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Newer technique in surfactant administration



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ABSTRACT

Respiratory distress syndrome (RDS) is a morbidity often found in premature infants. The incidence of RDS is inversely proportional to gestational age and decreases with the presence of antenatal steroids. Surfactant is a phospholipid produced by type 2 pneumatocytes. Surfactant coats the alveoli and bronchioles so that their surface tension is reduced. Thus, the alveoli and bronchioli remain open, allowing gas exchange. After surfactants are known to benefit RDS, the next question is when is the right time to give them. There are 2 alternative times for surfactant therapy, namely before symptoms appear or a diagnosis is made (prophylaxis) and after RDS symptoms appear (rescue). Several Newer techniques in surfactant administration will be discussed in this article.

Keywords: *administration, newborn, Respiratory-distress syndrome, surfactant.*

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INTRODUCTION

Respiratory distress syndrome (RDS) is a morbidity often found in premature infants. The incidence of RDS is inversely proportional to gestational age and decreases with the presence of antenatal steroids.¹

In the 1960s, it was first noticed that there were cases of premature babies with respiratory distress due to a lack of a substance so that the lungs could function as a gas exchange. Subsequent research found that this substance is a surfactant, which reduces the alveoli's surface tension so they do not collapse. The expanding alveoli are necessary for the exchange of O₂ and CO₂. Subsequent studies are about the manufacture of surfactants, therapeutic strategies, and ways of administering surfactants.² In this paper, we will discuss new strategies for surfactant administration.

SURFACTANT

Surfactant is a phospholipid produced by type 2 pneumatocytes. Surfactant coats the alveoli and bronchioles so that their surface tension is reduced. Thus, the alveoli and bronchioli remain open, allowing gas exchange. The physiological effects of surfactant are improved oxygenation,

increased functional residual capacity, and improved lung compliance. Another effect is on the cardiovascular system, where pulmonary resistance decreases, and blood flow to the lungs increases.^{1,2}

The fetus begins to produce surfactant early in the second trimester of pregnancy and increases until it is sufficient to develop alveoli at 34 weeks gestation. If a premature baby has a surfactant deficiency, exogenous surfactant is needed to help the alveoli expand. In this condition, surfactant can save the life of premature babies.²

Fujiwara carried out the first surfactant therapy research in 1980, and thereafter other researchers employed the randomized controlled trial (RCT) design in their investigations. Systematic reviews and meta-analyses of surfactant therapy have been published. The surfactants used for RDS therapy were initially extracted from animals, cows, and pigs; then synthetic ones were made.²

The results of studies have consistently shown good benefits in premature infants, namely dramatically improving clinical symptoms of RDS and reducing mortality. The era of commercial surfactants began in the 1990s. RDS mortality before the surfactant era was 40%. After the surfactant era, this mortality has more

than halved, and neonatal mortality has decreased by 25%. The mortality rate due to RDS continues to decline, as well as the neonatal mortality rate, both in developed and developing countries. Complications related to lung immaturity and ventilator use are reduced. There are minimal side effects of surfactant therapy, such as bradycardia, hypoxia, hypotension, re-opening of the ductus arteriosus, and pneumothorax.²

Surfactants have been the most widely studied drugs in the neonatal field in the past 4 decades. Research includes therapeutic strategies, instillation methods, and types of surfactants. The primary strategy of surfactant therapy is prophylaxis and rescue. At present, surfactant is the standard therapy for RDS administered after resuscitation and stabilization and in the neonatal intensive care unit.¹ Surfactant is initially administered via an endotracheal tube (ETT). However, it is realized that intubation is an invasive procedure that can cause trauma,¹ so an alternative to giving surfactant is considered in another, less invasive way.

Resuscitation strategies with early continuous positive airway pressure (CPAP) and stabilization with non-invasive airway support minimize intubation.

Modification of surfactant administration with INTubate, SURfactant, and Extubate (INSURE) still requires intubation. Alternative ways of administering surfactants are intraamniotic instillation, pharyngeal instillation, laryngeal instillation, a thin endotracheal catheter (TCA), and nebulization in spontaneously breathing infants.¹

SURFACTANT DELIVERY STRATEGY

After surfactants are known to benefit RDS, the next question is when is the right time to give them. There are 2 alternative times for surfactant therapy, namely before symptoms appear or a diagnosis is made (prophylaxis) and after RDS symptoms appear (rescue). Prophylactic surfactant is given to infants with risk factors for RDS,³ namely gestational age and/or suspected to have a high risk of RDS,⁽⁴⁾ and aims to prevent its severity. Surfactant prophylaxis is recommended in infants <26 weeks' gestation and mothers who are not receiving antenatal steroids or preterm infants who require intubation during stabilization in the delivery room⁵ or increased oxygen requirements after resuscitation.⁴

At first, both strategies are effective. In this era, using CPAP in the delivery room was not routine. Current prophylactic surfactants reduce mortality and air leak in preterm infants. However, with the increasing use of CPAP in premature infants in the delivery room, both early in resuscitation and stabilization, the benefit of prophylactic surfactant has been called into question. It has been demonstrated by later research that prophylactic surfactants do not improve the outcome of routine CPAP usage in preterm newborns. In addition, infants receiving preventive surfactant therapy have an increased risk of mortality and bronchopulmonary dysplasia (BPD).³⁻⁵

Rescue surfactant therapy is divided into two, namely early and late. Early rescue is the recommended strategy. Surfactant administration is carried out immediately, within 1-2 hours after birth, when RDS symptoms appear.⁵ At the onset of RDS symptoms, oxygen demand is relatively low, so clinical symptoms can quickly improve and prevent CPAP

failure. FiO₂ >30% in premature infants' first hours of life is a strong predictor of CPAP failure.⁴

In RDS babies who are breathing spontaneously with non-invasive breathing assistance, should they be intubated? This question led to the idea of administering surfactant without intubation. So, the INSURE technique was developed. In the INSURE method, intubation is carried out briefly, only for surfactant instillation, so the risk of BPD and air leakage is minimal. One meta-analysis demonstrated that INSURE, compared with delayed selective surfactant administration, reduced the need for mechanical ventilation, BPD, and air leaks. Subsequent evidence shows that surfactant therapy using the INSURE and CPAP methods given to infants with clinical symptoms of RDS is safe, has better outcomes, and reduces the need for surfactant and intubation.³

The timing of surfactant administration to intubated infants due to RDS in the first 2 hours after birth (early) compared to when the RDS was already in progress (>2 hours) shows that early surfactant administration is better than late. With early surfactant administration, mortality, BPD, and air leak were lower, and there was no increased incidence of pulmonary or severe intraventricular hemorrhage.^{3,6}

The limitation of oxygen requirements as an indicator for oxygen administration shows that a low oxygen limit (FiO₂ <30%) is better than a high one before RDS worsens. At lower oxygen thresholds, the need for intubation, the incidence of air leaks, and the incidence of BPD are lower. Administration of surfactant before the baby is transported is associated with lower oxygen requirements during transport and shorter ventilator use.^{3,6}

REPEAT DOSE

Repeat administration of the second, even third, surfactant in RDS is performed if there is no clinical improvement and the need for ventilation and oxygen is high. Re-administration of surfactant with a higher dose effectively reduces oxygen demand and mortality. Repeat doses are calculated based on postnatal body weight. It is necessary to pay attention to the maximum dose that may be given, according to the surfactant manufacturer's

recommendation. In the absence of clinical improvement after surfactant therapy, other causes of respiratory distress should be considered, such as sepsis and hypoxic-ischemic encephalopathy.³⁻⁵

SURFACTANT REPLACEMENT THERAPY BEFORE BIRTH

Surfactant therapy can be given when the baby is not yet born or during labor. This therapy is prophylaxis because it is given when RDS has not yet been diagnosed. Surfactants are given before the baby is born through intra-amniotic instillation and during labor through pharyngeal instillation.¹

Intra-amniotic instillation of surfactant

In this method, the surfactant is given at the time of delivery. After the membranes rupture, the surfactant is instilled using a fiberscope through the cervix into the amniotic cavity, and the surfactant is injected into the baby's mouth. Research about this method is very limited. In series 3, cases reported no complications. However, this method is complicated and invasive, making it challenging to apply in daily practice.¹

Pharyngeal instillation

The baby inhales after birth and closes the glottis when attempting to exhale, which produces positive transpulmonary pressure and pushes fluid from the alveoli into the lung's interstitial spaces. This is the physiological basis for administering surfactants by pharyngeal instillation. This results in loss of alveolar integrity, cytokine release, serum protein leakage, and inactivation of endogenous and exogenous surfactants in premature newborns with surfactant deficiency.¹ These physiological processes are exploited to deliver exogenous surfactant in the pharynx. Fetal lung fluid can be evacuated from the upper airway and supplied with a surfactant solution while the chest is still compressed within the birth canal. The newborn aspirates surfactant, which is injected into the throat, as the chest enlarges.¹

Surfactant instillation can also be given before the umbilical cord is cut or within the first 5 minutes in infants <29 weeks.

This method uses the surfactant as a rapid bolus through a flexible catheter inserted into the pharynx. After the baby is born, positive pressure ventilation (PPV) is carried out or given CPAP assistance.

In 2004, a preliminary report utilizing the pharyngeal surfactant instillation approach was released. Following nasopharyngeal suctioning, 23 infants (560 to 1804 g) delivered between 27 and 30 weeks gestation were given medication in the nasopharynx before shoulder delivery. The infant was then given CPAP with positive end-expiratory pressure (PEEP) 10 cm H₂O with a mask while the infant started breathing and continued with 6 cm H₂O for at least 48 hours. According to research, this method of vaginal delivery is simple and generally safe. Regretfully, this method necessitates the delivery of the head and a baby that is breathing on its own. Babies that are born malpresented, with an abdominal birth canal, or in fetal distress cannot be treated with this technique.⁷

A side effect of the pharyngeal surfactant instillation procedure is upper airway obstruction requiring suctioning and PPV. The limitation of this method is that it cannot control the amount of surfactant instilled in the pharynx that enters the lungs. While pharyngeal surfactant instillation is a less intrusive procedure than tracheal catheter insertion or intubation, there are benefits to other less invasive techniques as well. Research on the installation of this method still needs to be completed. The short-term outcome of this method is the reduced need for intubation. One publication on this method examined the effects of surfactants rather than the procedure. The Cochrane review found no articles comparing this method with no treatment or treatment with intubation and surfactant.¹

INTUBATION

Surfactant administration to the RDS via the ETT has been the standard therapy for decades. This invasive method requires skilled personnel and complications of intubation can arise, namely airway trauma. Therefore, it thought of a simpler, cheaper, and less invasive way. The easy and simple procedure also aims to be

implemented in developing countries to reduce neonatal mortality globally. INSURE is an effort to simplify the procedure for administering less invasive surfactants. In this way, intubating is still necessary, even if only for a short time.²

INSURE is a surfactant instillation method that has been extensively studied. Compared to the previous method, immediate removal of the ETT after installation is feasible, safe, and beneficial. The advantage of prompt ETT removal is reduced risk of barotrauma, BPD, and death. This method is given to premature babies who breathe spontaneously with the support of CPAP. The inserted ETT is used only as a channel for surfactant instillation. After that, the ETT was removed, and the baby was assisted again with CPAP.²

Meta-analysis proves that the INSURE method is profitable. Not exposing premature babies to mechanical ventilators lowers the incidence of BPD and death.⁸ However, this method still requires skilled health workers to perform intubation. Intubation of premature infants is at risk of failure to place the ETT and airway trauma. According to a systematic review by De Bisschop,⁹ one-third of the subjects failed after INSURE and required mechanical ventilator assistance. Factors that influence this failure are birth weight, gestational age, and RDS severity.⁹ The failure rate is inversely correlated with birth weight and gestational age. One of the reasons for this is the difficulty in intubating tiny babies. Therefore, a surfactant instillation method is considered that does not require intubation.⁹

CATHETER

Installation of surfactant through a small catheter was a further development. This method is called thin catheter surfactant administration (TCA). In this method, the surfactant is instilled through the catheter directly into the baby's trachea, and no intubation is required. This method is performed on babies breathing spontaneously with the help of non-invasive breaths. The advantage of this method is that it reduces the risk of trauma to the airway, and the staff does not need to be skilled at intubating. However, laryngoscope insertion skills in premature infants are still required.¹

Less Invasive Surfactant Administration (LISA) and Minimally Invasive Surfactant Therapy (MIST) are the two most used TCA versions. With the use of CPAP, this technique is applied to infants who are breathing on their own without the need for a laryngoscope. Surfactant is instilled through a small catheter that is inserted into the trachea. The catheter used is an angio-catheter or feeding tube. Compared to INSURE, the advantage of the TCA method is that there is no need for intubation and PPV. Even though it is short, PPV in INSURE increases the risk of alveoli damage.^{7,10} Reducing airway problems from ETT insertion and improving the effectiveness of CPAP following surfactant therapy are the ultimate goals of the TCA technique.¹⁰

There are 2 main variations of MIST, namely the Hobart and Cologne methods. The Hobart method was first described by Dargaville et al. This method uses a rather stiff catheter without Magill's forceps and premedication. Not using Magill's forceps can prevent trauma to the upper airway and vocal cords. Magill's forceps insert the catheter past the vocal cords in the Cologne method. The Hobart method is more widely accepted because it is simpler than the Cologne method.¹¹

The TCA technique lowers the need for intubation, mechanical ventilator support, oxygen requirements, duration of stay, and mortality, according to systematic reviews and meta-analyses. Other morbidities, such as periventricular leukomalacia, intraventricular hemorrhage, and necrotizing enterocolitis, have also decreased.^{10,12-15} TCA increases the occurrence of air leaks that require drainage.¹³

Inserting a catheter into the trachea is identical to intubation because it requires a laryngoscope. Thus, it still requires skilled staff to use a laryngoscope and risks trauma to the airway.² The development of new methods of administering surfactants that do not require a laryngoscope at all is by laryngeal mask and nebulization.

LARYNGEAL MASK

Surfactant instillation via laryngeal mask was first reported by Brimacombe et al. in 2004,¹⁶ where surfactant administration was carried out in 2 cases of RDS.

Subsequent research was conducted by Trevisanuto et al. in 2005.¹⁷ This study was a series of 8 cases. The subjects were infants aged <72 hours with a median gestational age of 31 weeks (range 28-35 weeks), median birth weight 1700 grams (range 880-2520 grams) with CPAP support of 5 cm H₂O, who were diagnosed with RDS. An evaluation at 3 hours after surfactant therapy showed clinical improvement. The investigators concluded that surfactant administration via laryngeal mask may be a non-invasive alternative to surfactant administration, and RCT studies are needed to confirm the technique and efficacy of this method.¹⁷

The proposed protocol for instilling surfactant via a laryngeal mask is inserting a laryngeal mask according to the manufacturer's instructions and injecting the surfactant in 2-4 aliquots. Surfactant is instilled with the help of a feeding tube or flexible catheter, which is inserted until the tip of the catheter is at the distal end of the laryngeal mask. In this way, the surfactant can be instilled over the vocal folds. In between aliquots, PPV was carried out until the surfactant disappeared from the laryngeal mask. After the instillation of the last aliquot, PPV is carried out for 1-5 minutes, then the laryngeal mask is removed and continued with CPAP support and further management.^{7,17} The instilled surfactant can be either early or rescue.⁷

To provide surfactant below the vocal cords, the catheter tip was moved into the trachea in one research, much like intubation. Catheter and Laryngeal Mask Endotracheal Surfactant Therapy (CALMEST) is the name of this procedure.⁷ At the time of training in this procedure, the success rate on the first attempt was 93.3%. According to the neonatologist who participated in this study, this method is comfortable, applicable, and done quickly.⁷

The CALMEST method was tested on 4 patients with birth weight between 1900-3624 grams. Evaluation after surfactant therapy with the CALMEST method showed clinical improvement, which included a respiratory distress score, oxygen requirements up to 21%, and saturation >95%. This procedure takes 5 minutes and is well tolerated by

the patient; there are no severe effects such as bradycardia, desaturation, or coughing, and it does not require analgesia or sedation.¹⁸ Another method similar to CALMEST is Surfactant Administration through Laryngeal or Supraglottic Airways (SALSA). Publications on the SALSA method, both RCTs and systematic reviews, attest to the safety and efficacy of this method. The laryngeal mask is inserted in the SALSA method, and surfactant is instilled over the vocal cords. The skill required for this method is simpler and faster than TCA because there is no laryngoscope insertion and Nagill's forceps.^{2,17}

The following research was a pilot study with RCT design comparing RDS subjects treated with rescue surfactant through CPAP and CPAP alone. The inclusion criteria were birth weight >1200 grams, <72 hours, CPAP with FiO₂ 30-60%. The postintervention saturation target is 88-95%. In the intervention group, there was an immediate decrease in the need for FiO₂. Neither investigator has concluded that surfactant administered via laryngeal mask can reduce FiO₂ requirements, but further RCT studies are needed. Only this study met the inclusion criteria in the Cochrane systematic review published in 2011.¹⁹

Side effects of surfactant instillation via laryngeal mask are hypoxia, laryngospasm, and malposition. Another limitation is the availability of a small laryngeal mask. This technique is non-invasive and easy to perform, but further research is needed to prove its efficacy and safety.¹

The advantages of instilling surfactant via a laryngeal mask are that it is faster, easier, less invasive, and reduces the risk of glottic and subglottic trauma.² One multicenter study attempted to install a laryngeal mask in 88 seconds (range 12-500 seconds) with 67% success by untrained health workers previously trained.²⁰ Therefore, this method helps develop countries where intubation and ventilator facilities are limited,²¹ and it is expected to accelerate the reduction of neonatal mortality.²

To date, 8 RCTs of surfactant administration via laryngeal mask have been used. Typical inclusion criteria were <36 weeks, CPAP >30-40% and PEEP

>5-6 cm H₂O, recruits <36-48 hours, and birth weight of at least 810 g.⁷ Publications comparing surfactant administration via laryngeal mask with other methods, such as MIST and INSURE, it was found that in general surfactants administered via laryngeal mask were effective, safe, and less invasive than previous methods.^{10,22-25}

Several meta-analyses published in the last 2 years have concluded that this aligns with individual RCT studies. The outcomes measured were surfactant repetition, oxygen demand, mechanical ventilation, intubation, mortality, BPD, and pneumothorax. Administration of surfactant via laryngeal mask reduced oxygen demand (decreased FiO₂) with an average difference of 1.82 (-6.01 to 9.66); reduced intubation (RR: 0.17; CI-95%: 0.05-0.57); use of mechanical ventilators (RR: 0.44; CI-95%: 0.31-0.61); and there was no difference in the outcome of death, BPD, or pneumothorax, IVH.^{2,26}

AEROSOL

Another method of giving surfactants is using nebulization.⁷ The nebulization method can deliver surfactants to reach the alveoli. The advantages of administering surfactant by nebulization are that it is the least invasive, minimal airway manipulation, is easy, economical, and can be given to babies breathing spontaneously. In the future, this method is the best for surfactant administration.^{1,2}

Experiments on animal lungs have shown that surfactant administered via nebulization lowers the surface tension of the alveoli. The results of further experimental animal studies found that the aerosolization method distributes surfactant evenly in the lungs and reduces vascular resistance. Changes in cerebral blood flow are better than instillation through an ETT.²⁷ Early studies of surfactant nebulization used nasal CPAP. The results were improvement in clinical parameters (respiratory distress score) and blood gases (PaCO₂ and O₂ gradient). However, several other studies have failed to demonstrate clinical and blood-gas benefits. Subjects in this early study varied widely (ranging from 30 minutes to less than 3 days) and used different types of surfactants. The nebulizers used in these studies are jet, ultrasonic, and vibrating

membrane nebulizers.¹ Each nebulizer has advantages and disadvantages.²⁷

Furthermore, an in vitro study was carried out with 6 different nebulizers. As a result, the vibrating membrane nebulizer is the most effective tool for delivering surfactant due to its maximal material output and minimal leftover volume.¹

Subsequent studies on RDS patients have used a lot of vibrating and jet membrane nebulizers. Surfactant deposition with membrane vibration is better than jet nebulization.⁷ Studies have shown that factors influence the success of surfactant nebulization. Individual patient factors are body weight, minute ventilation, and peak inspiratory patient. In contrast, external factors are the size of the aerosol particle, the type of aerosol generator, the aerosol flow, and the type of surfactant.^{1,7}

The short-term outcome is the same oxygen saturation as the standard surfactant administration method. The need for intubation and mechanical ventilator assistance within 72 hours post-therapy and other outcomes did not differ. The failure of this aerosol method could be due to the significant loss of surfactant in the CPAP circuit and the delay in starting surfactant therapy.⁷

Apart from the nebulizer, other tools used in this method are the interface, which includes a face mask, nasopharyngeal tube, and short prong nasal cavity. The nebulizer can be connected close to the interface or an inspiratory tube by non-invasive respiratory support.⁷ Until now, no commercial aerosolization devices are available on the market. This tool is still in the process of being reviewed for distribution permit approval by the authorized agency.^{2,7} A standard nebulizer is needed for this method to be effective, workable, have a long duration of therapy, and have adequate costs. So that this method can be used in daily clinical practice.⁷

The dose of surfactant in the nebulization method ranges from 72-200 mg/kg/dose.⁷ For the surfactant to remain effective, it needs to be made in the form of an aerosol, the correct particle size so that it can enter the lungs and not stick to the airways, particles can collect again in the alveoli, and its biological activity remains good.¹

The blockage of the nasal prongs, increased secretions that need to be suctioned, foaming around the interface, and an increase in oxygen demand are all side effects of surfactant nebulization. Nevertheless, there is no need for intervention because this effect is not considerable.^{7,27}

Until 2021, there were 11 published studies, consisting of 6 RCTs, 3 preliminary studies, 1 phase 1 study, and 1 phase 2 study. These studies showed consistent safety and feasibility results but less efficacy consistency. In one multi-center RCT study involving 457 subjects with RDS, the result was that in the aerosol group, a 50% reduction in intubation requirements, with a number needed to treat 5. A phase 2 study compared 4 different doses of surfactant with 2 different nebulizers. However, the methodology in this study needed to be stronger because it used a retrospective control and a small number of subjects. Another phase 2 study is still ongoing.²⁷

One systematic review and meta-analysis compared nebulized versus invasive surfactant administration for treating RDS. There were only 2 eligible RCTs. The result is that there is no difference in blood gas parameters, SpO₂, and A/APaO₂ at 1 hour after treatment. However, the duration of ventilator use in the nebulization group was shorter than in the invasive group. It was concluded that the surfactant administration using nebulization is safe and as effective as the invasive method. However, this still needs verification because research is limited.^{27,28} There have yet to be long-term outcome studies. Research results are still limited to outcomes up to 28 days in the respiratory system and are still inconclusive.

SUMMARY

Infants with RDS need to be given surfactant with an early rescue strategy if the baby requires >30% FiO₂ at PEEP >6 cm H₂O. However, surfactant is given immediately in cases requiring intubation at the time of stabilization. Repeat the surfactant dose if there is no clinical improvement after the first surfactant administration. Surfactant is attempted to be administered in the least invasive way, namely laryngeal masks and nebulization.

However, the limitations of giving surfactant via laryngeal mask are the limitations of equipment for tiny babies and nebulizer devices that still need to be commercially available on the market

CONFLICT OF INTEREST

None.

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ETHICAL STATEMENT

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AUTHOR CONTRIBUTION

All authors contributed equally to this study.

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