REVIEW ARTICLE

Practical Considerations in the Selection and Use of Pulmonary Surfactant Therapy for Neonatal Respiratory Distress Syndrome in the Intensive Care Setting

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Pulmonary surfactant is the treatment of choice for neonatal respiratory distress syndrome, as it significantly reduces infant morbidity and mortality. Extensive clinical trials compare the surfactant products and their optimal usage, but often the practical administration issues are less frequently discussed. Herein, a panel of respiratory therapists and neonatal nurse practitioners share their experience regarding surfactant usage. According to the panelists, the primary criteria for surfactant selection are the ability to rapidly decrease ventilatory requirements toward extubation, a low incidence of adverse effects, cost-effectiveness, and ease of use. In most cases, surfactant is most efficacious when given as early as possible where indicated. The surfactant products differ in their storage, handling, preparation, and administration traits, and this may affect rapid dosing of the surfactant during acute treatment. During and after administration, optimal response to therapy depends on efficient management of ventilator settings, which requires vigilant monitoring of the infant. Common adverse effects include endotracheal tube reflux, bradycardia, and desaturation. Using a surfactant which requires a small dosing volume may decrease the incidence of these adverse effects. An emerging trend in clinical practice is the quick extubation of the infant to nasal continuous positive airway pressure after surfactant administration. This practice can reduce the need for ventilation and reduce the risk of ventilator-related lung damage. Nebulization of surfactant may be a future avenue of delivery, but further research is required to determine its precise role. The practical considerations summarized in this discussion may be useful for other clinicians in their own practice.

KEYWORDS administration, beractant, calfactant, poractant alfa, respiratory distress syndrome

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INTRODUCTION

Respiratory distress syndrome (RDS) is responsible for significant morbidity and mortality among very premature infants and those of very low birth weight.[1] RDS is primarily attributed to a deficiency in endogenous surfactant production by the type II pneumocytes; therefore, exogenous surfactant is the treatment of choice for neonatal RDS. Pulmonary surfactant therapy clearly exhibits reductions in infant

ABBREVIATIONS BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; FIO_2, fraction of inhaled oxygen; NICU, neonatal intensive care unit; PEEP, positive end-expiratory pressure; PIE, pulmonary interstitial emphysema; PIP, peak inspiratory pressure; RDS, Respiratory Distress Syndrome; RR, relative risk; SP-B, surfactant-associated protein B

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morbidity and mortality[2] and reduces the overall use of resources in the neonatal intensive care unit (NICU).[3] To date, surfactants derived from natural sources demonstrate superior outcomes compared to synthetic surfactant products.[4,5] A meta-analysis of clinical trials comparing natural and synthetic surfactants shows a significant reduction in the risk of pneumothorax (RR 0.63; 95% CI, 0.53-0.75) and the risk of mortality (RR 0.87; 95% CI, 0.76-0.98) with the use of the natural products.[5] The presence of surfactant-associated proteins, particularly surfactant-associated protein B (SP-B), may contribute to the differences observed between the natural and synthetic surfactant preparations.

Extensive clinical trials have compared surfactant treatment versus conventional treatment, and further trials have compared natural and synthetic surfactants, optimal dosage regimens, and optimal respiratory management of the infant with RDS. Sometimes lost in the clinical trials of surfactants are the practical administration issues relevant to neonatologists and their support staff at the bedside. To provide a review of these factors, a panel of respiratory therapists and neonatal nurse practitioners was assembled and asked a series of questions designed so that they may share their clinical experience regarding practical issues related to surfactant use in the neonatal intensive care setting. A summary of those questions and the panelists' responses form the basis for this discussion of pragmatic considerations involving surfactant therapy.

QUESTION 1. What criteria should be considered when selecting the ideal surfactant?

All FDA-approved natural surfactants decrease morbidity and mortality in preterm infants with RDS. The ideal surfactant has a low rate of acute serious adverse effects such as pulmonary hemorrhage and pneumothorax, as well as long-term outcomes such as bronchopulmonary dysplasia (BPD). The optimal surfactant is efficacious in that it allows for a rapid reduction in the fraction of inhaled oxygen (FIO_2) and ventilatory settings toward early extubation and demonstrates improvement in the infants' chest x-ray findings. Decreasing the time of intubation, mechanical ventilation, and exposure to supplemental oxygen can lead to a decrease in acute lung injury,[6] which may lead to a decrease in the incidence of BPD.

In addition to the ideal surfactant having a rapid onset of effectiveness, it must be well absorbed at the site of action with a low rate and extent of endotracheal tube reflux, which can potentially prevent surfactant from reaching the alveoli and may obstruct the endotracheal tube. The ideal surfactant must be well tolerated by the infants, with a low rate of transient adverse effects during administration, such as bradycardia, oxygen desaturation, clinical decompensation, transient hypotension, and endotracheal tube blockage. A surfactant that produces the same or better effects with a small infusion volume such as poractant alfa (Curosurf, DEY LP, Napa, CA) can increase tolerance by reducing the rate of obstruction and reflux, thereby reducing the rate of associated adverse effects.[7-10] Even though the volume of a required dose may affect tolerability in patients, it is also suggested that patient tolerability is dependent on the clinical delivery technique.[10] Finally, clinicians look for a surfactant that is quick to prepare, fast to administer, cost-effective, and easy to monitor both during and after administration.

QUESTION 2. What is the optimal timing for surfactant administration in the early rescue setting?

Different institutions may have varying protocols regarding their criteria for surfactant administration. In clinical trials, early surfactant administration has demonstrated superior outcomes compared to later surfactant administration.[11,12] Many institutions have surfactant available in the delivery room for early administration to infants that present with RDS and for those that may be high risk. Infants at high risk for RDS include those of very early gestational age and those of very low birth weight.[1] Ideally, in high-risk infants or in infants in whom RDS has already developed, surfactant should be administered as soon as it is clinically feasible,[12,13] preferably within 15 to 30 minutes, according to the panelists.

The availability of surfactant in both the delivery room and the NICU is optimal to assure an early surfactant rescue approach, which is proven to decrease the number of subsequent surfactant doses needed, the time to reach extubation, and the overall cost.[12,14,15] Factors that can delay the administration of

surfactant include transportation of an infant to a suitably equipped facility with trained and experienced personnel or improper insertion of the endotracheal tube. Neonatal transport teams serving outlying hospitals should carry and be trained to give surfactant and make appropriate clinical adjustments to prevent delay in surfactant administration.

In some cases where surfactant is not readily available in the delivery room or the NICU, a treatment delay can also result from the time it takes to order and receive the surfactant from a central or satellite pharmacy. Steps should be taken to minimize surfactant therapy treatment delays for the infant with acute RDS in order to optimize patient response and outcome.

QUESTION 3. What storage and handling requirements exist for the surfactants, and are there any differences among preparations?

At present, three surfactants are commercially available in the United States: poractant alfa, calfactant (Infasurf, Forest Pharmaceuticals, Inc., St. Louis, MO), and beractant (Survanta, Ross Products Division, Abbott Laboratories, Inc., Columbus, OH). All of these surfactant preparations are suspensions and require gentle turning or swirling of the vial for complete mixing. Shaking should be avoided to prevent foaming of the product and possible chemical changes secondary to denaturation of the proteins. In cases where floor stock is unavailable, the surfactant should be hand-carried from the pharmacy, as opposed to being delivered via pneumatic tube systems, to avoid agitation of the product.

In addition, all surfactant products require storage in a refrigerator and protection from light.[16-18] Unopened, unused vials of the surfactants that are warmed to room temperature may be returned to refrigerated storage for future use, but this is not to be done more than once.[16-18] For stability, unused beractant must be re-refrigerated within eight hours,[18] compared to 24 hours for calfactant and poractant alfa,[16,17] which may affect cost and wastage. Treatment delays can be reduced by having a refrigerator in the NICU or delivery room to store surfactant. Each surfactant is available in a single-use vial for entry one time only, and any unused surfactant remaining in the vial after the first entry is to be discarded.[16-18]

QUESTION 4. What should be considered when preparing the various surfactant products?

Because the surfactants are refrigerated, they should be warmed prior to administration; surfactant should not be given cold. The commercially available surfactants can be warmed by setting the vial out at room temperature or by holding the vial in the hand for several minutes prior to administration.[16,18] The standard methods for warming the surfactant may vary slightly between institutions, but the products should not be warmed by methods other than those recommended by the manufacturers, as warming of the product too quickly may cause denaturation of any surfactant-associated proteins. Furthermore, it is important that the surfactant not be left out of the refrigerator at room temperature for too long, as this can cause instability in the product. As stated previously, the products are not to be left at room temperature for longer than eight to 24 hours, depending on the specific surfactant used, and products warmed to room temperature may only be returned to refrigeration once.[16-18]

Products that require a longer warming time or those that require special equipment for preparation may be less advantageous in the acute treatment setting compared to products with less complicated preparation,[19] as relatively extensive preparation may delay the time to administration. Also, product vials that contain larger volumes of surfactant may take longer to warm to room temperature than vials of smaller volume. These hindrances may delay rapid administration of surfactant to the infant.

For rapid administration, the surfactant is held in the hand until room temperature is achieved. The manufacturer of beractant specifically recommends warming in the hand for eight minutes.[18] Also, dividing the surfactant into small aliquots in individual syringes that contain appropriate amounts for unilateral dosing helps to facilitate warming by decreasing the volume to be warmed. These individual aliquots can then be warmed in hand or at room temperature prior to administration.

QUESTION 5. Can the technique used to administer surfactant influence the optimal response, and, if so, how can practitioners ensure the best therapeutic outcome with the product?

The products should be administered in

a closed, sterile system to reduce the risk of contamination and infection. Because the ideal surfactant should have a rapid response, it is advisable not to disconnect the infant from the ventilator during administration so that transient settings can be adjusted appropriately, maintaining a stable positive end-expiratory pressure (PEEP) and tidal volume. Optimal response depends primarily on proper and prompt adjustment of the ventilator to avoid injury to vulnerable infant lungs. Although the technique has not been examined in controlled clinical trials, one panelist finds it clinically advantageous to increase the PEEP by 1 cm H_2O during administration, then decreasing the PEEP after the endotracheal tube is clear. This can assist with clearing the surfactant from the tube, facilitating dispersion, and reducing reflux.

The surfactant dose is divided into syringes in appropriate dosage aliquots so that it is better distributed and tolerated during administration. Although two of the surfactants (poractant alfa and calfactant) are normally given in two divided aliquots,[16,17] according to the manufacturer's recommendations, one of the surfactants (beractant) is given in four aliquots with repositioning of the infant before each aliquot.[18] The panelists prefer a surfactant that requires fewer aliquots and a smaller volume that can be given with a more gentle approach, decreasing stressful handling of the infant, thereby possibly reducing the incidence of adverse effects.

Repositioning of the infant so that the surfactant is equally divided between the left and right lungs is recommended by each of the surfactant manufacturers.[16-18] Generally, the panelists prefer a surfactant that can be administered without placing the infant in a downward incline position, as this may increase the incidence of reflux or other adverse effects. Overall, minimal handling and repositioning of the infant is favorable to minimize stress and trauma.

QUESTION 6. How should one monitor infants, both short term (first few hours) and longer term?

Institutional protocols and clinicians' preferences may vary when monitoring an infant after surfactant administration, although the common goal is to quickly and safely wean then extubate the infant from mechanical ventilation. Well-trained staff and support personnel are required for safe surfactant administration and monitoring. Practitioners must remember to maintain sterility during surfactant administration to avoid infection, particularly in light of the immaturity of the infant's immune system. Due to the rapid onset of surfactant action and the range of possible adverse effects, infants must be observed vigilantly. Proper management of the infant and the ventilator settings is essential, especially within the first few hours after dosing.

Safety and efficacy are assessed on an ongoing basis for each patient. Immediate clinical responses are assessed continuously; such responses include the infant's skin color, oxygen saturations, chest wall movement, heart rate, blood pressure, respiratory effort, state of agitation or calmness, and patency of the endotracheal tube. If an adverse response occurs, immediate steps are taken to address the problem, which may include an increase in FIO_2 and/or mechanical breaths until the infant returns to baseline stability. After the immediate dosing time period, close monitoring of vital signs, blood gases, chest wall movement, and general clinical appearance are necessary. Monitoring chest x-ray findings, including the presence of atelectasis, over-distention, and pulmonary interstitial emphysema (PIE) among other findings, is critical to the formation of a proper clinical management plan.[7,16-18]

The panelists agree that the best practice involves drawing one or more blood gases within the first few hours after surfactant administration to monitor oxygen and carbon dioxide levels. A follow-up chest x-ray within 30 minutes after administration can be compared to the pre-dose chest x-ray to monitor distribution and response, as well as to monitor for adverse events such as pneumothoracies. Other important monitoring parameters include pulse oximetry, visual compliance, end tidal CO_2, and vital signs. When possible, the panelists prefer to monitor oxygenation and ventilation non-invasively to avoid additional stress on the infant. Transcutaneous PCO_2 can be monitored depending on the skin integrity of the infant. Furthermore, if blood gases do not improve substantially enough to wean aggressively, the panelists recommend drawing fewer blood gases to minimize blood loss to the infant and monitoring based on end tidal CO_2, O_2 saturations and chest x-ray findings. Monitoring these parameters allows the clinician to

adjust PEEP, peak inspiratory pressure (PIP), tidal volume, and FIO_2 appropriately.

If one or more subsequent dose(s) of surfactant are required based on the infant's clinical condition, the timing of those doses is dependent on the specific surfactant being used. The recommended dosing interval for beractant is every six hours for up to a total of four doses,[18] compared to every twelve hours for poractant alfa and calfactant for a total of up to three doses.[16,17] Research has shown that significantly fewer infants require more than one dose of surfactant when poractant alfa is used.[20,21] These variables also influence the clinician's time requirements for administration and monitoring of the infant, as well as stress to the infant and cost-effectiveness.

QUESTION 7. What should a practitioner assess when monitoring for safety and efficacy?

It is critical to manage the ventilator settings as described to avoid over-distension and possible acute lung injury and BPD.[22] An emerging trend among some clinicians is to allow a relatively higher CO_2 level (permissive hypercapnea) while weaning oxygen, PIP, tidal volume, PEEP, and other ventilator settings toward early extubation to avoid barotrauma, volutrauma, and endotrauma.[6,22] Some clinicians may allow brief desaturation to avoid large swings in oxygenation, but if it persists for more than a few minutes, the FIO_2 should be gradually increased by 2-5%, or manual breaths should be given through the ventilator or resuscitation bag. Preferably, FIO_2 should be weaned to assure oxygen saturation levels are maintained in the high 80s or low 90s. Ultimately, although surfactant use requires extensive monitoring, the ideal surfactant is one that minimizes complications, maximizes safety and efficacy, and allows quick and successful weaning and extubation from supplemental FIO_2.

QUESTION 8. What observations can be made concerning reflux, bradycardia, and desaturation, and what can be done to minimize these adverse effects?

In regard to endotracheal tube reflux, bradycardia, and desaturation, the panelists tend to notice a higher incidence of these events with administration by newer personnel, usually relating to the rate of infusion. Again, administration of a smaller volume may assist in reducing reflux[10] and subsequent obstruction and distention of the terminal airways.[7] Also, a transient increase in PEEP as described might assist in reducing the incidence of reflux and desaturation. One panelist noted that reflux tends to occur more frequently with repeat doses. Usually, infants with compromised lungs will likely tolerate the initial surfactant dose well, but the clinician should be more vigilant for reflux and desaturation with subsequent doses. Conversely, if the infant has trouble tolerating the first dose or two, the clinician should anticipate greater monitoring with subsequent doses and plan accordingly. Using a surfactant that is well tolerated by the infant will reduce associated adverse effects and reduce the time and resources utilized by the attending staff.

The panelists agree that when surfactant is properly administered and ventilator settings are managed, adverse effects occur relatively infrequently. They primarily attribute their low rate of adverse effects to the use of a surfactant with low viscosity and a small dosage volume, and to very close clinical monitoring.

QUESTION 9. What ventilator setting adjustments should be made with surfactant therapy, particularly regarding endpoints and timing for adjustments?

It is important to monitor the ventilator settings both during and after surfactant administration to prevent lung injury.[22] Important settings to manage include FIO_2, PEEP, PIP, and tidal volume. Although institutional protocols may vary, the literature supports tidal volume levels to be about 5 to 9 mL/kg.[23,24] Some ventilators may vary in where tidal volume is measured, so the panelists recommend measuring tidal volume at the endotracheal tube, as opposed to at the ventilator, to avoid overdistention of the lung. One panelist recommends increasing PEEP by 1 cm H_2O during surfactant administration to decrease reflux and subsequent adverse effects, then decreasing PEEP back to baseline after dosing, although generally not less than 5 cm H_2O. After surfactant administration, the panelists recommend aggressive weaning of ventilator pressures within the first hour, to take advantage of the improvements in compliance provided by the

surfactant.[22] A surfactant with a rapid onset and earlier efficacy may increase the rate at which supplemental oxygen can be weaned.[20]

QUESTION 10. When do you give additional doses of surfactant, and what parameters do you use to define the need for additional doses?

The interval between doses differs between the various surfactant products as described previously.[16-18] Redosing protocols may vary between institutions, although generally repeat doses are considered for those infants who remain intubated with high FIO_2 requirements (≥ 30-40%) and in whom their respiratory status is persistent or deteriorating.[16] A chest x-ray may also assist in the decision by allowing assessment of atelectasis or overdistention. The ideal surfactant is one that is effective in one dose, reduces intubation time, and reduces adverse effects associated with mechanical ventilation. Ultimately, the panelists express that appropriate management of the ventilator after dosing is critical in optimizing infant response and reducing the need for additional doses.

QUESTION 11. How important is product wastage, and how can this be addressed by institutions?

Pharmacoeconomic studies of surfactant have demonstrated that product wastage can be a significant cost driver.[25] Pulmonary surfactants are available only in single-use vials, to be entered one time then discarded, according to manufacturers' recommendations.[16-18] Due to advances in medical treatment, more infants of very low birth weight are surviving. Surfactant is dosed on a mL/kg basis. As smaller infants survive, it is more cost effective to have smaller surfactant vials. Surfactants are now more readily available in smaller vials, thus reducing wastage and costs associated with drug wastage. When considering vial size, it is important to also consider per-mL cost of surfactant (i.e., that a 3 mL vial costs exactly twice as much as a 1.5 mL vial). Unfortunately, at times product wastage is unavoidable. The practitioner can minimize product wastage by having different sizes of surfactant vials available.

QUESTION 12. Describe how continuous positive airway pressure (CPAP) should be part of an institution's standard of care for neonates?

Recent research indicates that extubation to nasal CPAP can reduce the need for mechanical ventilation, the days on mechanical ventilation and oxygen therapy, days on CPAP, days in the NICU, and the need for surfactant redosing.[14] Reducing the time on mechanical ventilation reduces the possibility of damage to the lungs such as pneumothoracies, BPD, and associated adverse consequences which include intraventricular hemorrhages secondary to high intrathoracic pressures.[6] The panelists also prefer CPAP simply because it is a more gentle, non-invasive mode of ventilation. Therefore, many institutions, including those of the panelists, are more aggressive in attempting to extubate qualified infants to CPAP after surfactant administration, within 30 minutes or less whenever possible. Infants should have good breath sound quality and good respiratory drive to be considered for transition to CPAP. A rapid-acting and easy-to-administer surfactant can reduce the time to extubation to CPAP. Other factors that can expedite transition to CPAP include a surfactant that is quickly absorbed and well tolerated without inducing decompensation. Although CPAP is non-invasive, adverse effects are still possible, for which the infant must be monitored. Possible adverse effects associated with CPAP include apnea[15] and inflammation due to dry nares or tissue trauma.

QUESTION 13. What is the value of surfactant nebulization?

Surfactant nebulization is an area of recent and current clinical investigation, as the ultimate surfactant product is one that could be administered non-invasively. Nebulization provides the obvious benefit of reducing or preventing intubation and its associated complications. Theoretically, nebulization may also offer more uniform surfactant distribution,[9] but studies presently indicate that aerosolized surfactant tends to be preferentially deposited in well-ventilated and less-injured areas of the lung.[26]

There are other drawbacks presently associated with surfactant nebulization. Loss of product due to deposition in the tubing, swallowing by the infant, or absorption through mucous membranes may be costly and may impede proper dosing.[27] Administration via nebulization would be more time consuming

Table 1. Summary of considerations regarding the optimal surfactant and its role in clinical practice

- Vigilant management of the infant's response and the ventilator settings is critical.
- The best surfactant is one that will reduce morbidity and mortality, improve short-term ventilator settings and long-term patient outcomes, allow for rapid extubation, and have a low incidence of adverse effects.
- In most cases, particularly in the acute RDS treatment setting, it is preferable to administer surfactant as early as possible.
- It is important to consider the storage, handling, preparation, and administration requirements of the surfactant, as these may differ between products.
- Surfactant volume is an important consideration, as a smaller volume can ease administration and reduce the incidence of several adverse effects.
- Use of a surfactant that minimizes the number of aliquots and handling of the infant can reduce stress, adverse effects, and cost.
- Early extubation to nasal CPAP may offer several advantages and reduce the rate of long-term lung damage due to mechanical ventilation.

CPAP, continuous positive airway pressure; RDS, respiratory distress syndrome

compared to bolus dosing, which may delay initial response. Furthermore, it is possible that nebulization may increase the duration of exposure to high concentrations of inspired oxygen. Clearly, these issues need to be resolved before surfactant nebulization can be considered a viable alternate administration method.

CONCLUSIONS

The consensus of the panel is that surfactant therapy is essential in improving outcomes in neonatal RDS, but an important consideration in optimal surfactant usage is vigilant management of the infant and the ventilator both during and after surfactant administration. This discussion provides many useful practical points that clinicians may consider for their practice. A summary of these considerations is provided in Table 1. While the prospects of surfactant nebulization may be promising, further research is required to determine the benefits and define the role of this type of administration.

Overall, further research is necessary to validate many of the finer points of surfactant use, but the clinical experiences provided within may assist practitioners in their use of surfactant and perhaps provide an avenue for further investigation.

DISCLOSURES Karen E. Corff, MS, ARNP, NNP, Steve Greubel, RRT, AS, Debra L. McCann, MS, ARNP, and Richard Williams, RRT, NPS are all consulting and therapy advocates, DEY, LP.

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