Surfactant

Rob Graham, R.R.T./N.R.C.P.

I dedicate this column to the late Dr. Andrew (Andy) Shennan, the founder of the perinatal program at Women's College Hospital (now at Sunnybrook Health Sciences Centre). To my teacher, my mentor and the man I owe my career as it is to, thank you. You have earned your place where there are no hospitals and no NICUs, where all the babies do is laugh and giggle and sleep.

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Despite being used routinely for over 30 years, controversies remain regarding the method of administration and surfactant formulations themselves. Adverse events such as spontaneous airway obstruction, pneumothorax, pulmonary hemorrhage, changes in cerebral perfusion, bradycardia, and desaturations have been reported (1). There is also great variation in the delivery methods and positioning of infants during surfactant administration.

Controversy also remains regarding the safety and effectiveness of various surfactant formulations and animal-derived vs. synthetic products, with some studies indicating no difference and others favouring animal-derived formulations. I have personal experience with three formulations: bovine lipid extracted surfactant (bLES, a bovine extract available in Canada), beractant (Survanta), and poractant alpha (Curosurf). In my limited experience with Curosurf, I have found the need for second dosing higher than with bLES. Units in Canada used Survanta for approximately one year due to temporary closure of the facility that manufactures bLES. Anecdotally, I found the incidence of pneumothorax greater with Survanta (an observation shared informally between colleagues from other units). Survanta also has a slower onset of action and seemed to require a second dose more frequently than bLES. These observations are not consistent with some published literature (2). There are no studies comparing bLES to other formulations to the best of my knowledge, although calfactant appears to be more beneficial initially (3). That being said, another Toronto NICU was trading two vials of Survanta for one of our vials of bLES still in stock during that "year without bLES."

The lower volume dose of poractant compared to bLES, calfactant, and beractant (2.5 ml/kg vs. 5 ml/kg) may be beneficial in extremely small babies and may be preferred with minimally invasive surfactant administration. In the unit in which I practice, a recent trial of poractant using both invasive and minimally invasive administration was inconclusive. We did, however, find the need for a second dose was greater with poractant than with calfactant. This is at odds with published studies which indicate a decrease in both mortality and second dosing with poractant compared to calfactant or beractant (4). (bLES was not studied).

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Some studies have shown an increased mortality rate in the sub-600-gram population with calfactant (5). This may be atypical, and the reason is unclear. Several possibilities come to mind. Calfactant (and bLES) has a very rapid onset of action. This results in an immediate increase in compliance and a concurrent drop in pulmonary vascular resistance (PVR). If ventilation is not adjusted immediately to compensate, there is a risk of pneumothorax. If a large patent ductus arteriosus is present, the rapid drop in PVR may precipitate a pulmonary hemorrhage. Caution is in order if left to right shunting is suspected. In my personal experience using bLES exclusively, these complications are very rare. Another factor may be spontaneous blockage of the endotracheal tube. I have not experienced this, but colleagues have. This may be related to the viscosity of the surfactant. After 15 minutes at 37 degrees Celsius, the viscosity of calfactant increases exponentially, and at 30 minutes is 20 times higher than after ten minutes(6). Thus calfactant (and beractant) should be given as soon as possible after thawing/warming and within 15 minutes. (This fact was unknown to me before writing this column). There is no reason to believe bLES is any different in this regard.

Synthetic surfactants have been on the market for many years, although early studies demonstrated the superiority of animal-based products. There is a theoretical concern of infectious and antigenic complications with animal-derived products, although there is no evidence of this to date (7). First-generation synthetic

products lacked key proteins that are essential to success and are generally no longer in use. There are also pro-inflammatory mediators present in animal-derived products (perhaps this is one reason why chronic lung disease (CLD) rates have not decreased with surfactant use) that are not present in synthetic formulations (8). Lucinactant is a relatively new second-generation synthetic surfactant formulated with proteins and peptides that mimic natural surfactant proteins. Trials have shown Lucinactant to be superior to colfosceril (a first-generation synthetic surfactant) and beractant. Calfactant was not studied. Another trial comparing Lucinactant to poractant failed to enroll sufficient infants to draw conclusions but showed no difference between the two products (7). The dosing volume of Lucinactant is higher than any other formulation at 5.8 ml/kg, which has implications for adverse effects during instillation.

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Changes in cerebral blood flow following surfactant administration are likely secondary to hyper or hypoventilation with resulting extremes in CO_2. Hypoventilation can be minimized by carefully monitoring ventilation during instillation, and hyperventilation can be avoided by prudent adjustments to ventilator settings following instillation.

When I first started administering surfactant, the procedure was to deliver it in 3 aliquots; 1/3 with the baby on the right side, 1/3 with the baby supine, and 1/3 with the baby on the left side. Evidence does not support this regimen, instead favouring bolus administration and supine positioning (6).

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We know that manual ventilation with a resuscitation bag is associated with lung injury. At present, it is very common to "bag in" surfactant. This practice seems counter-intuitive to me, and I cannot help but wonder if the practice contributes to chronic lung disease. My approach is to give surfactant while on the ventilator with the flow sensor inline using a multi-access catheter inserted through the side suction port. One must note that the higher viscosity of surfactant requires both more time and pressure to get down the ETT. In conventional ventilation (CV) using assist-control with targeted volume, this can be achieved by increasing inspiratory time and maximum peak pressure while maintaining targeted volume during the procedure.

High-frequency oscillation (HFO) with volume targeting is the standard first intention in the unit in which I practice, and I give surfactant in HFO mode. First, I increase the pressure setting on the manual (sigh) breath, then instill surfactant as above until the flow graphic on the ventilator indicates obstruction. I then use the manual inspiration button to drive the surfactant down the ETT until the flow is evident on the graphics screen. This process is repeated until all surfactant has been given. Doing this affords a degree of lung protection over manual ventilation, and volume targeting helps reduce over and under ventilating. Care must be taken to hold the flow sensor up and vertical to prevent surfactant from entering the flow sensor. I have had good results using this technique and credit Dr. Jane Pillow of Perth, Australia, for introducing it to me.

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Whether using CV or HFO, volume-targeted ventilation may mitigate inadvertent increases or decreases in ventilation and subsequent hypo/hypercarbia. The risk of pneumothorax through over-expansion of the lung as compliance increases is also decreased as the machine will automatically increase peak inspiratory pressure during instillation and reduce it as compliance improves.

Another important consideration is lung recruitment prior to surfactant administration. Failure to recruit may result in surfactant preferentially going to recruited areas with subsequent over-distention of these areas. Recruitment maneuvers and generous PEEP prior to administration may reduce the potential for lung injury secondary to surfactant administration from non-uniform distribution (6).

No analysis is complete without considering the cost. In Canada, the cost of bLES is far less than any other preparation. One in-depth analysis comparing calfactant and poractant showed a significantly higher cost with poractant. Interestingly there was also a significant increase in the need for second dosing with poractant (9). This is consistent with personal experience. Another analysis comparing poractant and beractant showed a significantly higher cost associated with beractant as well as a significantly higher mortality rate with beractant in infants <32 weeks gestation. Beractant was also more likely to require a second dosing (10), again consistent with personal experience. The surfactant cost listed from least to most expensive is bLES, calfactant, poractant, Lucinactant, and finally beractant. The cost comparison between Lucinactant and beractant considered total NICU costs associated with each product's use, including the length of stay(11). Lucinactant, however, must be used once prepared or discarded.

In conclusion, regardless of the product used, administration and positioning methods are important, as is follow up with lung-protective ventilation strategies.

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Corresponding Author

Rob Graham, R.R.T./N.R.C.P.
Advanced Practice Neonatal RRT
Sunnybrook Health Science Centre
43 Wellesley St. East
Toronto, ON
Canada M4Y 1H1
Email: Rob Graham <rcgnrcp57@yahoo.ca>
Telephone: 416-967-8500