<100/\text{min}$) required PPV with a T-piece device during the procedure in the Take Care group, whereas all patients in the InSurE group received PPV.

Pulmonary outcomes of both procedures are presented in Table 2. Forty percent of patients ($n = 40$) in the Take Care and 49% ($n = 49$) in the InSurE group required MV support at some time during hospitalization. Mean duration of both nCPAP (78 vs 116 hours, $P = .002$) and MV (35.6 vs 64.1 hours, $P = .006$) were significantly shorter in the Take Care group. The MV requirement, which was described as nCPAP failure in first 72 hours of life, was significantly lower in the Take Care group when compared with the InSurE group (30% vs 45%, $P = .02$, RR –0.52, 95% CI –0.94 to –0.29) (Table 3).

The incidence of neonatal morbidities, such as patent ductus arteriosus (28% vs 32%), necrotizing enterocolitis (5% vs 6%), intraventricular hemorrhage (10% vs 16%), and retinopathy of prematurity (3% vs 4%), were similar between groups ($P > .05$). However, the incidence of moderate to severe BPD among patients who survived to discharge was significantly higher in the InSurE group (20.2% vs 10.3%, $P = .009$). Four patients in the InSurE and 1 patient in the Take Care group constituted patients with severe BPD and were discharged to home with supplemental oxygen treatment. The BPD rate was significantly lower among the infants treated with the Take Care technique (RR –0.27, 95% CI –0.72 to –0.1) (Table 3).

Subgroup analysis, including preterm infants at $\leq 28$ weeks’ gestation, revealed that BPD was significantly lower among patients in the Take Care group in comparison with the InSurE group (13.6% vs 26.2%, $P = .008$, RR –0.21 95% CI –0.65 to –0.07) (Table 3). Overall mortality rates were similar in both groups (16% and 13%, $P = .68$). No
significant difference between groups was reported for the combined outcome of BPD or death (22% and 32%, $P = .15$).

**DISCUSSION**

This single-center prospective randomized controlled trial demonstrated that bolus surfactant administration during spontaneous breathing via a thin nasogastric tube, dubbed the Take Care technique, was feasible and it successfully reduced the MV requirement in first 72 hours of life, shortened MV duration, and resulted in a lower BPD rate when compared with the InSurE technique.

There is an ongoing discussion in the literature about alternative ways of surfactant administration without applying any PPV. The oldest idea in this context was surfactant nebulization; however, there are still technical problems to solve and surfactant nebulization has not been introduced as a widespread therapy. Reports on surfactant application via laryngeal mask are interesting but refer to only a small number of patients. Administration of surfactant via a thin catheter during spontaneous breathing with CPAP has been used since 2001. In this method, generally the catheter is placed with Magill forceps into the trachea under direct laryngoscopy and surfactant is applied over a period of 1 to 3 minutes. Dargaville et al described the use of a more stable vascular catheter for the procedure, which allowed placement without use of the Magill forceps. The Take Care technique is the combination of both techniques described previously; we use a thin shortened nasogastric tube for easy replacement without Magill forceps and premedication, and administer surfactant in a shorter duration (30–60 seconds).

We observed fewer peridosing events, such as failure of the first attempt of
catheterization, bradycardia, surfactant reflux, and PPV requirement, by using this technique in comparison with Dargaville et al’s report.18 A major difference in perising events in comparison with previous reports was that only Kribs et al,12 who used atropin for premedication, reported a lower rate of bradycardia (7.4%) than our procedure. Although Göpel et al9 used different surfactant choices, we used a single one: poractant α. We chose poractant α because its favorable efficacy in smaller volumes gives the opportunity for easy bolus administration; therefore, a considerably lower rate of reflux would be observed. In a previous study, we reported that poractant α had rapid onset of action, less need for redosing, rapid extubation, and higher survival free of BPD in preterm infants.24 Moreover, Ramanathan et al25 also reported similar findings that encouraged treatment with poractant α in our study. The sustained reduction in FiO2 after Take Care indicated that an adequate dose of exogenous surfactant was delivered, overcoming some of the atelectasis related to high surface tension in the airspaces of the surfactant-deficient lung. Even in instances in which surfactant reflux into the oropharynx was noted, significant reductions in FiO2 occurred in time, suggesting deposition of a sufficient quantity of surfactant into the lung in patients on nCPAP.

One of the most striking results of the Take Care technique was a successful reduction in BPD rate (10.3%) in comparison with the InSurE (20.2%) method. Although the study was not designed with sufficient power for reduction in BPD, lesser need for MV in first 72 hours of life and lower duration of respiratory support in the Take Care group seem to be major factors that influenced this reduction. Kribs et al11 reported fewer deaths or BPD and need for any respiratory support in patients who received surfactant without intubation during spontaneous breathing, although these infants were smaller and more immature when compared with infants who received standard care. However, this report was not a randomized controlled study. Recently Göpel et al9 reported the results of a multicentric prospective randomized trial including 12 centers and demonstrated that the application of surfactant via a thin catheter to spontaneously breathing preterm infants receiving nCPAP reduced the need for MV. In their trial, the Avoid Mechanical Ventilation trial, the authors concluded that although they observed shorter duration of MV in patients who received surfactant by catheter, there was no difference between groups in rates of death and serious adverse events, including BPD. We think that difficulties in standardization of a novel technique might affect the success of surfactant application without intubation on BPD. Although it has been demonstrated as feasible, results obtained in the Take Care trial, which was a single-center study with only poractant α as surfactant choice, support that standardization should be considered for the efficacy of the technique.

To avoid MV and thus lung injuries in preterm infants, several approaches have been studied.26–29 Stabilization with nCPAP after birth and administration of rescue surfactant via intubation are the main characteristics of these relatively noninvasive approaches. In 1994, Verder et al4 published the first randomized controlled trial of surfactant instillation during nCPAP, showing that a single dose of surfactant reduced the need for MV by half, from 85% to 43% and demonstrated that the effect was even more pronounced if surfactant was given as early rescue treatment.4,5 More recently, nCPAP and rescue intubation were studied in large cohorts of very preterm infants in Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT),30 Continuous Positive Airway Pressure or Intubation at Birth Trial (COIN),31 and combining prophylactic surfactant and early nasal continuous positive airway pressure in very preterm infants (CURPAP)32 trials. In the SUPPORT trial, the MV (83%) rate was significantly higher than our current rate. Although MV and BPD rates reported in COIN51 (59% and 25%) and CURPAP32 (33% and 21%) trials were hardly similar to our findings, the duration of MV was significantly shorter in our study. We considered that the need for intubation and even brief PPV by bagging to administer surfactant in the InSurE method may be harmful to an immature lung and by these properties it seems to be more invasive than the Take Care technique. Björklund et al12 demonstrated that manual ventilation, even

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**TABLE 3** The Rates of BPD and MV Requirements among Groups

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Take Care n = 100</th>
<th>InSurE n = 100</th>
<th>P</th>
<th>RR</th>
<th>95% CI</th>
<th>NNT</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any MV, %</td>
<td>30</td>
<td>45</td>
<td>.02</td>
<td>−0.52</td>
<td>−0.94 to −0.29</td>
<td>6.02</td>
<td></td>
</tr>
<tr>
<td>Any MV, %</td>
<td>40</td>
<td>49</td>
<td>.12</td>
<td>−0.56</td>
<td>−1 to −0.29</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>BPD, n (%)</td>
<td>9 (10.3)</td>
<td>17 (20.2)</td>
<td>.009</td>
<td>−0.27</td>
<td>−0.72 to −0.1</td>
<td>10.005</td>
<td></td>
</tr>
<tr>
<td>≤28 wk</td>
<td>n = 59</td>
<td>n = 55</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early MV, %</td>
<td>32</td>
<td>52</td>
<td>.02</td>
<td>−0.43</td>
<td>−0.91 to −0.19</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Any MV, %</td>
<td>45</td>
<td>59</td>
<td>.09</td>
<td>−0.42</td>
<td>−0.94 to −0.47</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>BPD, n (%)</td>
<td>6 (13.6)</td>
<td>16 (26.2)</td>
<td>.008</td>
<td>−0.21</td>
<td>−0.65 to −0.07</td>
<td>7.004</td>
<td></td>
</tr>
</tbody>
</table>

with a few large breaths, may cause lung injury and blunt the effect of subsequent surfactant treatment. On the other hand, passing a catheter between the cords means the infant can probably maintain an essentially unchanged respiratory pattern and perhaps continue to benefit from nCPAP. In contrast, tracheal intubation makes expiratory braking almost impossible and the lung will inevitably be derecruited. Giving manual inflations to reexpand the lungs and facilitate surfactant spreading may perhaps have the opposite effect, resulting in a more uneven surfactant distribution than during spontaneous breathing. We suggest that elimination of these hazardous effects of PPV with intubation in the Take Care procedure may play an important role in reduction of BPD.

Our trial had some limitations, which should be considered in future studies. First, during the study period, all infants who might have been eligible for the study could not be enrolled because of the concern for standardization of the procedure. Second, probable estimated challenges (experience of physicians, availability or variability of equipment) in standard care did not allow us to conduct a multicentric study. However, results of the study, especially reduction in the BPD rate, supported our hypothesis. Third, we used only poractant α because of its smaller volume as surfactant choice. Although it helped to have low rate and volume of surfactant reflux, we could not comment on our technique with other surfactant choices. Fourth, we did not use premedication before the procedures. Although premature neonates are very sensitive to pain and vulnerable to its long-term effects, the need for sedation before tracheal intubation is still discussed because of concerns of side effects, but many neonatologists would prefer to use it.

We conclude that the Take Care technique is feasible for the treatment of RDS in infants with very low birth weight and it significantly reduces both the need and duration of MV support. Avoiding MV and administering surfactant during spontaneous breathing without intubation and PPV could have a domino effect in reducing major morbidities, such as BPD. We suggest that this kind of minimally invasive approach may result in a change in neonatal practice; however, further studies concerning the effect on BPD with sufficient power and meta-analysis are needed.

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