Study protocol (including SAP) for:

Efficacy of rescue surfactant delivery via endotracheal intubation (INSURE technique) versus laryngeal mask airway (LMA) for respiratory distress syndrome (RDS) in preterm neonates

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Efficacy of rescue surfactant delivery via endotracheal intubation (INSURE technique) versus laryngeal mask airway (LMA) for respiratory distress syndrome (RDS) in preterm neonates.

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A. Study Background and Purpose

Pulmonary surfactant deficiency manifested as respiratory distress syndrome (RDS) is common in preterm newborns and remains a major cause of neonatal morbidity and mortality. Surfactant replacement therapy improves clinical outcomes in preterm infants with RDS. Multiple clinical trials and meta-analyses have shown that surfactant is immediately effective in improving the need for respiratory support (Stevens, Harrington, Blennow, & Soll, 2007). Surfactant administered prophylactically to infants at high risk of developing RDS (before 28 to 30 weeks' gestation) is most effective in diminishing mortality (Yost & Soll, 2000). Surfactant is also used as rescue therapy for clinically significant RDS, most often within 12 to 48 hours of life, but better outcomes are obtained when surfactant is administered relatively early in the disease course (Halliday, 2008). Surfactant therapy is also effective in larger preterm infants with RDS (Engle, 2008; Kattwinkel et al., 1993); in placebo-controlled trials, larger and more mature preterm neonates have a lower incidence of death or bronchopulmonary dysplasia when treated with surfactant (Engle, 2008). Early treatment with surfactant in larger preterm infants with RDS improves oxygenation, reduces the need for subsequent mechanical ventilation and decreases the risk of pneumothorax, while decreasing the incidence of bronchopulmonary dysplasia (Verder et al., 1999; Stevens et al., 2007). In recent years, optimal combinations of non-invasive ventilation (nasal CPAP or nasal IPPV) and surfactant have been sought in order to minimize the use of invasive mechanical ventilation, which increases the risk of developing chronic lung disease (Verder et al., 1999; Stevens et al., 2007). Thus, variations of the INSURE approach (transient INtubation, SURfactant administration, and immediate Extubation) have emerged in neonatal care (Welzing et al., 2009).

The standard method of surfactant delivery involves tracheal intubation with positive pressure ventilation (PPV) (American Academy of Pediatrics & American Heart Association, 2006) (Infasurf package insert, ONY, Inc.; available at www.infasurf.com). Intubation causes pain and physiological instability in the neonate, leading to hypoxemia and bradycardia while increasing systemic and intracranial pressure (Dempsey, Al Hazzani, Faucher, & Barrington, 2006; Friesen, Honda, & Thieme, 1987; Marshall, Deeder, Pai, Berkowitz, & Austin, 1984). The use of premedication to minimize pain and stress in neonates undergoing intubation is supported by evidence showing that intubations following premedication may be safer and more effective than awake intubations (Carbajal, Eble, & Anand, 2007; Shah & Ohlsson, 2002). However, premedication often leads to respiratory depression and persistent hypoventilation, precluding extubation to CPAP as intended after surfactant administration (Santana-Rivas, Pinheiro, & Pezzano, 2013); intubation with premedication may thus contribute to the need for invasive mechanical ventilation in some neonates, an outcome that surfactant therapy aims to prevent. It is notable that the American Academy of Pediatrics and the Canadian Paediatric Society have recommended premedication for neonatal intubation as intended for mechanical ventilation, but not specifically for INSURE, where intubation is only a transient route for surfactant delivery and ventilation is undesirable (Barrington & Canadian Paediatric Society, 2011; Kumar, Denson, Mancuso, & Committee on Fetus and Newborn, 2010).
Furthermore, in a significant proportion of neonates, as high as 21%, (Hipolito, Milstein, & Sherman, 2001) the endotracheal tube (ETT) is initially placed in a mainstem bronchus, which promotes unequal distribution of surfactant between the lungs, a risky and undesirable condition.

Esophageal intubation with gastric administration of surfactant is a less common, ineffective and unintended complication of the procedure. Other complications of surfactant therapy, including airway obstruction with surfactant stasis in the ETT, have lead clinicians to modify the surfactant administration strategies used in research protocols, including dose, frequency and treatment procedure. The route of administration of surfactant has been a topic of research in the last 5 years, particularly considering the use of the laryngeal mask airway.

The laryngeal mask airway (LMA) is a supraglottic airway device used to administer positive pressure ventilation (PPV) in adult, pediatric and neonatal patients (Trevisanuto et al., 2005). It has been used since 1988 in over 200 million patients for routine and emergency procedures. The mask conforms to the contours of the hypopharynx with its lumen facing the laryngeal opening, and it is designed to be a minimally-stimulating device for anesthesia or airway support. The LMA can be inserted easily and quickly with minimal training, and it results in less misplacement and failure of ventilation than endotracheal intubation, even when performed by pre-hospital providers (Chen & Hsiao, 2008); associated discomfort and trauma are minimal in comparison with tracheal intubation (Trevisanuto et al., 2004; Schmiesing & Bock-Utne, 1998). In neonatal resuscitation, the LMA is an alternative to manage the difficult neonatal airway, when intubation is difficult (American Academy of Pediatrics & American Heart Association, 2006).

The LMA has also been used as a conduit for the pulmonary administration of various drugs, but as noted in the Neonatal Resuscitation Program "There is insufficient evidence to recommend the laryngeal mask when intratracheal medications are required" (American Academy of Pediatrics & American Heart Association, 2006). After case reports and a small case series by Trevisanuto et al. demonstrated the feasibility and apparent effectiveness of minimally invasive administration of surfactant via LMA in preterm infants with RDS (Brimacombe, Gandini, & Keller, 2004; Trevisanuto et al., 2005), a controlled trial aiming to study the efficacy of surfactant administration by LMA was started at the University of Virginia (Stewart, Attridge, & Kattwinkel, 2008), but stopped early because of slow enrollment (personal communications to J. Pinheiro, by J. Kattwinkel and A. Paget-Brown, 2008 and 2009), with only 11 babies in the LMA arm (Attridge, Stewart, Stukenborg, & Kattwinkel, 2013).

Contemporaneously, in the Albany Medical Center NICU, premedication with morphine and atropine was used for elective and semi-urgent intubations, including INSURE procedures. We thus undertook and recently completed a randomized trial on preterm newborns with mild-moderate RDS, to compare the effectiveness of surfactant administration via LMA versus transient intubation (using our traditional INSURE technique, with morphine for premedication). We found that the LMA group had a significantly decreased rate of failure of non-invasive ventilatory support (30%) in comparison to the INSURE (ETT) group; further, the early timing and pattern of failure in the INSURE group strongly suggested that morphine premedication contributed to the respiratory depression and unintended need for invasive ventilation (Santana-Rivas, Pinheiro, & Pezzano, 2013).
Another recent randomized trial of intubation techniques in preterm neonates concluded that "Because of circulatory changes and neurophysiological depression found during and after the intubation in infants given morphine, premedication with morphine should be avoided" (Norman et al., 2011). Based on current evidence, the Canadian Pediatric Society now recommends that

an optimal protocol for premedication for neonatal intubation should include a vagolytic, a rapid-acting analgesic and a short-duration muscle relaxant (Barrington & Canadian Paediatric Society, 2011). However, neither these nor other expert recommendations exist for premedication in the context of INSURE, and a variety of approaches – including no premedication – have been used. Based on our own data and on recent publications, our new preferred premedication for INSURE combines a vagolytic (atropine) with a rapid-acting, short-duration analgesic (remifentanil), while muscle relaxants and longer acting analgesics are avoided, as they might increase the need for ventilatory support. Remifentanil has been studied mostly in neonates undergoing persistent intubation, with demonstrated effectiveness but some risk of chest wall rigidity at higher doses (Choong et al., 2010). At lower doses of 2 μg/kg, remifentanil has been used successfully for INSURE, without adverse effects (Welzing et al., 2009).

The results of our recent LMA trial indicate that surfactant delivery via LMA produces immediate improvements in oxygenation comparable to delivery via ETT, and decreased need for subsequent ventilatory support. However, because our previous INSURE approach for ETT delivery of surfactant included morphine, a slow-onset, long acting analgesic which likely contributed to the need for invasive ventilation, it remains unclear whether LMA delivery of surfactant is as effective as our new INSURE technique, which is designed to avoid respiratory depression.

Since our last trial began, the results of a small randomized trial were published, where the 11 babies who received surfactant via LMA showed improvements in oxygenation comparable to those in our study, whereas no change occurred in the surfactant-untreated (CPAP-only) group (Attridge, Stewart, Stukenborg, & Kattwinkel, 2013). In a piglet model of RDS, surfactant administered via LMA had physiologic effects similar to those of ETT administration (Roberts et al., 2010). The only ongoing clinical trial on delivery of surfactant via LMA to human neonates with RDS (Roberts et al., NCT01116921 at www.clinicaltrials.gov) is examining the effectiveness of this procedure (versus no surfactant treatment) in decreasing the need for later mechanical ventilation.

From the foregoing, it is apparent that clinical trials are still needed to address the relative efficacy of surfactant delivered via LMA versus optimized INSURE approaches. In this proposal, we extend our investigations of surfactant delivery by LMA to the current clinical context in which premedication for INSURE comprises atropine and remifentanil.

Hypothesis:

Surfactant therapy delivered via LMA is not inferior to surfactant therapy delivered via transient intubation (INSURE technique) with short-acting narcotic premedication for mild to moderate RDS in preterm neonates.

Aims:

1. To compare the rate of failure of surfactant therapy delivered via LMA to the rate of failure of surfactant therapy delivered via transient intubation (INSURE technique) in avoiding mechanical ventilation in neonates 27 to 36 weeks' gestation with mild to moderate RDS.

1a. To evaluate the success of remifentanil as premedication for transient intubation (INSURE technique) as compared to morphine used in our previous trial.

2. To further evaluate the safety of surfactant administration via LMA.

B. Study Design/C. Subject Population

- Multi-center, randomized controlled trial. The participating centers are Albany Medical Center, Bellevue Woman's Center at Ellis Hospital, and Golisano Children's Hospital. Each center will obtain approval from that center's own Institutional Review Board. It is anticipated that the study will take 2 years to complete.

Patient Enrollment:

- The investigators and/or study coordinator will evaluate all infants admitted to the NICU who are less than 48 hours of life from 27 through 36 completed weeks' gestation with mild-moderate RDS.

- If they meet the pre-defined inclusion criteria and informed consent is obtained, they will be randomized to either the INSURE group or LMA group for the initial surfactant administration. Patients will be block randomized in one of three gestational age groups: 27 0/7 - 28 6/7 weeks, 29 0/7 - 32 6/7 weeks, 33 0/7 - 36 6/7 weeks.

- Randomization process: An anticipated 130 patients will be enrolled in the study. Patients will be randomized into three groups using a blind randomization selection method. After computer-generated block randomization, the 130 numbered cards will be placed in sealed, numbered envelopes, and kept in a NICU nurse practitioner office. Each card will indicate LMA or INSURE group and include an identifier code number. After obtaining the signed consent form, the investigators or coordinator will open the next envelope in the appropriate gestational age block.

- Inclusion Criteria:

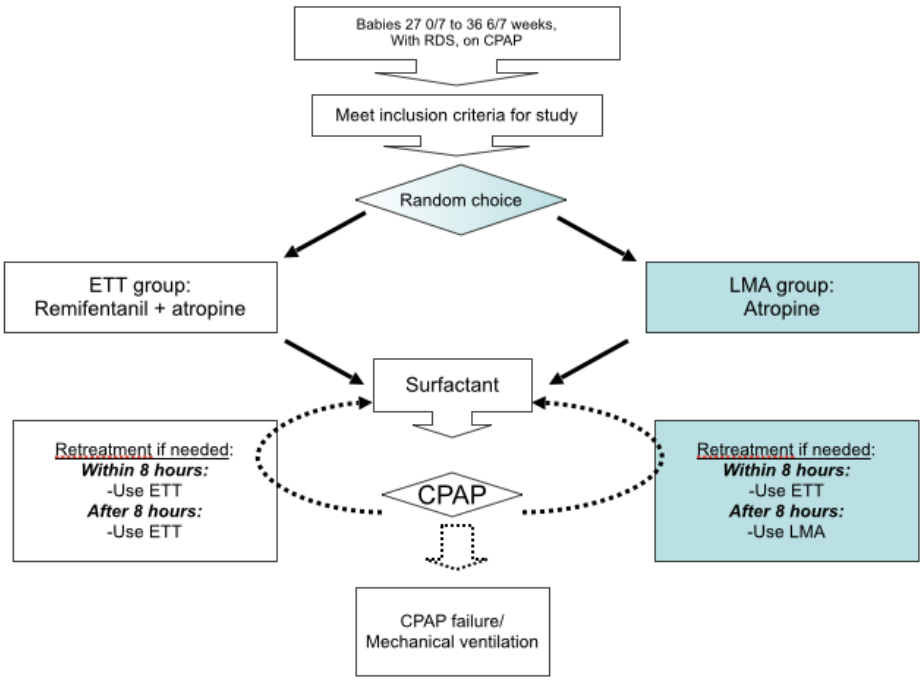
  - Gestational age (GA) 27 0/7 weeks to 36 6/7 weeks
  - Age < 48 hours
  - Mild-moderate RDS as defined by an FiO_2 requirement of 0.30 - 0.60 on either CPAP or nasal intermittent positive pressure ventilation (NIPPV) for at least two hours to maintain SpO_2 90-95%
  - Written consent obtained

- Exclusion Criteria:
  - Prior tracheal intubation

- Prior surfactant therapy
- Evidence of pneumothorax, pneumomediastinum, or pneumopericardium
- $FiO_2 > 0.60$
- Craniofacial or other airway malformation
- Major congenital malformation (cardiac and thoracic defects)
- Apgar score of ≤ 3 at 5 minutes of life or evidence of encephalopathy
- Weight less than 800 grams

Study/Intervention:

The diagram below is a graphic depiction of the study protocol. Criteria for assisted ventilation and other respiratory support will be the same for both groups.



- **INSURE (control group): Atropine + remifentanil + intubation (ETT) + Infasurf**

  - The neonates randomized to standard management will be given premedication with atropine (0.1 mg/kg) and remifentanil (2 mcg/kg) for endotracheal intubation according to the new standard AMC premedication order sheet.

  - A CO_2 detector will be used to verify endotracheal intubation

  - Surfactant (Infasurf) therapy will be delivered via ETT, at a dose of 3mL/kg, in 2 aliquots. Surfactant is drawn up in a syringe with a Luer adaptor.

  - This is followed by positive pressure ventilation (PPV) for a minimum of 5 minutes before extubation to nasal CPAP (if possible) by 15 minutes after completion of surfactant therapy.

  - However, the baby will remain intubated and continue to mechanical ventilation via ETT if one or more of the following occurs:
    - Persistent apnea
      - If this is thought to be related to sedative medication, a one-time dose of naloxone (0.1 mg/kg) may be administered as part of the study protocol
    - Severe retractions (as judged by an attending neonatologist or fellow)
    - Inability to wean $FiO_2 < 0.60$ to maintain target SpO_2 90-95%

  - Management of RDS, mechanical ventilation, concurrent neonatal issues, and any complications that may arise will be at the discretion of the clinical care team.

- **LMA group: Atropine + LMA + Infasurf**

  - The neonates randomized to LMA management will be given atropine (0.1 mg/kg) before the insertion of the size 1 classic LMA. The LMA cuff will be inflated with 2-4 mL of air.

  - A CO_2 detector will be used to verify the placement of the device.

  - Adequate PPV will be verified by observing adequate chest movements and SpO_2 for at least 1 minute.

  - The tip of a T-connector (or, a 5-French catheter) will be cut to reach the distal end of the LMA, to instill a 3 mL/kg dose of Infasurf in 2 aliquots.

  - Surfactant will be drawn up in a syringe with a Luer-type adaptor.

  - Following surfactant therapy, manual PPV will be provided for a minimum of 5 minutes.

- After spontaneous respirations are judged adequate, the LMA will be removed and nasal CPAP resumed.

- Indications for intubation to initiate assisted ventilation will be one or more of the following:
  - Persistent apnea
  - Severe retractions (as judged by an attending neonatologist or fellow)
  - Inability to wean $FiO_2 < 0.60$ to maintain target SpO_2 90-95%

- Management of RDS, mechanical ventilation, concurrent neonatal issues, and any complications that may arise will be at the discretion of the clinical care team.

Since surfactant administration procedures are already standardized in the AMC NICU, babies will have had at least one clinically indicated chest x-ray before the intervention, and a blood gas is obtained 30 to 60 minutes after the treatment, as per the routine surfactant administration protocol. The study does not alter these routine clinical protocols. Similarly, routine monitoring during the instillation of surfactant will continue, including monitoring of pulse rate, SpO2, colorimetric CO_2 exhalation, chest wall rise and auscultation as indicated, in all subjects.

Babies at risk for apnea of prematurity are routinely treated with caffeine. The two lower gestation age groups in this study will continue to undergo prophylactic caffeine therapy for apnea of prematurity.

Only one routine procedure will be standardized due to the study protocol. Babies with RDS on nasal CPAP all have an indwelling orogastric tube; gastric residuals are aspirated and aspirate volumes are recorded, but not always at consistent time points. For this study, the gastric residual will be suctioned before surfactant therapy in each patient, and also 15 minutes after the treatment. The amount of new gastric residual will be recorded.

Failures:

The criterion for **Early Failure** is the need for mechanical ventilation within 1 hour of surfactant therapy due to either persistent apnea, apnea despite naloxone, severe retractions, or the inability to maintain $FiO_2 < 0.60$ for target SpO_2 90-95%

The criteria for **Late Failure** are one or more of the following:
- a sustained $FiO_2 > 0.60$ required to maintain target oxygen saturation,
- a second dose of surfactant within 8 hours of the first dose,
- more than 2 doses of surfactant, or
- the need for mechanical ventilation within the first 120 hours of life.

- Re-dosing of surfactant
  - Criteria for re-dosing are defined as $FiO_2 > 0.60$ or $FiO_2 > 0.30$ with associated clinical signs of worsening RDS.

- If **re-dosing surfactant before 8 hours** has elapsed from the time of initial administration, the dose will be administered via ETT for all study patients, regardless of the group to which they had been randomized.
- If **re-dosing surfactant more than 8 hours** after the initial dose, patients in the LMA group will have a second dose given via the LMA; any surfactant doses beyond the second will be given via ETT. In the ETT group, all doses are given via the ETT.

Although the study interventions are limited to the airway used for surfactant administration in the first 1 to 3 days of life, and clinical management or follow-up are not otherwise conditioned by the study, all subjects enrolled will continue in the study up to discharge from AMC, for the purposes of data collection. This will include:

- the FiO_2 and mode of respiratory support before enrollment and at 0, 1, 12, 24, and 48 hours, and 7 and 28 days after initial surfactant administration,
- any need for additional doses of surfactant,
- any need for intubation, and
- any need for mechanical ventilation.

D. Data Analysis

A copy of the data collection sheet that will be used for the study is included.

Primary Outcome Measures: The primary outcome will be success of the surfactant administration strategy in avoiding mechanical ventilation in the first 120 hours of life.

Secondary Outcome Measures:

- Number of surfactant doses
- Days on assisted ventilation
- Day on any noninvasive respiratory support (CPAP/NIPPV modes)
- Days until off respiratory support (supplemental oxygen and/or pressure support)
- Rate pneumothorax and/or pneumomediastinum
- Rate of BPD as defined by oxygen dependence at later of 28 days or 36 weeks' postmenstrual age
- Complications during insertion of LMA or ETT
- Mortality rate

Planned post-hoc analyses include timing of failure by treatment group, which should illuminate the mechanisms of failure by treatment strategy.

➢ Baseline comparability:

Baseline differences between ETT group and LMA group will be compared using t-tests for continuous variables (birth weight, gestational age, age and FiO2 at enrollment) and chi-square test for categorical variables (race, sex, prenatal care, antenatal steroids, mode of delivery, multiple gestation)

➢ Primary outcome measure:

Our primary outcome for the study is the proportion of infants that will reach the early and/or late failure criteria. The incidence of the failure criteria will be compared using chi-square statistics.

➢ Sample size/Power analysis:

The sample size was estimated based on results from the recent study on this population, at the Albany Medical Center NICU. We will thus expect that 30% of the LMA group will meet failure criteria, i.e., the LMA success rate in avoiding later intubation and ventilation will be 70%. For a non-inferiority design, with a clinically relevant non-inferiority margin of 20%, a sample of 130 patients (65 per group) will be needed to conclude non-inferiority of the LMA method compared to INSURE (calculated using a one-sided α=0.05, β error=0.20).

➢ Secondary outcome measures:

Groups will be analyzed for secondary outcome differences using chi-square statistics for categorical data, and t-test or non-parametric tests for continuous data, as appropriate for the distribution obtained. The FiO_2 response to surfactant treatment strategies will be compared from baseline to 1 and 8 hours using repeated measures ANOVA and post-hoc Dunnett's test. Time to wean off respiratory support will be compared between groups using Kaplan-Meier analysis, with censoring at discharge.

➢ Interim Analyses:

Reports for the IRB will be prepared after one year of initiation of the trial or enrollment of 50 patients, whichever comes first. Data on the primary outcome, mortality, and major adverse events on the first 50 patients, will be submitted to Dr. Ashar Ata for purposes of safety monitoring. A difference in primary outcome at the $p<0.01$ level, or a consistent trend towards differences in major adverse events will constitute criteria for recommending that the study be stopped.

E. Risks

- Risk category: Greater than minimal.

This study is considered as a greater than minimal risk study. The study design includes a decreased use of laryngoscopy for tracheal intubation, which is currently the standard method of surfactant delivery. Laryngoscopy is associated with apnea, minor abnormalities in cardiac rhythm, obstructed respiration, increase in systolic blood pressure, decreased heart rate and transcutaneous oxygen tension in preterm neonates during the laryngoscopy (Carbajal, 2007)

(Marshall, 1984). ETT insertion causes pain and discomfort, coughing, laryngospasm, and vagal responses including apnea and bradycardia; it may cause trauma to the airway including the vocal cords, subglottic edema, and stridor; more than one attempt at insertion is usually necessary, and esophageal intubation is common, requiring re-intubation. As many as 21% of "successful" tracheal tubes end up in a mainstem bronchus (Hipolito et al., 2001), which can cause trauma, hypoventilation, desaturation, pneumothorax, cardiac arrest, and asymmetric delivery of surfactant.

The hemodynamic effects of laryngoscopy and intubation are expected in most subjects during the procedure; we will follow our current procedures for intubation; this includes continuous monitoring of heart rate and SpO_2 throughout the procedure, and a post-intubation chest X-ray to verify the ETT position, if the ETT is to remain in place.

The adverse physiologic consequences of laryngoscopy and intubation can be attenuated with the appropriate use of premedication (VanLooy, Schumacher, & Bhatt-Mehta, 2008; Sarkar, Schumacher, Baumgart, & Donn, 2006; Greenwood & Colby, 2009). Premedication with intravenous remifentanil and atropine will be used, as per current practice (standardized order set). Remifentanil is a synthetic opioid with a half-life of only 3-5 minutes. It could cause adverse effects such as hypotension and bradycardia (Penido, 2010; Welzing, 2009). There have been reports in the literature of remifentanil causing chest wall rigidity (Choong, 2010), however, this was at higher doses. Remifentanil has successfully been used for INSURE at lower doses without any adverse effects (Welzing, 2009). If there is any concern of chest wall rigidity in this trial, the infant will be give naloxone, and, if necessary, vecuronium.

Decreased exposure to endotracheal intubation-related procedures among study patients would be expected to decrease the risks and discomfort associated with this method.

Atropine is an anticholinergic drug, used commonly in conjunction with other medications to reduce episodes of bradycardia by decreasing vagal responses. Bradycardia can result from vagal stimulation during laryngoscopy, endotracheal intubation, or insertion of the LMA. Tachycardia, restlessness, impaired gastrointestinal motility and dry secretions could be potential secondary effects observed.

LMA insertion may result in kinking or malposition of the device, which may result in obstruction at the base of the tongue. In this case the mask must be removed and the procedure restarted. The overall incidence of complications after removal of the LMA is about 10-13%, including coughing, laryngospasm, retching, breath holding, vomiting, stridor, desaturation and excessive salivation (Trevisanuto, Micaglio, Ferrarese, & Zanardo, 2004; Schmiesing & Bock-Utne, 1998). A survey of almost 12000 patients of all ages managed with LMA over a period of 2 years reported only 0.15% (18) critical incidents related to airway management, and none required intensive care management (Trevisanuto et al., 2004).

We will use Infasurf®, sterile intratracheal suspension of calf lung surfactant extract, FDA approved for prophylaxis and treatment of RDS (Infasurf package insert, ONY, Inc.; available at www.infasurf.com). The most common adverse reactions with Infasurf dosing procedures are cyanosis (65%), airway obstruction (39%), bradycardia (34%), reflux of the surfactant into the ETT (21%), requirement of manual ventilation (16%) and re-intubation (3%). These events were generally transient in the controlled trials with Infasurf. If any one of these events occurs the administration of the surfactant will be interrupted until the neonate's condition is stabilized. Other conditions observed in trials of prophylaxis using Infasurf were incidence of pneumothorax (10%); the overall incidence of pneumothorax in our recent rescue treatment trial was 17%, similar in both groups. If a pneumothorax is suspected, transillumination and/or chest X-ray will be done, and the pneumothorax is managed according to the clinicians' judgment.

Adverse events (AEs):

An AE is any untoward clinical occurrence including sign(s), symptom (s), and/or laboratory finding(s) concurrent with the use of a drug or device in humans. AEs include worsening of any baseline symptoms. An AE need not have a causal relationship with the use of the drug or device. AEs may be detected by the investigators, or other competent observers. The investigators will also evaluate significant changes in laboratory values and imaging results; if they determine that a laboratory or imaging abnormality is clinically significant, it will be documented, along with a determination of whether or not the abnormal finding is consistent with the current diagnoses.

Reporting period: AEs will be recorded from the time of informed consent until 72 hours following the last use of the LMA or ETT for non-serious AEs, and until 30 days after the last use of the LMA or ETT for serious AEs. Any AE that occurs between the time informed consent is obtained and the initial airway insertion, that is considered related to a protocol-specified procedure, must be reported.

Procedures for assessing, recording and reporting AEs: Throughout the duration of the study, the investigators will closely monitor each subject for clinical evidence of device-related events, and monitor all clinically information for evidence of AEs. AEs not explained by the infant’s underlying illness which occur during the course of the study will be reported in detail on the appropriate forms to the IRB, and followed until resolved or stable. All serious AEs will be reported to the IRB within 24 hours.

Grading of AEs:

• Mild - sign or symptom noticeable, but easily tolerated by the patient, and not expected to have a clinically significant effect on the baby’s overall health and well-being. Not likely to require specific medical attention.

• Moderate - causes interference with usual function or affects clinical status. May require medical intervention.

• Serious - incapacitating or significantly affecting clinical status. Likely requires medical intervention and/or close follow-up.

Expected adverse events (AEs):

The following AEs associated with prematurity, the clinical course of RDS, or treatments for these conditions, are expected with the approximate frequencies listed in the Table. These AEs are actually or may be potentially relevant to the LMA study protocol.

Adverse events	Expected %
During surfactant administration procedure	
Desaturation > 1 min	5% to 20%
Airway obstruction	39%
Bradycardia	34%
Surfactant reflux onto CO2 detector	5%
Re-intubation	5%
LMA replacement	5 to 10%
Others (observer, specify):	
Clinical complications of prematurity and RDS	
Pneumothorax	6 to 17%
Other pulmonary air leak	15%
Pulmonary hemorrhage	1 to 7%
Hypotension	15%
Oliguria	10%
Intraventricular hemorrhage (grade ≥ 2)	0.5% to 10%
Relevant Outcomes	
Chronic lung disease	5% to 15%
Mortality (depends on gestational age)	1% to 5%

Serious adverse events (SAE):

A SAE is defined as an adverse effect that meets any of the following serious outcomes:

- Is fatal;
- Is life-threatening;
- Results in persistent or significant disability;
- Is an important medical event for which the subject may require medical or surgical intervention to prevent the outcomes above described;
- It requires or prolongs inpatient hospitalization

SAEs will be recorded from the time of informed consent until the baby is discharged or removed from the study. A Serious Adverse event form must be completed and signed by the principal investigator, and submitted to the IRB within 24 hours after the event. Furthermore, the investigator will complete and submit follow-up SAE information including diagnosis, outcome, and results of specific investigations.

The intensity or severity of SAEs:

- SAEs will be classified as possibly related (little or no relationship with the study), probably related (likely to be related to the study) or definitely related (a strong relationship with the study).
- If a SAE is believed to be at least possibly related to the study device, it will be additionally reported to the manufacturer and the FDA.

F. Benefits:

There are no economic benefits for subjects or their families for participating in the research. The medical benefits will be evaluated as result of the research.

G. Confidentiality:

Every subject will have an identification code number (ICN) after the randomization that will identify the therapeutic method. The data collection form will have the ICN. All the data will be

stored in password protected files on a computer in the Neonatology fellows' office. There will be two password protected files. The final dataset for analysis will be de-identified, including only the subjects' ICN and the study data. The second dataset will include the subjects' name, MR number, date of birth and the ICN; this file will be used for cross-verification only, if needed.

The principal investigator and/or co-investigator or study coordinator will release the preliminary information only to the IRB. Significant device-related adverse event information will be communicated to the IRB, the LMA manufacturer, and the FDA. Final aggregate data will posted on clinicaltrials.gov, and submitted for publication.

H. Options

The subjects that could be potentially enrolled in the trial, but whose parents do not agree to participate will receive the standard of care for patients with RDS, as outlined in the ETT group, and including premedication, intubation, rescue surfactant therapy and respiratory support as needed.

Sponsor/materials:

1. LMA-classic: One size 1 device was previously donated by LMA North America, and another purchased by AMC. These are reusable devices, which could be used up to 40 times each. If these are unavailable, a disposable LMA from a neonatal resuscitation box may be used.

2. Infasurf®: Infasurf is already a stock item in the AMC Pharmacy. If, at the end of the study, a significant excess of Infasurf doses are used in the LMA group, the manufacturer, ONY, Inc., will donate the excess doses to AMC Pharmacy. No other materials are donated or reimbursed. ONY, Inc. will support the study through an educational grant.

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