Minimally Invasive Surfactant Administration in Preterm Infants
A Meta-narrative Review

Kiran More, MD, FRACP; Pankaj Sakhuja, MD; Prakesh S. Shah, MSc, MD, FRCPC

**IMPORTANCE**
Surfactant administration by minimally invasive methods that allow for spontaneous breathing might be safer and more effective than administration with endotracheal intubation and mechanical ventilation; however, the efficacy and safety of minimally invasive methods have not been reviewed.

**OBJECTIVE**
To conduct a meta-narrative review of the efficacy and safety of minimally invasive surfactant administration using a thin catheter, aerosolization, a laryngeal mask airway, and pharyngeal administration in preterm infants with or at risk for respiratory distress syndrome.

**DATA SOURCES**
We searched the PubMed, EMBASE, Cochrane, and CINAHL databases, published journals, and conference proceedings from inception to June 30, 2013.

**STUDY SELECTION**
Randomized clinical trials or observational studies of preterm infants who were given surfactant for respiratory distress syndrome by minimally invasive methods.

**DATA EXTRACTION AND SYNTHESIS**
An overall meta-narrative review was conducted encompassing the evolution of noninvasive surfactant therapy. Risk ratios and 95% confidence intervals are reported when appropriate.

**MAIN OUTCOMES AND MEASURES**
Chronic lung disease diagnosed by the need for oxygen therapy at a postmenstrual age of 36 weeks, need for mechanical ventilation within the first 72 hours of birth, need for mechanical ventilation any time during the hospital stay, and adverse events associated with administration of surfactant by various methods.

**RESULTS**
We included 10 studies (6 randomized and 4 observational) of 3081 neonates. Thin catheter administration was evaluated in 6 studies (2 randomized and 4 observational); aerosolization, in 2 randomized studies; and laryngeal mask and pharyngeal administration, in 1 observational study each. The meta-narrative review confirmed the slow evolution and challenges of the different modes of administration, with thin catheter administration being the most studied intervention. Two randomized studies of surfactant administration using a thin catheter revealed no significant difference in the outcome of bronchopulmonary dysplasia but a potential reduction in the need for mechanical ventilation within 72 hours of birth when compared with standard care.

**CONCLUSIONS AND RELEVANCE**
Surfactant administration via a thin catheter may be an efficacious and potentially safe method; however, further studies are needed. Further studies are also needed for other methods of minimally invasive surfactant administration.
Neonatal respiratory distress syndrome (RDS) is associated with high mortality and morbidity in preterm infants. Surfactant therapy for RDS has been a major achievement in the care of the preterm newborn.1,2 Surfactant administration traditionally requires endotracheal intubation and mechanical ventilation for a certain period. This exposure to artificial ventilation, no matter how brief, is responsible for mechanical (volutrauma and barotrauma) and inflammatory mediator–induced (biotrauma) responses in neonates that set the stage for chronic inflammatory processes leading to bronchopulmonary dysplasia (BPD).3 The use of noninvasive approaches such as nasal continuous positive airway pressure (CPAP) without use of exogenous surfactant has increased.4 However, nasal CPAP may lead to pneumothorax in high-risk, surfactant-deficient preterm infants.5 Moreover, conflicting results in terms of reduction in BPD with early nasal CPAP compared with intubation have been noted.5,7

To counter the effects of mechanical ventilation and optimize benefits of early surfactant administration,8 the innovative approach of intubation, surfactant administration during brief mechanical ventilation, and extubation (the INSURE technique) was introduced by Victorin et al.9 This concept became popular.10-11 The INSURE technique, however, involves intubation with a brief period of apparent loss of spontaneous breathing by infants. Subsequently, less invasive modifications of the INSURE method for delivering surfactant to avoid even brief intubation and mechanical ventilation have been conceptualized, implemented, and empirically evaluated with the aim of reducing intubation-related complications and improving the success of nasal CPAP after surfactant administration. These modifications include intratracheal surfactant instillation with the help of a thin catheter (eg, nasogastric tube or vascular catheter),12-17 aerosolized administration,18-20 pharyngeal administration,21 and laryngeal mask airway (LMA)-guided administration.22-24 All of these techniques have the underlying premise of administering surfactant while maintaining spontaneous breathing but have produced variable success. Many centers around the world have adopted some of these practices based on preliminary results.

Our objective was to perform a meta-narrative review encompassing the conceptualization, implementation, and evaluation of the efficacy and safety of minimally invasive methods of surfactant administration in preterm infants with or at risk for RDS with the potential for meta-analysis of studies comparing similar interventions. The INSURE technique has been well studied in a Cochrane review by Stevens et al25 and moreover involves brief loss of spontaneous breathing, so it was not included in our meta-narrative review.

Methods

We used the method described by Greenhalgh et al26 to conduct this meta-narrative review27 and planned traditional methods for conducting meta-analyses when appropriate. This method is used when various techniques or interventions on a theme have been conceptualized differently and has been studied by different research groups over time.27 In this meta-narrative review, we sought to identify and evaluate different techniques of surfactant administration while the infant is breathing spontaneously and then to synthesize them by means of an overarching narrative. Review of search, study selection, data extraction, risk of bias assessment, and analyses were performed by two of us (K.M. and P.S.) independently, and discrepancies were resolved by discussion and arbitration by the third author (P.S.S.).

Guiding Principles

A preliminary review of the literature identified 4 different methods of surfactant administration. We evaluated the evolution, safety, and efficacy of the following methods:

1. Thin catheter administration
2. Aerosolized or nebulized route
3. LMA-guided administration
4. Pharyngeal route

Scoping of the Literature

After extensive discussion, we developed and finalized search terms in consultation with an experienced librarian. Initial searches were led by prior knowledge, content experts’ publications, and review of nonsystematic reviews. We searched the PubMed, EMBASE, Cochrane, and CINAHL databases from inception until June 30, 2013. We used database-specific terms without language restrictions. The reference lists of identified studies, key review articles, and conference proceedings of the annual meetings of the Pediatric Academic Society (2008-2013) were searched (details are available in the eMethods in the Supplement).

Mapping Phase

The next steps involved mapping the various approaches according to theoretical construct, concept development, and methodologic implementation. The following factors were central to the development of this phase. First, we considered the type of participants and interventions. We included studies of preterm infants (gestational age, <37 weeks) who received surfactant for RDS or received prophylactic surfactant because they were considered at risk for RDS. Surfactant administration for term infants was not included. Second, we considered the type of studies. We restricted this review to randomized clinical trials (RCTs) and observational studies with concurrent or historical controls. Case reports, case series, letters to editors, editorials, review articles, and commentaries were read to identify theoretical background, concept development, and progress but were not included in the synthesis. Duplicate reports were excluded. Third, we considered outcomes, including efficacy and safety. Efficacy outcomes included BPD or chronic lung disease diagnosed by the need for oxygen at a postmenstrual age of 36 weeks and the need for mechanical ventilation within the first 72 hours of birth. Safety outcomes included adverse events during interventions, such as bradycardia, desaturation, apnea, pneumothorax, and pulmonary hemorrhage.
Minimally Invasive Surfactant Administration

Selection and Appraisal Phase
We extracted data on conceptual modeling, theoretical construct, and implementation strategies in the form of study design, patient characteristics, and outcomes. We contacted the principal authors of studies included in this review for clarifications and/or additional data when needed.

For appraisal of evidence in randomized studies, we used the Cochrane Handbook’s risk of bias assessment tool. For observational studies, the risk of bias in selection, exposure assessment, outcome assessment, attrition, and confounding factors was assessed using the Newcastle-Ottawa Scale.

Analysis and Synthesis Phase
Two methods of synthesis were applied. First, a narrative account of each method of surfactant administration was described. This description included detailing the historical aspects of each method, eventual concept modifications, and later comparative evaluations. This narrative was used as the main frame of this review. Second, a quantitative summary was planned as traditional meta-analysis in the absence of significant clinical heterogeneity. Because conceptual and methodologic differences exist between RCTs and observational studies, we did not combine information from RCTs and observational studies in a single statistical analysis. This hybrid method allowed for exploration of the full spectrum of the underlying construct of minimally invasive surfactant administration.

Results

Selection and Appraisal Phase
The results of the literature search, the study selection log, and the number of studies are reported in Figure 1. The baseline characteristics of the 10 studies selected under each method of surfactant administration, which include a total of 3081 neonates, are described in Table 1. We excluded 20 studies, and the reasons for exclusion are given in the eTable in the Supplement. The timeline of the evolution of different methods of surfactant administration is described below.

Risk of Bias Among Included Studies
The risk of bias assessment among the included RCTs and cohort studies is reported in Table 2 and Table 3, respectively. Most studies had low to moderate risk of bias (score, 6-8 of a total 10). Most bias stemmed from selection of control subjects and lack of adjustment for confounders. The results of our appraisal of the evolution and efficacy of the methods of surfactant administration of interest are described below.

Method 1: Thin Catheter
The use of a thin catheter for surfactant administration was first described in 1992 by Verder et al in 6 of 34 infants in a pilot study of neonates primarily treated with nasal CPAP. Kribs et al reported the first quantitative assessment of the outcome of surfactant instillation using a thin, flexible intratracheal catheter in a feasibility study. Since then, a series of studies in different gestational age groups has demonstrated improving success over time as their learning curve improved. This technique has been adopted increasingly and was tested further in another observational study and 2 RCTs. Dargaville et al introduced a modified thin catheter technique by using a semirigid vascular catheter in 25 preterm infants with gestational ages of 25 to 34 weeks. More results were reported after the study was extended to 2 more centers.

This method of less invasive surfactant administration by thin catheter or vascular catheter has been studied in 4 comparative observational studies and 2 RCTs included in our meta-narrative review, encompassing a total of 2631 neonates. In the included studies, surfactant was administered as rescue therapy after meeting predefined respiratory criteria except for the study by Klebermass-Schrehof et al, in which surfactant was administered prophylactically to all extremely premature infants (gestational age, 23-27 weeks) in the intervention group.

Evidence From Observational Studies

Efficacy
Kribs compared outcomes after surfactant administration via a thin catheter with those of a historical cohort who received standard care. In the first study of 64 extremely low-birth-weight infants by Kribs et al, the investigators demonstrated the feasibility of using this new technique. They found no significant reduction in the need for mechanical ventilation or BPD. In a subsequent historical comparative study, Kribs et al described a significant reduction in BPD and the need for mechanical ventilation within 72 hours (Table 1). On

Figure 1. Flow Diagram Describing Study Selection for Inclusion in Meta-narrative Review
Table 1. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Design and Population</th>
<th>Comparison</th>
<th>Method</th>
<th>Participants and Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kribs et al., 2007</td>
<td>Nonrandomized feasibility study; ELBW infants with GA, 23-27 wk</td>
<td>ET instillation</td>
<td>29 I and 34 C; Fio₂, &gt;0.4; 100 mg/kg surfactant</td>
<td>BPD: 14% I vs 15% C (NS); mortality: 12% I vs 35% C (P = .025)</td>
<td></td>
</tr>
<tr>
<td>Kribs et al., 2010</td>
<td>Prospective cohort study; VLBW infants or GA, &lt;31 wk</td>
<td>ET instillation</td>
<td>319 I and 1222 C</td>
<td>MV in first 72 h: 29% I vs 53% C (P &lt; .001); BPD: 11% I vs 18% C (P = .004)</td>
<td></td>
</tr>
<tr>
<td>Güpel et al., 2011</td>
<td>RCT; VLBW infants or GA, &lt;28-29 wk; age &lt;12 h</td>
<td>CPAP followed by ET instillation</td>
<td>108 I and 112 C</td>
<td>MV on day 2-3: RR, 0.64 (95% CI, 0.42-0.88); MV at any time: RR, 0.42 (95% CI, 0.31-0.59); BPD: RR, 0.62 (95% CI, 0.27-1.40)</td>
<td></td>
</tr>
<tr>
<td>Dargaville et al., 2013</td>
<td>Nonrandomized study; historical controls; GA, 25-34 wk; age, ≥24 h</td>
<td>Routine CPAP and ET instillation</td>
<td>38 I and 41 C: GA, 25-28 wk; 23 I and 56 C: GA, 29-34 wk</td>
<td>MV at 72 h: GA, 25-28 wk: OR, 0.21 (95% CI, 0.08-0.55); MV at 72 h, GA, 29-34 wk: OR 0.34 (95% CI, 0.11-1.0); BPD: 29% I vs 29% C (P = .85)</td>
<td></td>
</tr>
<tr>
<td>Klebermass-Schrehof et al., 2013</td>
<td>Nonrandomized study; historical controls; GA, 23-27 wk, at birth</td>
<td>CPAP, ET instillation</td>
<td>224 I and 182 C</td>
<td>MV need at 3 d: 23% I vs 52% C (P &lt; .001); BPD: 16% I vs 12% C (NS)</td>
<td></td>
</tr>
<tr>
<td>Kanmaz et al., 2013</td>
<td>RCT; GA, &lt;32 wk; age, &gt;72 h</td>
<td>INSURE method</td>
<td>100 C and 100 I (porcine surfactant, 100 mg/kg)</td>
<td>MV within 72 h: 30% I vs 45% C (P = .03 (reported); MV at any time: 40% I vs 49% C (P = .08); BPD: 10% I vs 20% C (P = .009)</td>
<td></td>
</tr>
<tr>
<td>Berggren et al, 2000</td>
<td>RCT; GA, 27-36 wk; randomized at 2-36 h; Fio₂, &gt;0.4</td>
<td>CPAP</td>
<td>16 C and 16 I (porcine surfactant, 480 mg/kg)</td>
<td>Need for MV: 38% C vs 31% I (NS); BPD: 12.5% C vs 0% I (NS)</td>
<td></td>
</tr>
<tr>
<td>Minocchieri et al., 2013</td>
<td>RCT; GA, 25-33 wk; Fio₂, 0.22-0.30 in first 6 h; after birth</td>
<td>CPAP</td>
<td>N = 64; I (porcine surfactant* ) vs C</td>
<td>Need for intubation in the first 72 h: RR, 0.56 (95% CI, 0.34-0.93); BPD: no difference (numbers not given)</td>
<td></td>
</tr>
<tr>
<td>Attridge et al, 2013</td>
<td>RCT; BW, ≥1200 g; age at inclusion, ≥272 h</td>
<td>ET instillation</td>
<td>13 I (calfactant surfactant, 3 mL/kg) and 13 C</td>
<td>MV need within 96 h: RR, 1.0 (95% CI, 0.25-4.07)</td>
<td></td>
</tr>
<tr>
<td>Ten Centre Study Group, 1987</td>
<td>RCT; GA, 25-29 wk</td>
<td>Saline</td>
<td>43 I and 32 C: 25-26 wk; 116 I and 117 C: 27-29 wk</td>
<td>Mortality: 19% I vs 30% C (P &lt; .01); respiratory support in first 10 d: I group, 19 h less in &gt;30% oxygen (P &lt; .05) and 20 h less ventilation (P &lt; .05)</td>
<td></td>
</tr>
</tbody>
</table>

Method 1: Administration of Surfactant via Thin Catheter

Method 2: Surfactant Administration via Aerosol

Method 3: Surfactant Administration via LMA

Method 4: Surfactant Administration via Nasopharyngeal Instillation

Abbreviations: BPD, bronchopulmonary dysplasia; BW, birth weight; C, comparison; CPAP, continuous positive airway pressure; ELBW, extremely low birth weight; ET, endotracheal; Fio₂, fraction of inspired oxygen; GA, gestational age; I, intervention; INSURE, intubation, surfactant administration during brief mechanical ventilation, and extubation; LMA, laryngeal mask airway; MV, mechanical ventilation; NS, not significant; OR, odds ratio; RCT, randomized clinical trial; RDS, respiratory distress syndrome; RR, relative risk; VLBW, very low birth weight.

* Indicates Curosurf (Chiesi USA, Inc).

** Indicates CPAP plus nebulized surfactant.

Figure 2. Timeline for Evolution of Techniques for Surfactant Administration While Maintaining Spontaneous Breathing

<table>
<thead>
<tr>
<th>Method</th>
<th>Source</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin catheter administration</td>
<td>Verder et al, 1992</td>
<td>1992</td>
</tr>
<tr>
<td>Aerosolized administration</td>
<td>Joch et al, 1997</td>
<td>1997</td>
</tr>
<tr>
<td></td>
<td>Berggren et al, 2000</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>Minocchieri et al, 2013</td>
<td>2013</td>
</tr>
<tr>
<td>LMA-guided administration</td>
<td>Trevisanuto et al, 2005</td>
<td>2005</td>
</tr>
<tr>
<td></td>
<td>Attridge et al, 2013</td>
<td>2013</td>
</tr>
<tr>
<td>Pharyngeal administration</td>
<td>Ten Centre Study Group, 1987</td>
<td>1985</td>
</tr>
<tr>
<td></td>
<td>Dambeau et al, 1997</td>
<td>1997</td>
</tr>
<tr>
<td></td>
<td>Kattwinkel et al, 2004</td>
<td>2004</td>
</tr>
</tbody>
</table>

LMA indicates laryngeal mask airway.

* Indicates randomized clinical trial.
the contrary, Dargaville et al31 reported a reduction in mechanical ventilation at 72 hours but no difference in BPD using the thin catheter technique. A slightly modified approach was used by Klebermass-Schrehof et al.17 They used high-flow CPAP delivered initially by facial mask followed by nasopharyngeal tube, followed in turn by administration of surfactant via a thin catheter inserted with help of laryngoscope and Magill forceps without any premedication. They reported significant reduction in mechanical ventilation at days 1 and 3 and in the first week of life but no significant difference in BPD between the study group and controls (Table 1). Two studies17,31 reported outcomes for extremely premature infants (gestational age, <28 weeks) and showed that thin catheter intervention can also be useful by reducing early need for mechanical ventilation, but no difference in BPD was identified. However, the number of infants with younger gestational ages described in these studies remains small.

Safety | All 4 observational studies4,14,17,30,31 reported few episodes of bradycardia or desaturations during the procedure, requiring a temporary halt in the procedure or the use of positive pressure ventilation. The study by Dargaville et al31 was an exception, with episodes of bradycardia of longer than 10 seconds occurring in 39% of infants with gestational ages of 25 to 28 weeks. None of the studies reported any significant harm with any of the techniques.

Efficacy | Two RCTs12,16 have evaluated the thin catheter intervention. Kanmaz et al16 compared the INSURE method with intratracheal surfactant administration using nasogastric tubing as a catheter in 200 preterm newborn infants. They described a reduction in the need for mechanical ventilation at 72 hours in the thin catheter group. The incidence of BPD was also relatively low in the intervention group. Göpel et al12 compared the standard method of care with surfactant administration via a thin catheter in 220 very-low-birthweight neonates with gestational ages of less than 29 weeks and reported a reduction in the need for mechanical ventilation in the intervention group. Kanmaz et al16 reported a significant reduction in the incidence of BPD (P = .009) in the intervention vs control groups; however, we could not reproduce the results from the numbers given in their study (P = .08).

Table 2. Risk of Bias Assessment for Included Randomized Clinical Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>Random Sequence Generation</th>
<th>Allocation Concealment</th>
<th>Performance: Blinding of Participant and Personnel</th>
<th>Detection: Blinding of Outcome Assessment</th>
<th>Attrition: Incomplete Outcome Data</th>
<th>Selective Reporting</th>
<th>Other Sources</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanmaz et al,16 2013</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Minocchieri et al,32 2013</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Moderate risk</td>
</tr>
<tr>
<td>Göpel et al,12 2011</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>High risk</td>
<td>Moderate risk</td>
</tr>
<tr>
<td>Attridge et al,13 2013</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Moderate risk</td>
</tr>
<tr>
<td>Berggren et al,18 2000</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>High risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Ten Centre Study Group,34 1987</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Moderate risk</td>
</tr>
</tbody>
</table>

Table 3. Risk of Bias Assessment for Included Cohort Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Representativeness of the Exposed Cohort</th>
<th>Selection of the Nonexposed Cohort</th>
<th>Ascertainment of Exposure</th>
<th>Demonstration That Outcome of Interest Was Not Present at Start of Study</th>
<th>Comparability of Cohorts on the Basis of the Design or Analysisb</th>
<th>Study Controls for Any Additional Factor</th>
<th>Assessment of Outcome</th>
<th>Follow-up Long Enough for Outcomes to Occur</th>
<th>Overall Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kribs et al,14 2007</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Kribs et al,30 2010</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Dargaville et al,31 2013</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Klebermass-Schrehof et al,17 2013</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

*a Indicates a maximum of 4 points.
*b Indicates a maximum of 2 points.
*c Indicates a maximum of 3 points.
*d Indicates a maximum of 9 points.
Because of apparent clinical heterogeneity between study groups and the method for selection for outcome assessment, we have not conducted a meta-analysis with these data. We presented them for comparative evaluation in eFigure 1 in the Supplement.

Safety | Kanmaz et al\textsuperscript{16} reported that bradycardia and desaturation rates were similar in both groups in their study; however, they observed that surfactant reflux during administration via a thin catheter was significantly higher than in the INSURE group (21% vs 10%; \(P = .002\)). Twelve percent of infants had severe apnea lasting 20 seconds and bradycardia (<100 beats/min) requiring positive-pressure ventilation with a T-piece device during surfactant administration via a thin catheter. Göpel et al\textsuperscript{12} reported episodes of bradycardia and significant desaturation in 5% of the neonates in their intervention group.

Method 2: Aerosolized or Nebulized Route
Aerosolized surfactant was evaluated in animal studies in the early 1990s; however, the first human study was published in 1997 by Jorch et al,\textsuperscript{39} who conducted an uncontrolled multicenter feasibility study in 20 infants. Since then, this method has been tested in 2 RCTs.\textsuperscript{18,32} Arroo et al\textsuperscript{46} conducted an uncontrolled observational study in preterm infants and demonstrated no benefits from nebulized surfactant. Finer et al\textsuperscript{41} conducted a feasibility study and suggested that aerosolized surfactant was well tolerated and might reduce the need for endotracheal intubation. No adverse effects were reported apart from transient desaturation.

Berggren et al\textsuperscript{18} compared infants treated with aerosolized surfactant with control infants who did not receive surfactant and reported no difference in the need for mechanical ventilation or incidence of BPD. Minocchieri et al\textsuperscript{12} conducted an RCT of aerosolized porcine surfactant (Curosurf; Chiesi USA, Inc) vs CPAP alone and demonstrated a decrease in the need for intubation in the first 72 hours; however, they found no difference in the incidence of BPD.

Method 3: LMA-Guided Administration
The first attempt at surfactant instillation using an LMA was described in a case series of 8 infants by Trevisanuto et al\textsuperscript{29} with limited demonstrable benefits. This method was subsequently tested in 1 RCT of 26 newborns by Attridge et al\textsuperscript{39} who reported that surfactant administration via an LMA resulted in a reduction in the mean fraction of inspired oxygen requirement for 12 hours after the intervention; however, no significant difference was reported in the subsequent need for mechanical ventilation or BPD (Table 1). Adverse events reported included hypoxia and bradycardia during surfactant administration, laryngospasm, and malposition of the LMA.\textsuperscript{33}

Method 4: Pharyngeal Route
The first trial of nasopharyngeal surfactant administration was conducted by the Ten Centre Study Group in 1987 in 328 infants.\textsuperscript{34} A decrease in the severity of RDS, the use of mechanical ventilation in the first 10 days, and incidence of mortality were observed (Table 1). However, with the theoretical uncertainty about the amount of surfactant that actually gets delivered into the trachea, this approach has only been investigated further in a small case series by Kattwinkel et al.\textsuperscript{21}

Synthesis Phase
We found significant clinical heterogeneity among included studies with differences in study design, gestational age, specific surfactant products, and indication of therapy, so meta-analysis was not performed. In addition, the standard care mentioned in the control group varied between studies, as indicated in Table 1. The data from Kanmaz et al\textsuperscript{16} and Göpel et al\textsuperscript{12} were included for comparison but not for meta-analysis owing to clinical heterogeneity.

Bronchopulmonary Dysplasia
We found no statistically significant reduction in BPD in both studies\textsuperscript{12,16} in which infants underwent analysis on an intention-to-treat basis (eFigure 1 in the Supplement). We caution that Kanmaz et al\textsuperscript{16} reported a treatment effect (\(P = .05\)) in favor of surfactant administration via a thin catheter, a result that we could not reproduce using the published numbers.

Need for Mechanical Ventilation Within 72 Hours of Birth
Göpel et al\textsuperscript{12} reported the reduction in the need for mechanical ventilation from 25 to 72 hours of birth. Kanmaz et al\textsuperscript{16} described a significant reduction in mechanical ventilation within 72 hours of birth for the intervention group compared with the INSURE group (eFigure 2 in the Supplement).

Discussion
To our knowledge, this review is the first systematic narrative to examine various minimally invasive methods of surfactant administration while maintaining spontaneous breathing in the preterm infant with or at risk for RDS. This review of 10 studies (a combination of RCTs and observational studies) indicates a growing interest in such methods of surfactant administration. Current evidence suggests that administration via a thin catheter is a feasible, potentially effective, and safe method of minimally invasive surfactant administration. Meta-analysis was not conducted in lieu of significant heterogeneity between studies. We found synchrony in the results from observational studies and RCTs for thin catheter use and neonatal outcomes. The thin catheter method may also be safe and effective in infants born at an extreme gestational age of less than 28 weeks. On the other hand, administration by an aerosolized, a pharyngeal, or an LMA-guided route was not shown to be beneficial to neonatal outcomes in a small series of studies. From the safety perspective, all described methods were well tolerated except for the occurrence of short-lasting events such as bradycardia and desaturations that reversed back quickly with minor interventions.

Bronchopulmonary dysplasia described in the presurfactant era was mainly the consequence of barotrauma and the toxic effects of oxygen administration. Thus, approaches to minimize mechanical damage to the lungs were developed with
an increasing trend toward use of noninvasive ventilation techniques such as early nasal CPAP. Large randomized trials such as the COIN (Continuous Positive Airway Pressure or Intubation at Birth) trial\(^3\) and the Surfactant Positive Airway Pressure and Pulse Oximetry Randomised Trial (SUPPORT)\(^4\) have demonstrated that early use of nasal CPAP is a safe and efficacious alternative to intubation and prophylactic surfactant administration. However, these trials did not show a significant reduction in BPD.

For infants to benefit from surfactant therapy followed by noninvasive ventilation, use of the INSURE technique increased.\(^9\)\(^11\)\(^39\) The INSURE method, however, requires intubation and brief mechanical ventilation, which in a preterm neonate can cause significant hemodynamic instability, including hypoxia, bradycardia, blood pressure fluctuation, and an increase in intracranial pressure, and can trigger pulmonary and systemic inflammation owing to apparent asynchrony.\(^42\)\(^44\) Indeed, BPD results from the interaction of many factors such as prolonged mechanical ventilation and colonization of the airway with pathogens that may trigger an inflammatory cascade.\(^3\) Although the overall incidence of BPD has not been substantially modified by surfactant therapy, the severity of BPD has been reduced.\(^44\)

The lack of a reduction in the overall incidence of BPD after surfactant administration is likely owing to a reduction in mortality, but it could also be due to the need for surfactant administration with a period of endotracheal intubation and exposure to barotrauma. Thus, attempts to evolve surfactant therapy into a minimally invasive technique that can be used while the infant is breathing spontaneously were initiated. Attempts at aerosolizing surfactant or administering it via an LMA have indicated that these methods are potentially feasible. However, the delivery of surfactant to the alveoli is highly unreliable, and aerosolization of surfactant is still a technical challenge owing to the particle size and the small airways of preterm neonates.\(^45\) The thin catheter technique appears to be safer because it allows an infant to maintain spontaneous breathing and ensures administration of surfactant into the trachea in reasonable amounts.

This technique might have an equal appeal in resource-rich and resource-poor settings. However, it requires patience and skill. Despite being minimally invasive, the technique still involves the use of a laryngoscope and a maneuver to visualize the vocal cords in a relatively awake infant, which might be perceived as equally traumatic, especially in hands of untrained individuals. One of the major issues in mastering this skill will be achieving success while avoiding the need for sedatives and analgesics. Thus, other opportunities to keep infants comfortable during this time need to be identified. Furthermore, the application of different surfactant types and volumes using this technique needs to be assessed. The amount of surfactant lost and the need for repeated administration of surfactant owing to loss during the procedure also needs careful attention. The learning curve described by Kribs et al\(^13\)\(^30\)\(^37\)\(^38\) is a perfect example of the understanding and realization of the challenges one might face while attempting this approach.

Conclusions

Overall, this meta-narrative review comprehensively summarizes the methodologic details, effectiveness, and safety of the different methods of surfactant administration while maintaining spontaneous breathing. However, the RCTs were limited in their description of the individual methods and included small samples. Observational studies\(^27\)\(^38\) had larger samples but they were not looking at the specific question of thin catheter instillation vs intubation as a method of surfactant administration. The choice of surfactant also differed between the studies, thus affecting generalizability. In addition, none of the studies evaluated early childhood neurodevelopmental outcomes. Further, large RCTs are required to assess the neonatal and childhood outcomes of infants treated with early stabilization by CPAP followed by selective surfactant administration by thin catheter compared with those of infants treated with intubation as the method of surfactant administration.

ARTICLE INFORMATION

Accepted for Publication: May 27, 2014.

Author Contributions: Drs More and Shah had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: Sakhuja, Shah.

Drafting of the manuscript: More, Sakhuja.
Critical revision of the manuscript for important intellectual content: Sakhuja, Shah.

Statistical analysis: More, Shah.
Study supervision: Shah.

Conflict of Interest Disclosures: None reported.

Funding/Support: Dr Shah is the recipient of an Applied Research Chair Award in Reproductive and Child Health Services and Policy Research from the Canadian Institutes of Health Research to conduct research projects involving maternal and child health.

Role of the Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Information: This study is registered with the PROSPERO International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO/). Identifier: CRD42013004455.

Additional Contributions: Wolfgang Göpel, MD, provided additional data for inclusion in this review from his study. Elizabeth Ueryk, BA, MLS, Hospital for Sick Children, helped in conducting searches for this project. Ruth Warre, PhD, from the Maternal-Infant Care Research Centre, Mount Sinai Hospital, provided editorial support. The Maternal-Infant Care Research Centre is supported by the Ministry of Health and Long-term Care, Ontario, Canada.

REFERENCES

5. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB; COIN Trial Investigators. Nasal CPAP...