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ORIGINAL ARTICLE

Severe airway obstruction during surfactant administration using a standardized protocol: a prospective, observational study

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Objective: The objective of this study was to evaluate the occurrence of adverse effects during surfactant delivery, using a standardized protocol for administration and management of complications.

Study Design: The protocol was developed, implemented and used for 6 months. Vital signs and ventilatory parameters were prospectively recorded during the procedure. Infants were classified into three groups, based on the occurrence and severity of complications: no, minor or major.

Result: A total of 39 infants received surfactant and 19 presented some complication: 11 minor and 8 major. Six of the major complications were episodes of severe airway obstruction (SAO) and five occurred in extreme low birth weight (ELBW) infants that had more severe lung disease before surfactant delivery. Two cases of persistent pulmonary hypertension occurred in infants with birth weight > 1000 g.

Conclusion: This study identified a high rate of SAO and provides data to support changes in the protocol, which should include faster and more robust increases in positive inspiratory pressures in ELBW infants presenting with SAO.

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Introduction

Surfactant is a widely used and effective therapy for the treatment of respiratory distress syndrome (RDS) in newborns, but has been associated with complications occurring during or following its administration. These complications have been reported with the use of different techniques, protocols of administration and types of surfactant, making it difficult to generate any comparisons.[1]

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In our neonatal intensive care unit, a bovine lipid extract surfactant (bLES, Biochemicals, London, Ontario, CA) is the only type of surfactant routinely used since 2004. Over the last years, we observed a number of adverse effects during its administration, with some infants presenting with severe airway obstruction (SAO). These episodes were characterized by sudden and significant deterioration in oxygenation and ventilation, with complete absence of chest movement despite significant increases in ventilatory assistance. However, the incidence of this complication and magnitude of the problem was difficult to assess and categorize due to variations in the delivery techniques used in our unit and lack of a well-delineated monitoring and management process.

Given the nature of the problem, there was a general sense of urgency to implement changes that could improve care and practice. Although we recognized that a randomized controlled trial would be a powerful and unequaled study design, this would require a long time and large sample size. Therefore, we developed and implemented a surfactant protocol to standardize the administration, and actively and objectively studied the effects of this change. A period of 6 months was chosen as the time frame between the implementation and analysis. The primary objective of this study was to evaluate the occurrence and management of significant adverse effects during bLES surfactant administration using the standardized protocol.

Methods

From July 2005 to December 2007, the entire process of surfactant administration within the neonatal intensive care unit setting was re-examined. Actions included modification of the delivery system (in-line catheter adopted), contact other centers experienced with the use of bLES and follow strictly the manufacturer's recommendations. We contacted the manufacturer and a thorough and detailed analysis of samples of bLES was conducted to verify any problem in the composition, solubility and stability of the substance. In the interim, a protocol for bLES administration was developed by a multidisciplinary team composed of neonatologists, pharmacists, respiratory therapists, nurse practioners and neonatal

fellows. The protocol was based on the available scientific literature, manufacturer's recommendations, and included indications for surfactant administration, method of delivery and a monitoring process. From January to June 2008, all infants that received a first dose of bLES for treatment of RDS were included. Retreatment and surfactant given for other indications were also performed according to the protocol, but was not included in this analysis. This study is a retrospective analysis of the data prospectively collected during the 6-months period. The study was approved by the Hamilton Health Science Ethics Board.

Indications for surfactant administration

According to the protocol, prophylactic surfactant was given only to infants with a gestational age (GA) $\geqslant 23$ and <24 weeks (10 to 30 min of life). Infants with a GA $\geqslant 24$ weeks received surfactant as an early treatment (<2 h of age), if they were intubated immediately after birth, except if the infant was on room air and minimal ventilatory support following admission at the neonatal intensive care unit. These infants should be immediately extubated to nasal ventilation or nasal continuous positive airway pressure. If these infants were initially treated with nasal continuous positive airway pressure, intubation and surfactant administration should be performed in the presence of one of the following criteria: a) fraction of inspired oxygen (FiO_2) >0.5 to maintain oxygen saturation (SpO_2) $>88\%$ or a $PO_2>45$ mm Hg (arterial), b) partial pressure of carbon dioxide (PCO_2) >55 to 60 mm Hg (arterial) with a pH <7.25, c) apnea requiring bag and mask ventilation or d) evidence of significant work of breathing (retractions, grunting and chest wall distortion). All infants were ventilated according to the neonatal intensive care unit protocol.[2]

Surfactant administration

Surfactant was administered by a respiratory therapist, with a neonatal fellow present at the bedside during the whole procedure for monitoring and intervention. During a period of 2 months before its implementation, all respiratory therapists and fellows received instructions and training about the new protocol. Before surfactant administration, chest X-rays, endotracheal tube (ETT) suctioning and pre-oxygenation to achieve $SpO_2>95\%$ was performed. Surfactant was delivered through an in-line catheter with the tip located at the mid trachea level. After warming the surfactant to room temperature and mixing the medication for 20 min (without shaking), a dose of 5 ml kg^{-1} (135 mg phospholipids kg^{-1}) of bLES was given as bolus infusion (10–20 s), divided into four aliquots, with infants kept in the horizontal position during the whole procedure. A minimum period of 60 s between the aliquots was used if infants remained stable.

The multidisciplinary team decided to exclude the routine use of ventilatory recruitment maneuvers before bLES administration due to the risks of lung injury. All infants stayed connected to the ventilator before and during the procedure. However, when infants presented with signs of clinical deterioration (SaO_2 $<80\%$ and/or heart rate (HR) <100 beats per minute (bpm)), stepwise changes in ventilatory settings were to be made every 20 s and included increases in ventilatory rate by 10 bpm at a time (up to 60 bpm) and peak inspiratory pressure (PIP) by 2 cmH_2O steps up to a maximum of 30 cmH_2O for the first 2 min. These changes in pressure and rate could be done simultaneously. After this period, if no improvement was noted, the infant was to be disconnected from the ventilator and manual bagging, using a flow-inflating bag with a positive end expiratory pressure valve that was pre-set at 5 cmH_2O, was performed for another minute. During this procedure, similar or even higher pressures and rates could be applied to overcome a suspected obstruction. If despite all these maneuvers, no chest movement and clinical improvement were observed and surfactant was visualized inside the lumen, the ETT should be suctioned. If no improvement, the ETT should be removed and a new ETT inserted. All infants were ventilated with the Servo-I ventilator (Maquet Critical Care AB, Solna, Sweden) using a pressure limited mode (assisted control ventilation or synchronized intermittent mandatory ventilation). Tidal volume was monitored and recorded during the procedure, but a significant and variable leak was noted in several patients who precluded the use of this data for analysis.

Data collection and definitions of complications

We recorded the birth weight (BW), GA, use of antenatal steroids, mode of delivery, presence of chorioamnionitis, severity of RDS (based on chest X-ray[3]), the most recent blood gases before bLES administration (arterial or capillary), type of initial ventilatory support and time of surfactant administration. SpO_2, FiO_2, PIP, positive end expiratory pressure, ventilator rate and heart rate were monitored during the entire procedure, and recorded before and after each aliquot.

SAO, persistent pulmonary hypertension (PPHN), pulmonary hemorrhage and tension pneumothorax were classified as major complications. SAO was defined as the complete absence of visualization of chest movement in infants that presented with sudden and severe desaturation (SpO2 $<70\%$), bradycardia (HR <100 bpm), and did not respond to increases in ventilator pressures or bagging for $\geqslant 3$ min and required suctioning of the surfactant or replacement of the ETT. PPHN was defined as an increase in FiO_2 to 1.0, presence of pre- to post-ductal SpO_2 difference of $\geqslant 20\%$ and echocardiogram findings on later assessment. Pulmonary hemorrhage was defined as the presence of fresh blood into the ETT lumen and tension pneumothorax was defined as the sudden deterioration with positive transillumination of the chest or chest X-ray, showing free air into the thoracic cavity with mediastinal structures shift.

Episodes of bradycardia, desaturation, reflux of surfactant and hypercapnia that recovered spontaneously or with minimal changes in the ventilator settings (increases in rates of <20 bpm

Table 1 Patient characteristics and clinical management of infants who developed major complications during bLES administration

	#1	*#2*	*#3*	*#4*	*#5*	*#6*	*#7*	*#8*
BW (g)	1010	1290	640	790	820	1050	830	560
GA (weeks)	27	30+6d	25+1d	25	25+4d	29+1d	26+5d	26
ETT (mm)	3.0	3.0	2.5	2.5	2.5	3.0	2.5	2.5
Mode of ventilation	AC	SIMV/PS	AC	AC	SIMV/PS	SIMV/PS	SIMV/PS	AC
Volume of bLES given before complication (ml)	1	2.8	2.4	2	4	2.4	4.2	2.1
Number of aliquots received before complication	1	2	3	2	4	2	4	2
Complication	Severe drop in SpO_2	No chest movement	No chest movement	No chest movement	No chest movement	Severe drop in SpO_2	No chest movement	No chest movement
Management	PIP = 30 HFOV+iNO	PIP = 32 PEEP = 8	PIP = 30 bLES suctioned	PIP = 30 re-intubation	PIP = 32 re-intubation	PIP = 30 HFOV+iNO+dopamine	PIP = 33 re-intubation	PIP = 31 re-intubation (× 2)
ETT plug after extubation	—	—	—	Complete	—	—	Partial	Complete (2 ×)
Final diagnosis	PPHN	SAO	SAO	SAO	SAO	PPHN	SAO	SAO

Abbreviations: AC, assisted control ventilation; bLES, bovine lipid extract surfactant; ETT, endotracheal tube; GA, gestational age; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; PEEP, positive-end expiratory pressure, cmH_2O; PIP, peak inspiratory pressure, cmH_2O; PPHN, persistent pulmonary hypertension of the newborn; SAO, severe airway obstruction; SIMV/PS, synchronized intermittent mandatory ventilation/pressure support; SpO_2, oxygen saturation.

and PIP $<25\,cmH_20$) during the first 3 min following the delivery of each aliquot were classified as minor complications. Bradycardia was defined as HR <100 bpm and desaturation was defined as SpO_2 $<80\%$. Reflux of surfactant was defined by the visual presence of surfactant into the ETT lumen. Hypercapnia was defined as an increase in transcutaneous PCO_2 of more than 20% from baseline.

Statistical analysis

Continuous variables are expressed as mean ± s.d. and categorical variables are expressed as counts and percentages. The χ^2-test and the Fisher's exact test were used for categorical variables and the Student's *t*-test was used for continuous variables, when comparing differences between no, minor and major complication groups in the overall population and for the subgroup of extreme low birth weight (ELBW) infants. A P-value <0.05 was considered statistically significant. Analysis was performed with Stata SE 10.0 (Stata, College Station, TX, USA).

Results

Investigations conducted by the manufacturer revealed no problems related to the composition, solubility and stability of the product. During the 6-month period, all infants that received bLES as treatment for RDS were included in the study ($n = 39$), and the mean BW and GA were 1443 ± 141 g and 30.2 ± 0.7 weeks, respectively. The majority of these infants were inborn (97%) and 19 infants (49%) presented some type of complication during the delivery of surfactant: 11 (28%) minor and 8 (20%) major. In the overall population, infants that developed any type of complication had significantly lower BW (1193 ± 222 g versus 1681 ± 163 g; $P<0.05$) and GA (28.4 ± 1.0 weeks versus 32.0 ± 0.8 weeks; $P<0.05$), when compared with infants without complications.

The minor complications identified during the procedure were bradycardia, desaturation, reflux of surfactant into the ETT and hypercapnia. All these complications were transient (<30 s) and resolved spontaneously or with the use of the interventions proposed in the protocol.

The major complications identified were SAO and PPHN. The incidence of SAO in the overall population was 15%. Five of the six cases occurred in ELBW infants. Amongst ELBW infants, the incidence of SAO was 31%. Indeed, SAO was the only major complication occurring in these infants (Table 1), which had a more severe lung disease (based on chest X-ray scores) and higher ventilatory rates, when compared with ELBW infants with minor or no complications (Tables 2 and 3). The average total volume of bLES administered before the development of SAO was 3.5 ml kg^{-1} (range: 2 to 4.2 ml kg^{-1}) and all infants were treated similarly with regard to timing of surfactant administration (Table 3). In three out of four cases of SAO that required re-intubation, we observed a complete or partial obstruction of the ETT due to the presence of a plug. The rate of re-intubation was 50% (4/8) in infants that experienced a major complication and 10% (4/39) in the overall population.

The other type of major complication observed was the development of PPHN, which occurred in two infants with BW >1000 g. Baseline characteristics and management of all infants with major complications are presented in more detail in Table 1.

Table 2 Patient characteristics before bLES administration for infants with BW ⩽1000 g, according to the type of complications

	No+minor (n = 11)	*SAO (n = 5)*	P-*value*
BW (g)	753.2 ± 169.9	728 ± 121.1	0.39
Gestational age (weeks)	26.8 ± 2.4	25.7 ± 0.7	0.17
Antenatal steroids	5 (45)	3 (60)	1.0
Chorioamnionitis	5 (45)	1/4 (25)	0.60
Severe respiratory distress syndrome (X-ray)	7 (64)	5 (100)	0.25
Initial management with CPAP	3 (27)	1 (20)	—
Age of intubation (h)	13.5 ± 12.3	0.6	—
Age of administration (h)	14.1 ± 12.5	1.0	—
Initial management with intubation	8 (63)	4 (80)	—
Age of intubation (min)	2.1 ± 1.2	1.5 ± 0.3	0.19
Age of administration (h)	1.8 ± 0.9	2.2 ± 1.2	0.3

Abbreviations: bLES, bovine lipid extract surfactant; BW, birth weight; CPAP, continuous positive airway pressure; SAO, severe airway obstruction.
Values are expressed as mean ± s.d. or n (%).

Table 3 Blood gases, ventilatory settings and vital signs before bLES administration for infants with BW ⩽1000 g, according to the type of complications

	No+minor (n = 11)	*SAO (n = 5)*	P-*value*
Blood gases			
pH	7.3 ± 0.13	7.3 ± 0.02	0.49
pCO_2 (mm Hg)[a]	43.1 ± 9.6 (6/5)	44.5 ± 6.4 (2/3)	0.43
Ventilatory settings			
Fraction of inspired oxygen	0.6 ± 0.3	0.45 ± 0.1	0.08
Peak inspiratory pressue (cmH_2O)	20.0 ± 2.2	20.0 ± 2	0.47
Positive end expiratory pressure (cmH_2O)	6.5 ± 0.7	6.8 ± 1.1	0.23
Ventilator rate (bpm)	50.0 ± 7.9	58.0 ± 4.5	0.02
Vital signs			
Heart rate (bpm)	148.6 ± 12.4	152.2 ± 14.8	0.31
Oxygen saturation (%)	89.1 ± 6.3	86.0 ± 1.4	0.26

Abbreviations: bLES, bovine lipid extract surfactant; BW, birth weight; SAO, severe airway obstruction.
$P<0.05$.
[a]Number of samples recorded using values from transcutaneous CO_2 or arterial blood gas (n/n). Values are expressed as mean ± s.d. or n (%).

Discussion

Our study is the first to systematically report the occurrence of adverse events during bLES surfactant delivery, using a standardized protocol for administration and monitoring. A high incidence of SAO was observed in ELBW infants that had worse respiratory disease before surfactant administration. Previously to this standardized approach, these events were usually identified as an isolated occurrence likely related to drug preparation, administration technique employed and /or lack of adequate monitoring.

In this study, we used bLES, which is a chloroform:methanol extract of surfactant isolated by centrifugation from bronchoalveolar lavage of intact bovine lungs. The original form of this surfactant was previously used in clinical studies without any SAO reports during delivery of the drug.[4,5] The general processes of lavage, centrifugation and extraction methods of bLES are similar to those utilized in the preparation of other bovine extract surfactants such as Alveofact (Boehringer Ingelheim, Germany) and Infasurf (ONY, Amherst, NY, USA),[6] which have been associated with a 2 to 4% incidence of ETT obstruction in clinical trials.[7,8] However, a study comparing synthetic surfactant (Exosurf, Burroughs Wellcome, Research Triangle Park, NC, USA) with bovine surfactant (Infasurf), reported an incidence of obstruction between 20 to 50%.[9] Specifically, bLES was evaluated only in one unpublished randomized, controlled, double-blind, multicenter trial[10] and a randomized study comparing bLES with Survanta (Ross Laboratories, Columbus, OH, USA).[11] The first trial reported a 6% rate of ETT obstruction (not defined), but the second study did not comment on complications related to surfactant delivery. None of the trials or studies reported on the severity of ETT obstruction, specific subgroups of infants at higher risk of SAO or management of these episodes.

Although the best method of surfactant delivery is still under debate,[12] bolus administration through an in-line catheter was reported to result in better distribution and less dose-related adverse effects.[13,14] However, bolus administration has also been associated with airway obstruction[15] and all infants in our study received surfactant using this technique. Wheeler *et al*.[16] used assisted control volume guarantee ventilation during the administration of a surfactant with a volume of 1.25 ml kg^{-1} (Curosurf, Chiesi Farmaceutici SpA, Parma, Italy). Complete obstruction of the flow down the ETT was observed in 95% of the infants, but only 25% had prolonged episodes (>30 s and <52 s). Following surfactant administration, PIP increased in all patients up to 27 (23 to 30) cmH_2O to restore adequate ventilation.[16] No episodes requiring ETT replacement were reported. In our five ELBW infants with SAO, the average total volume of bLES administered before the complication was almost three times higher, and no improvement was observed despite stepwise increases in PIP up to a maximum of 33 cmH2O (Table 1). Airway obstruction can occur as a consequence of ETT lumen blockage or blockage of the airways immediately below the ETT. In three of the four cases that required ETT replacement, a complete or partial obstruction of the lumen with a plug (white–gray gelatinous material) was noted.

As ELBW infants with SAO had worse baseline lung disease, it is possible that a higher volume of surfactant:functional residual capacity ratio could have contributed to the occurrence of

obstruction. Preterm rabbits treated with surfactant before the first breath had increased mortality when volumes exceeded 16% of the functional residual capacity.[17] The functional residual capacity of preterm infants with RDS is significantly decreased and the reported values can vary from 6 to 10 ml kg^{-1}.[18,19] Future studies should address this potential risk factor. It is well known that smaller ETT have higher resistance,[20] which can contribute to decreased or slower clearance of surfactant and subsequent ETT block. Five out of six of these infants with SAO were intubated with a 2.5 mm endotracheal tube (outer diameter). However, all ELBW infants studied were intubated with this size of ETT and 75% of them did not develop SAO.

In animal studies, alveolar recruitment before and during surfactant administration has been demonstrated to improve drug distribution and the efficacy of treatment, but have not been correlated with the occurrence of SAO.[21,22] Our protocol did not include the routine use of these maneuvers before surfactant administration. During the monitoring process, we did not record the time intervals between patient deterioration and changes in ventilator settings and/or initiation of bagging. Although all professionals involved in the procedure were familiar with the 'new' protocol, it is possible that delays in performing ventilator adjustments or that the response to a sudden deterioration, using 'stepwise increments in PIP', instead of a more robust and fast intervention may have contributed to the occurrence of a severe obstruction. On the other hand, the lack of evidence with regard to the appropriate time interval and magnitude of ventilatory changes that should be initiated makes it difficult to determine the adequacy of this response. It is possible that a faster and more robust increase in positive inspiratory pressures and/or rates may overcome this problem and this should be investigated.

In conclusion, the use of a standardized protocol for surfactant delivery and management of adverse effects allowed us to identify in a systematic manner that SAO was a common complication in ELBW infants with worse baseline lung disease. This high rate of SAO could have occurred due to a combination of stepwise increments in PIP levels, lower maximum PIP levels and use of higher volumes of surfactant. The study provides data for targeted changes in the administration protocol when using this type of surfactant, which should include faster and more robust increases in positive inspiratory pressures in ELBW infants presenting with SAO.

Conflict of interest

The authors declare no conflicts of interests.

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