Less Invasive Surfactant Administration via Thin Catheter in Late Preterm Infants With Respiratory Distress Syndrome

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Abstract

Background: The use of less invasive surfactant administration (LISA) has been increasingly investigated, since neonatal respiratory distress syndrome (RDS) due to surfactant deficiency is associated with high morbidity and mortality in preterm infants. However, this technique has been barely studied in late preterm newborns with RDS. In the present study, we analyzed the use of LISA using a thin catheter in late preterm infants with RDS who required noninvasive ventilation (NIV).

Methods: A retrospective study was conducted on late preterm infants admitted to the Neonatal Intensive Care Unit – Virgen de la Arrixaca University Hospital in Murcia (Spain), between June 2017 and March 2020. Maternal and prenatal data, as well as safety and efficacy variables related to the technique were collected. Statistical analyses were performed using SPSS version 20.0.

Results: A total of 20 patients were included. The mean gestational age was 35 ($34^{1/7}$-$36^{6/7}$) weeks. There were 12 males (60.0%) and 8 females (40.0%). Seven infants (35.0%) received prenatal corticosteroids for fetal lung maturation. Mothers had a mean age of 31.0 (16-40) years and only one had a medical condition (HELLP syndrome). The more frequent type of delivery was C-section (75.0%). Ten newborns (50.0%) required resuscitation to breathe with nCPAP or nIPPV, with no signs of acute fetal distress. Before LISA, mean pCO_2, pH and FiO_2 values were 53 (40-81) mmHg, 7.28 (7.19-7.48), and 0.41 (0.3-0.6), respectively. Thirteen patients (65.0%) were treated with nCPAP and seven (35.0%) with nIPPV. Premedications administered were caffeine (50.0%) and ketamine/morphine sedation (20.0%). During LISA, oxygen saturation decreased in fifteen patients (75.0%). Redosing was needed in two infants (10.0%). Response was favorable, with a rapid and sustained reduction in FiO_2 (FiO_2 of 0.21 in 85.0% of cases) and NIV mean time of 70 hours. Patients with final diagnosis of RDS (90.0%) did not required invasive mechanical ventilation (IMV). No severe comorbidities and no deaths occurred.

Conclusions: LISA procedure was a safe and effective method of surfactant delivery in late premature neonates with RDS, improving respiratory outcomes with no need for IMV. These findings add to the knowledge of respiratory management of late preterm infants.

Background

Respiratory distress syndrome (RDS), also known as hyaline membrane disease, is the most common respiratory disorder experienced by premature infants, as well as the leading cause of neonatal respiratory morbidity and mortality [1]. The condition is caused by lack of surfactant in the lungs, which leads to atelectasis, decreased gas exchange and causes hypoxia [2]. Among premature newborns, late preterm infants —those born between $34^{0/7}$ and $36^{6/7}$ weeks of gestation— account for approximately 70% [3, 4]. Although these infants have been historically considered to be developmentally as mature as term newborns, they may be structurally and/or functionally immature and at greater risk for developing serious medical conditions, including respiratory disorders [5–8]. In fact, RDS remains a significant problem in premature babies because it often evolves into bronchopulmonary dysplasia (BPD) [9]. Consequently, management of RDS is primarily focused on providing appropriate respiratory support interventions to improve survival while reducing complications, ultimately BPD.

Administration of exogenous surfactant is a well-established therapy for RDS in preterm infants as it decreases morbidity and mortality [9, 10]. However, intratracheal administration requires intubation skills to minimize the harmful effects of both intubation and mechanical ventilation [9, 11]. Nowadays, the use of less invasive surfactant administration (LISA) methods avoids the need for intubation and allows to decrease duration of mechanical ventilation until the medication is administered. According to recent guidelines, the LISA procedure, also referred to as MIST (Minimally Invasive Surfactant Therapy), is considered one of the best approaches to administer surfactant in preterm neonates [9, 12–14]. The LISA technique most commonly utilized in spontaneously breathing infants involves the use of a thin endotracheal catheter, which is becoming widely employed in neonatal intensive care units (NICU) worldwide [15–17].

There is emerging evidence showing that the use of LISA reduces the need for respiratory support interventions and decreases the risk of death and/or BPD [12, 18]. Nonetheless, the potential benefit of the LISA procedure in late preterm neonates requires further investigation. In this study, we analyzed the safety and efficacy of the use of LISA through a thin catheter in late preterm infants with RDS on noninvasive ventilation (NIV), admitted to our NICU.

Methods

Study Design and Participants

This was a retrospective, single-center, observational study conducted between June 2017 and March 2020, in a level III NICU at Virgen de la Arrixaca University Hospital in Murcia (Spain).

The study included patients meeting the following criteria: preterm infants between $34^{0/7}$ and $36^{6/7}$ weeks of gestation with clinical and radiographic evidence of neonatal RDS, that required NIV as initial support, provided with either nasal continuous positive airway pressure (nCPAP) or nasal intermittent positive pressure ventilation (nIPPV); patients requiring a fraction of inspired oxygen (FiO_2) ≥ 30% and with a positive end-expiratory pressure (PEEP) of 6 cm of H_2O to maintain an oxygen saturation level ≥ 90%, who were administered exogenous pulmonary surfactant (poractant alfa) by direct laryngoscopy via thin catheter (vascular catheter or LISAcath®).

Procedures

Poractant alfa was dosed at 200 mg/kg for the first dose and then at 100 mg/kg every 6–8 hours, for up to 2 additional doses, while maintaining nCPAP or nIPPV. Surfactant administration was divided into slow boluses of 0.5 ml each administered through the catheter, according to the patient tolerability. A LISAcath® catheter was used in 85% (17/20) of patients, whereas a vascular catheter was used in the rest of cases (15%, 3/20).

Premedication administered in newborns of less than 35 weeks' gestation included atropine and caffeine. Various nonpharmacological methods were used as analgesic measures to alleviate pain in neonates, such as oral sucrose, non-nutritive sucking, and contention measures. Pharmacological methods included the administration of the anesthetics propofol (0.5 mg/kg), morphine and ketamine (1 mg/kg), when needed.

During and after surfactant instillation, aspiration of gastric contents was performed to confirm whether surfactant reached the lungs effectively, and if an additional surfactant administration was required.

Data recording

Maternal and neonatal data, collected retrospectively from the medical records, included sex, gestational age, birth weight, intrauterine growth retardation cases, multiple birth, type of delivery (eutocic, C-section or instrumental); Apgar score at 1, 5 and 10 minutes; need for cardiopulmonary resuscitation intervention with nCPAP or nIPPV; maternal age, prenatal corticosteroids, vertical sepsis, maternal gestational pathologies, first admission unit (intermediate neonatal care unit or NICU); type of NIV before LISA (nCPAP or nIPPV); maximum FiO_2, pCO_2 and pH values obtained from capillary blood gas measurements before LISA; chronological age at surfactant administration; number of surfactant doses administered; drug administration before or during LISA (atropine, caffeine and/or sedative medications); complications during LISA technique; NIV duration; need for invasive mechanical ventilation (IMV) after LISA; FiO_2 in the first 72 hours of life; neonatal morbidities such as BPD, necrotizing enterocolitis (NEC) and intraventricular hemorrhage (IVH); final diagnosis, length of NICU stay; and length of neonatal hospital stay.

Statistical analysis

Descriptive statistics were generated for all data. Continuous variables were described using the median and range (described by the minimum and maximum values of the variables). Categorical variables were described as absolute (n) and relative (%) frequencies. All statistical analyses were performed using SPSS version 20.0.

Results

The number of patients included was 20, who represented the 33.3% of all late preterm neonates with RDS admitted to the NICU during the study period. Demographic and clinical characteristics of mothers and preterm infants receiving surfactant with LISA technique are shown in Table 1. The mean gestational age was 35 ($34^{1/7}$-$36^{6/7}$) weeks, and 55.0% (11/20) of neonates were born between $34^{1/7}$-$34^{6/7}$ weeks. There were 12 males (60.0%) and 8 females (40.0%). The mean birth weight observed was 2,363 (1,640-3,300) g, with one intrauterine growth-retarded case. Seven infants (35.0%) received prenatal corticosteroids for fetal lung maturation. Mothers had a mean age of 31.0 (16-40) years and only one of them presented an underlying medical condition (HELLP syndrome). The more frequent type of delivery was C-section (15/20, 75.0%), and the multiple birth rate was 35.0% (7/20). Only three preterm infants (15.0%) were hospitalized on the first day of admission at the NICU, whereas the rest of neonates (17/20, 85.0%) were admitted to an intermediate neonatal care unit. Ten newborns (50.0%) required resuscitation to breathe with nCPAP or nIPPV, although no signs of acute fetal distress were observed (all births had a 5 min Apgar score >5).

Mean pCO_2, pH and FiO_2 values before LISA were 53 (40-81) mmHg, 7.28 (7.19-7.48), and 0.41 (0.3-0.6), respectively. Before LISA, thirteen patients (13/20, 65.0%) were treated with nCPAP and seven (7/20, 35.0%) with nIPPV. Premedications used before or during LISA were caffeine, which was administered to 50.0% (10/20) of infants; and ketamine or morphine sedation, in 20.0% (4/20) of cases.

Table 2 summarizes the characteristics of surfactant administration with LISA and the respiratory evolution of the preterm infants. The mean age at surfactant administration was 22 (2-48) hours of life. Fifteen patients (75.0%) had a decrease in oxygen saturation (SpO_2) levels at some time during the LISA procedure: 10 cases (50.0%) showed a mild decrease (SpO_2: 80-89%), 3 (15.0%) were moderate (SpO_2: 60-80%), and 2 (10.0%)

severe (SpO_2 <60%). LISA was interrupted in 2 patients (10.0%), one due to reflux of surfactant and technical complications, and another because of apnea. Surfactant redosing was needed in two infants (10.0%): LISA was used again in one patient with RDS, whereas the other one —with a final diagnosis of congenital pneumonia— received endotracheal intubation.

Surfactant was successfully administered via LISA in most cases, with a rapid and sustained reduction in FiO_2 at 72 hours of life (FiO_2 of 0.21 in 85.0% of infants), and a mean time on NIV of 70 (24-168) hours. Overall, the final diagnosis was RDS in 18 (90.0%) infants, one congenital pneumonia (5.0%) and one pulmonary interstitial glycogenosis (5.0%). The non-RDS patients improved their condition after surfactant administration, with a decrease in FiO_2 requirement, although improvement was transient and not sustained. The only infant requiring IMV was the one diagnosed with congenital pneumonia. None of the patients with a final diagnosis of RDS required IMV. No severe comorbidities as well as no deaths occurred. The intrauterine growth-retarded infant was diagnosed with periventricular leukomalacia of prenatal origin in the first cerebral ultrasound at 3 days of life. The mean length of NICU stay was 6 (2-23) days and the mean length of hospital stay was 17 (7-39) days.

Discussion

In this retrospective study, we assessed the efficacy and safety of surfactant administration using the LISA technique in late preterm infants diagnosed with RDS.

Data showed a reduced number of pregnant women (35.0%) receiving corticosteroid therapy for fetal maturation, and an elevated number of cesarean deliveries (75.0%). These two factors have been shown to be associated with RDS development. Antenatal steroid therapy, on the one hand, significantly reduces the risk of RDS and other neonatal morbidities in late preterm infants, although the use of antenatal corticosteroids in late preterm deliveries has been reported to be rare [19–21]. These observations are in agreement with our findings and with those observed in a recent multicentric study conducted in Spain, in which only 33.7% of preterm cases underwent prenatal steroids treatment [22]. On the other hand, cesarean delivery is a risk factor for the development of neonatal respiratory problems —including RDS— in preterm infants [23]. In our study, the C-section rate was much higher than the mean rate observed across the Spanish territory (75.0% versus 47.9%) [22]. The causes for this elevated rate were elucidated: in 46.6% of cases, this procedure was conducted after initiation of active labor for reasons that emerged suddenly during childbirth, such as fetal anomalies, placenta previa, or failure to progress; the rest of cases (53.4%) were scheduled for C-section because of trichorionic triamniotic multiple pregnancies, record of previous caesarean delivery, history of uterine rupture, mother's psychiatric illness, maternal HELLP syndrome, or premature rupture of membrane with fetal distress. Hence, and according to the clinical guidelines of The Spanish Society of Gynecology and Obstetrics, all C-sections were performed for a medically justified reason.

Among all preterm newborns, a high proportion of infants (50.0%) required resuscitation with nCPAP or nIPPV as initial respiratory support. Although these patients experienced difficulties during transition from intrauterine to extrauterine life, none of them had signs of acute fetal distress. Nonetheless, only three infants (15.0%) were hospitalized on the first day of admission at NICU, indicating a late RDS detection in the preterm newborns first admitted to an intermediate neonatal care unit. This fact would explain the higher FiO_2 values and mean

chronological age at surfactant administration as compared to the rest of preterm infants admitted in the NICU (mean FiO_2: 0.40 versus 0.37; mean age: 22 versus 8.5 h).

Despite the fact that two patients (10.0%) were clinically misdiagnosed with RDS, LISA procedure did not have any negative impact on them. On the contrary, FiO_2 levels were reduced after LISA, and IMV was only required in one case —the preterm newborn diagnosed with congenital pneumonia—. The infant diagnosed with pulmonary glycogenosis did not require IMV, except to perform lung biopsy, through which the definitive diagnosis was made. However, the observed clinical improvements were transient and clinicians suspected that patients could have been initially misdiagnosed with RDS. These observations highlight the need for a correct diagnosis of RDS, not only based on radiological findings and clinical course. We believe that the use of thoracic ultrasonography, which is considered an accurate and reliable tool in the diagnosis of RDS in the newborn [24, 25], could help early and rigorous diagnosis of the disease.

While the efficacy of surfactant therapy has been reported to improve respiratory function in late preterm infants with RDS [26–28], surfactant administration by minimally invasive methods is still being investigated in this population. The LISA method via thin catheter is widely adapted in Europe [29] and is a recommended method of care according to the latest consensus guidelines [9, 12, 30]. However, there is still large variability in the application of this technique regarding patient population that may benefit from this approach; the catheter type, the adequate dose and type of surfactant; the use of premedication; and the need of pharmacologic sedation during the procedure [31].

A meta-analysis conducted by Lau et al. [32] provides a comprehensive review of the use of LISA via thin catheter in preterm infants, examining the results of several studies [14, 33–35]. Overall, the authors underline the suitability of this technique in preterm infants. However, additional studies are required to address the infant selection issue in this vulnerable population. While the mentioned studies recommend the use of LISA in preterm infants, their outcomes should not be extrapolated to a different pediatric age range or other specific age subgroups.

Up to date, there is only one study reporting on the use of LISA in moderate and late preterm neonates between $32^{0/7}$ and $36^{6/7}$ weeks [36]. The authors compared standard RDS management (surfactant administration given only after intubation) with LISA procedure. Their results showed a reduction in mechanical ventilation exposure, RDS complications, and the length of hospital stay after LISA, as compared to standard therapy.

In our study, the LISA procedure performed on —exclusively— late preterm infants appeared to be of benefit for this particular subgroup of premature babies. This method improved respiratory outcomes with no need for IMV after LISA, reducing its associated complications. In addition, the adverse events documented during LISA (surfactant reflux, apnea and desaturation) were low, with mainly mild to moderate desaturations and a small rate of surfactant reflux, indicating that surfactant delivery was optimal for the vast majority of patients.

Other potential advantages of LISA, such as the reduction of the mean duration of NIV and the length of hospital stay, could not be assessed because of the lack of a control group for comparing surfactant administration methods.

Regarding the use of medications during the procedure, sedation and analgesia were administered at the discretion of each neonatologist, since there are not established protocols in our unit. In fact, administration of sedation and analgesia are controversial issues in RDS management [37]. More specifically, sedation for LISA is complex, because while low-dose sedation prior to laryngoscopy is technically attainable and makes the baby less uncomfortable, it increases the risk of CPAP failure. Thus, there is no clear consensus on whether or not to sedate routinely for LISA, and which sedative to use, leaving these decisions up to clinicians [9]. Our neonatologists have the subjective perception that in the absence of pharmacological sedation, technical complications during LISA arise more frequently in late preterm infants than in other premature newborns.

Our conclusions should be considered in light of some intrinsic limitations of the retrospective nature of this study. The single-group design did not allow us to compare the efficacy of different modes of surfactant administration among the study population. Therefore, randomized controlled trials are needed to further evaluate the benefits of LISA in late preterm infants, as well as to give a response to unresolved questions and clinical issues for its successful implementation.

Conclusions

The results of this study provide valuable information on the effect of the LISA technique via thin catheter in late preterm infants diagnosed with RDS. LISA appeared to be a good option for surfactant delivery in late premature neonates, improving respiratory outcomes with no need for mechanical ventilation. Moreover, adverse outcomes associated with LISA were low, with mild to moderate desaturations, and a small rate of surfactant reflux and apnea.

Declarations

Ethics approval and consent to participate

Due to the retrospective nature of the study informed consent was not required. Data were extracted from a database and anonymized, i.e., data had already been obtained through a standard medical practice and were statistically analyzed in this study. Therefore, ethical approval was not required.

Please refer to a clarification on the requirement of an ethical approval posted on the website of a Spanish Ethics Committee, point number two (https://www.sergas.es/docs/ceic/preguntas%20frecuentes%20cas_20101112.htm), stating that observational studies are exempt from requiring ethics approval when they use only clinical registries or anonymized data, and do not use human biological samples.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JJAA devised and designed the study; conducted, supervised and coordinated research activity; made substantial contributions to acquisition of data, data analysis and interpretation; participated in writing the initial draft; and reviewed and approved the final manuscript.

MVVG and MRPC conducted research activity; participated in writing the initial draft; and reviewed and approved the final manuscript.

CMG, OMM and MAS conducted research activity, and reviewed and approved the final manuscript.

MCP applied statistical and computational methods to analyze data; supervised and coordinated research activity; and reviewed and approved the final manuscript.

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Abbreviations

BPD: Bronchopulmonary dysplasia

FiO_2: Fraction of inspired oxygen

IMV: Invasive mechanical ventilation

IVH: Intraventricular hemorrhage

LISA: Less Invasive Surfactant Administration

MIST: Minimally Invasive Surfactant Therapy

nCPAP: Nasal continuous positive airway pressure

NEC: Necrotizing enterocolitis

NICU: Neonatal Intensive Care Unit

NIV: Noninvasive ventilation

nIPPV: Nasal intermittent positive pressure ventilation

PEEP: Positive end-expiratory pressure

RDS: Respiratory distress syndrome

SpO_2: Peripheral capillary oxygen saturation

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Tables

Table 1. Demographic and clinical characteristics of mothers and infants receiving surfactant administration with LISA technique.

Characteristic	Infants analyzed (n=20)
Sex, n (%)	
Male	12 (60.0)
Female	8 (40.0)
Gestational age (weeks)	35 ($34^{1/7}$-$36^{6/7}$)
Distribution of gestational ages, n (%)	
$34^{1/7}$-$34^{6/7}$	11 (55.0)
$35^{1/7}$-$35^{6/7}$	6 (30.0)
$36^{1/7}$-$36^{6/7}$	3 (15.0)
Birth weight (g)	2,363 (1,640-3,300)
Intrauterine growth retardation cases, n (%)	1 (5.9)
Multiple birth, n (%)	7 (35.0)
Type of delivery, n (%)	
Eutocic	5 (15.0)
Cesarean section	15 (75.0)
Instrumental	0 (0.0)
Apgar score >5 at 5 minutes, n (%)	20 (100.0)
Need for cardiopulmonary resuscitation intervention with nCPAP or nIPPV, n (%)	10 (50.0)
nCPAP	7 (35.0)
nIPPV	3 (15.0)
Maternal age (years)	31 (16-40)
Prenatal corticosteroids, n (%)	7 (35.0)
Vertical sepsis, n (%)	3 (15.0)
Maternal gestational pathologies, n (%)	1 (5.0)
First admission unit	
Intermediate neonatal care unit, n (%)	17 (85.0)
NICU, n (%)	3 (15.0)
NIV before LISA	
nCPAP, n (%)	13 (65.0)
nIPPV, n (%)	7 (35.0)
maximum FiO_2	0.40 (0.3-0.6)
pH before LISA	7.28 (7.19-7.48)
pCO_2 before LISA (mmHg)	53 (40-81)

Data are presented as mean (range) or n (%).
FiO_2: fraction of inspired oxygen; LISA: Less Invasive Surfactant Administration; nCPAP: nasal contin positive airway pressure; nIPPV: nasal intermittent positive pressure ventilation; N Neonatal Intensive Care Unit; NIV: noninvasive ventilation.

Table 2. Characteristics of surfactant administration with LISA and respiratory evolution of the preterm infants.

Characteristic	Infants analyzed (n=20)
Chronological age at surfactant administration (hours)	22 (2-48)
Number of surfactant doses administered, n (%)	
One dose	18 (90.0)
Two doses	2 (10.0)
Drug administration before or during LISA, n (%)	
Atropine	20 (100.0)
Caffeine	10 (50.0)
Sedative medications	4 (20.0)
Desaturation during LISA, n (%)	
Mild (SpO_2: 80-89%)	10 (50.0)
Moderate (SpO_2: 60-80%)	3 (15.0)
Severe (SpO_2 <60%)	2 (10.0)
NIV duration (hours)	70 (24-168)
Need for IMV after LISA, n (%)	1 (5.9)[1]
Neonatal morbidities (BPD, NEC, IVH), n (%)	0 (0.0)
Final diagnosis, n (%)	
RDS	18 (90.0)
Congenital pneumonia	1 (5.0)
Pulmonary interstitial glycogenosis	1 (5.0)
FiO_2 of 0.21 at 72 hours of life, n (%)	17 (85.0)
Length of NICU stay (days)	6 (2-23)
Length of neonatal hospital stay (days)	17 (7-39)

Data are presented as mean (range) or n (%).

[1]: neonate diagnosed with pulmonary interstitial glycogenosis.

BPD: bronchopulmonary dysplasia; FiO_2: fraction of inspired oxygen; IMV: invasive mecha ventilation; IVH: intraventricular hemorrhage; LISA: Less Invasive Surfactant Administration; necrotizing enterocolitis; NICU: Neonatal Intensive Care Unit; NIV: noninvasive ventilation.