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Incidence, predictors of success and outcome of LISA in very preterm infants

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Abstract

Objectives: The aim of this study was to examine the success rate of less invasive surfactant administration (LISA), to identify early predictive factors for the outcome of LISA, and to compare neonatal outcomes between the LISA failure group and the group of infants who were successfully treated with LISA.

Design: A retrospective cohort study.

Patients: Infants born at less than 33 weeks of gestation ($n = 158$) and treated with LISA for respiratory distress syndrome.

Results: LISA was successful in 86 cases (54.4%); 72 preterm infants (45.6%) needed additional surfactant therapy and/or mechanical ventilation in the first 72 h (LISA failure). In a multivariate logistic regression analysis, six independent predictors of LISA success were identified: core temperature at the time of admission (adjusted odds ratio (OR): 3.56), dose of poractant alfa (<200 mg/kg; adjusted OR: 0.254), elevated C-reactive protein (>10 mg/L) at 24 h of life (adjusted OR: 0.28), highest respiratory severity score (RSS) during the first hour of life or at the time of LISA (adjusted OR: 0.463), maternal age (adjusted OR: 0.923), and birth weight (adjusted OR: 1.003). The receiver operating curve created by using the identified factors indicates good predictive power with an area under the curve of 0.85. LISA failure was associated with a substantially higher risk of complications.

Conclusion: LISA success can be predicted by variables available before the intervention. Failure of LISA is relatively frequent event in very preterm infants and is associated with adverse outcomes. Prevention of hypothermia during early stabilization and appropriate dosing of surfactant may increase LISA success rates and improve patient outcome.

KEYWORDS

continuous positive airway pressure, respiratory distress syndrome in premature infants, surfactant

The research was primarily done at Division of Neonatology, Department of Pediatrics, Faculty of Medicine, University of Debrecen, 98 Nagyerdei korut, Debrecen, 4032 Hungary.

1 | INTRODUCTION

Respiratory distress syndrome (RDS), a condition caused by lung immaturity and surfactant deficiency, is one of the most prevalent complications associated with prematurity.[1] Continuous positive airway pressure (CPAP) is recommended as primary mode of respiratory support in preterm infants with RDS and avoiding mechanical ventilation improves neonatal outcomes.[2,3] Less invasive surfactant administration (LISA) has been increasingly used for surfactant delivery.[4] During the procedure, a thin catheter is passed through the vocal cords into the trachea for surfactant administration, while noninvasive ventilatory support is continued without interruption, and the infant can breathe spontaneously. Recent systematic reviews and meta-analyses have found that LISA is superior to other modes of surfactant delivery and it reduces the risk of bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), and the composite outcome of death or BPD.[5–8]

Although the introduction of LISA has increased the success rate of early prophylactic CPAP, 23%–62% of preterm infants undergoing LISA still require intubation and mechanical ventilation during their first 72 h of life,[9–14] which is associated with decreased survival without adverse events, prolonged invasive ventilation, higher need for supplementary oxygen at 28 days, more severe IVH, and higher risk of air-leaks.[11,13]

As LISA is being extended to smaller and more immature infants and to babies with more severe clinical illness, it is of interest to clinicians if the success or failure of LISA can be predicted from clinical data available before LISA is performed. However, only few publications have addressed this question. In a retrospective observational study conducted in two tertiary neonatal intensive care units, Janssen et al.[11] identified four independent risk factors predicting LISA failure (defined as the need for mechanical ventilation in the first 72 h of life): gestational age less than 28 weeks at birth, elevated C-reactive protein (CRP) levels 24 h after birth, lack of antenatal steroid (ANS) prophylaxis, and low dose (<200 mg/kg) of surfactant given during LISA. With a post hoc analysis of their prospective cohort study, Kruczek et al.[15] found that fraction of inspired oxygen (FiO_2) was an independent risk factor for LISA failure, while Ramos-Navarro et al.[13] noticed that a reduction in FiO_2 after LISA was a predictor of treatment success (defined as no need for intubation during the first 72 h of life).

In this study, our primary aim was to identify clinical factors predicting the success of the first LISA procedure in very preterm infants. Our hypothesis was that clinical variables available before the first LISA may predict its success rate. As a secondary question, we also studied the success rate of a repeat LISA procedure and avoidance of intubation and mechanical ventilation.

2 | METHODS

2.1 | Study group

This single-center retrospective study was conducted between January 2014 and December 2019 in the Division of Neonatology of the Department of Pediatrics of the University of Debrecen. Inborn preterm infants born before 33 completed weeks of gestation, and stabilized on CPAP in the delivery room, then treated with LISA, were included in the study. Preterm infants requiring intubation during delivery room stabilization or immediately after admission to neonatal intensive care unit (NICU), and those born with congenital anomalies were excluded.

2.2 | Delivery room care

Mothers at risk of preterm delivery received ANS prophylaxis (32 mg dexamethasone in divided doses) and magnesium sulfate for neonatal neuroprotection. A single repeat dose of dexamethasone was given when ANS prophylaxis was administered >2 weeks before delivery. Cord clamping was delayed by 30–60 s. Delivery room stabilization was started with early prophylactic CPAP using a T-piece ventilator with a face mask (Neopuff™, Fisher & Paykel), with a CPAP pressure of 6–9 cm H_2O and a FiO_2 of 0.3 for infants <28 weeks, 0.21–0.3 for patients between 28 and 31 weeks, and 0.21 for infants born at 32 weeks. FiO_2 was titrated to meet age-specific target oxygen saturation (SpO_2) values, guided by pulse oximetry. Tactile stimulation was performed to enhance spontaneous breathing. Positive pressure ventilation (PPV) with 20–25 cm H_2O peak inspiratory pressure was used in infants with persistent apnoe and/or bradycardia. Sustained inflations were not performed, and endotracheal intubation was reserved for babies not responding to PPV with supplemental oxygen.

After admission to the NICU, infants received nasal CPAP using a Dräger Babylog VN500 ventilator (Dräger Medical) or Infant Flow system (Care Fusion). Infants also received ampicillin plus gentamicin which were stopped when infection was ruled out. FiO_2 and CPAP levels were titrated to meet the target SpO_2 range of 90%–95%. A 20 mg/kg loading dose of caffeine-citrate followed by 5 mg/kg/day maintenance doses was given before the surfactant treatment.

2.3 | LISA

Before September 2017, exogenous surfactant (poractant alfa, Curosurf, Chiesi Pharmaceuticals) was indicated in accordance with the actual European Consensus Guideline;[16,17] after this date, surfactant replacement was indicated if FiO_2 requirement exceeded 0.3 and/or the Silverman-Anderson score was ≥5 in all preterm infants.[18–20] The recommended dose was 200 mg/kg, but dose rounding occurred occasionally as per the institutional protocol to reduce waste and healthcare costs. LISA was the preferred method in spontaneously breathing preterm infants; however, based on the clinical condition of the infant, the attending neonatologist could choose the option of intubation for surfactant therapy. LISA was contraindicated in infants with hemodynamic instability, severe RDS (FiO_2 > 0.6 and/or pH < 7.2, and/or prominent atelectasis on chest X-ray), recurrent apneas despite caffeine loading, known air leaks and possible lung hypoplasia. Nonpharmacologic measures (e.g., swaddling,

administration of colostrum) were encouraged to enhance comfort, and no premedication was given routinely before LISA. Nasal CPAP was continued during the whole procedure. Before laryngoscopy, an orogastric/nasogastric tube was inserted to help the identification of anatomical structures and for intermittent gastric aspiration aimed to assess potential surfactant misplacement. LISA was performed by the attending neonatologist in all cases. A 5 Ch, gamma-sterilized, flexible feeding tube (Sumi) was placed 1.5–2.0 cm below the vocal cords by direct laryngoscopy with or without Magill's forceps, the laryngoscope was removed, the mouth was kept closed, and surfactant was instilled in small (0.2–0.4 ml) aliquots over 2–3 min. If FiO_2 exceeded 0.4 and/or the Silverman-Anderson score remained >5, and other causes of respiratory failure had been excluded, and no criteria for mechanical ventilation was met, a second or third dose of surfactant was given using LISA during the first 72 h of life. The criteria for mechanical ventilation during the first 72 h (CPAP failure) were the following in all preterm infants: $FiO_2 \geq 0.5$, pH < 7.2, $pCO_2 > 60$ mmHg (8 kPa), frequent episodes of apnea requiring stimulation, or two episodes of apnea unresponsive to stimulation or requiring PPV within 12 h.

2.4 | Data collection

Our main aim was to examine the success rate of LISA (LISA-S; defined as no need for additional surfactant treatment and/or mechanical ventilation within 72 h after the first LISA), and to identify early predictive factors for the outcome of LISA. We also compared neonatal outcomes between the LISA-S group and the group of infants group who required mechanical ventilation and/or further surfactant treatment (LISA-F).

Data were collected from both written and electronic neonatal and maternal medical records. Maternal, perinatal, and neonatal data are listed in Table 1.

The study was approved by the Scientific and Research Ethics Committee of the University of Debrecen under the registration number of "DE RKEB/IKEB 5616-2020," and was conducted in accordance with the ethical standards of all relevant national and institutional committees and the World Medical Association's Declaration of Helsinki.

2.5 | Statistical analysis

Numeric variables were compared using unpaired Student's *T*-test or one-way analysis of variance (ANOVA). In the case of categorical variables, we performed Pearson χ^2 or Fisher's exact test. To identify the predictors for LISA-S, first we performed univariate regression analysis on all the potential risk factors (Table 1). For multivariate forward stepwise logistic regression model we used the variables with a *p* value lower than 0.1 at univariate level. Collinearity was analyzed using Pearson's correlation coefficient; if *r* value was >0.6, one of the indicated variables was excluded from the regression model. We calculated the crude odds ratios (OR) at univariate level, and adjusted OR values at multivariate level with 95% confidence interval (CI) to demonstrate the differences in regression analysis. Data analysis was performed using the SPSS V.25 program. Statistical significance was accepted when two-sided *p* was <0.05.

3 | RESULTS

During the study period 800 preterm infants were born at less than 33 weeks of gestational age, of whom 158 underwent LISA procedure (Image 1). Descriptive statistics of the preterm infants included in the study is summarized in Table 2. The respiratory outcome of the study population is presented in Image 1. The first LISA was successful without further surfactant administration or mechanical ventilation required (LISA-S) in 86 cases (54%). Seventy-two (46%) infants required one or more further LISA and/or endotracheal intubation (LISA-F). Endotracheal intubation and mechanical ventilation (CPAP failure, CPAP-F) was necessary in 54 cases (34%) in the first 72 h (reasons for intubation are provided in Image 1). Image 2 demonstrates that the success rate of LISA increases with increasing gestational age, and the rate of CPAP-F cases gradually decreases (except for the subgroup of infants born at 26 weeks of gestation). Compared to the group successfully treated with the first LISA (LISA-S), those with LISA-F had been born at a younger gestational age (28.6 vs. 27.1 weeks, $p < 0.001$), with lower birth weight (1134 vs. 895.56 g, $p < 0.001$), in worse general condition (1-min Apgar score of 6.78 vs. 6.28, $p = 0.03$) and with lower admission temperature (36.24 vs. 35.88°C, $p < 0.001$). We found no significant difference in the rest of the examined pre- and post-natal risk factors between the LISA-S and LISA-F group (Table 3).

In Table 1, we listed all the potential predictive factors for LISA-S ($n = 39$). Multiple variables showed significant difference in univariate analysis but after co-linearity examinations only nine remained for further calculations. In a multivariate logistic regression model, we could identify six independent risk factors that predict the probability of LISA-S. The core temperature at the time of NICU admission showed strong positive correlation with LISA-S (odds ratio [OR]: 3.56; 95% confidence interval [CI]: 1.715–7.394). Elevated CRP level (>10 mg/L, OR: 0.280; 95% CI: 0.101–0.775) decreased the possibility of LISA success. Birth weight (OR: 1.003; 95% CI: 1.002–1.004) and maternal age (OR: 0.923; 95% CI: 0.860–0.991) were also significant predictors. Of the postnatal variables, the highest respiratory severity score (RSS = CPAP level in cm $H_2O \times FiO_2$)[21] in the first hour of life or at the time of LISA (OR: 0.463, CI: 0.232–0.925), the dose of poractant alfa <200 mg/kg (OR: 0.254; 95% CI: 0.108–0.597) were found as independent risk factors. The odds of LISA success is decreased by 5.4% by for every 0.1 increment of RSS. In our sample, neither an incomplete nor a full ANS course showed significant effect even at univariate level. A receiver operating curve (ROC) using the predictive probabilities from the multivariate forward stepwise logistic regression model has an area under the curve (AUC) of 0.85 (E-image 1).

TABLE 1 Logistic regression analysis of risk factors for LISA-S

	Variable	Crude				Adjusted			
		P	OR	95% CI		*P*	OR	95% CI	
No significance	GDM	0.746	1.143	0.510	2.560				
	Preeclampsia/PIH	0.861	0.940	0.470	1.880				
	PROM	0.682	1.144	0.602	2.174				
	PROM > 24 h	0.100	2.324	0.851	6.344				
	No ANS	0.749	0.825	0.254	2.678				
	ANS course started	0.749	1.212	0.373	3.935				
	ANS course completed	0.485	1.259	0.659	2.404				
	Multiple pregnancy	0.817	1.078	0.569	2.045				
	Chorioamnionitis	0.250	0.549	0.198	1.526				
	$MgSO_4$ administration	0.579	1.195	0.637	2.240				
	SGA	0.706	1.160	0.538	2.500				
	C-section	0.324	1.455	0.690	3.068				
	C-section without labor	0.273	0.700	0.370	1.325				
	Apgar score at 5 min	0.728	1.073	0.723	1.591				
	Apgar score at 10 min	0.477	1.185	0.742	1.892				
	FM PPV in DR	0.395	0.758	0.400	1.436				
	Max. FiO_2 in the first hour[a]	0.113	0.055	0.001	1.996				
	Highest FiO_2 in the first two hours[a]	0.154	0.085	0.003	2.521				
	FiO_2 at the time of LISA	0.444	0.283	0.011	7.169				
	RSS at the time of LISA	0.113	0.680	0.423	1.095				
	Age at the time of caffeine loading	0.152	0.994	0.987	1.002				
	Dose of poractant alfa	0.871	1.001	0.991	1.011				
	CRP	0.289	0.985	0.958	1.013				
	Highest RSS in the first two hours[a]	0.109	1.471	0.917	2.359				
Significance at univariate level ($p < 0.1$)	Gestational age	<0.001	1.379	1.179	1.614				
	Highest FiO_2 in the second hour[a]	0.049	0.037	0.001	0.986				
	Highest level of CPAP in the first hour[a]	0.010	0.561	0.361	0.872				
	Highest level of CPAP in the second hour[a]	0.028	0.615	0.398	0.949				
	Highest level of CPAP in the first two hours[a]	0.028	0.615	0.398	0.949				
	Highest RSS in the second hour[a]	0.038	0.599	0.369	0.971				
Used in multivariate analysis after collinearity examination	Male	0.059	0.540	0.284	1.024				

TABLE 1 (Continued)

Variable	Crude				Adjusted			
	P	OR	95% CI		*P*	OR	95% CI	
Apgar score at 1 min	0.034	1.275	1.019	1.597				
Level of CPAP at the time of LISA	0.062	0.666	0.435	1.021				
Predictive factors based on multivariate regression analysis								
Birth weight	<0.001	1.002	1.001	1.003	<0.001	1.003	1.002	1.004
Maternal age	0.056	0.949	0.900	1.001	0.026	0.923	0.860	0.991
Temperature at admission	<0.001	3.351	1.758	6.388	<0.001	3.560	1.715	7.394
Highest RSS in the first hour[a]	0.024	0.526	0.301	0.918	0.029	0.463	0.232	0.925
Dose of poractant alpha < 200 mg/bw kg	0.036	0.504	0.266	0.955	0.002	0.254	0.108	0.597
CRP > 10 mg/L	0.002	0.275	0.120	0.627	0.014	0.280	0.101	0.775

Abbreviations: ANS, antenatal steroid prophylaxis; CPAP, continuous positive airway pressure; CRP, C-reactive protein; Fm-PPV in DR, face mask positive pressure ventilation in delivery room; GDM, gestational diabetes mellitus; LISA, less invasive surfactant administration; LISA-S, LISA success (defined as no need for additional surfactant treatment and/or mechanical ventilation within 72 h after the first LISA); PIH, pregnancy-induced hypertension; PROM, premature rupture of membranes; RSS, respiratory severity score (CPAP level in cm $H_2O \times FiO_2$); SGA, small for gestational age.

[a]Or at the time of LISA.

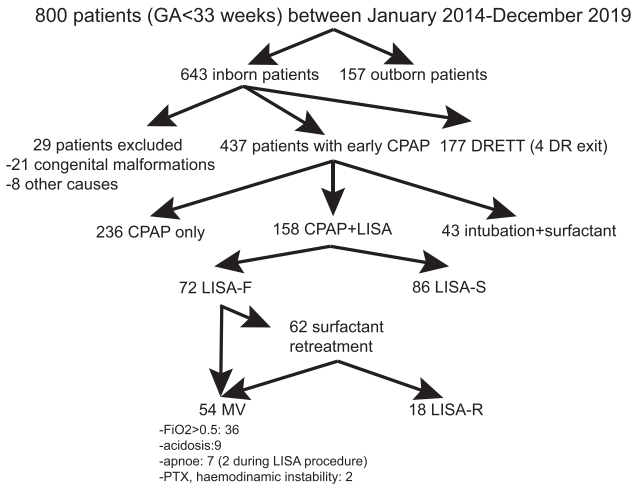

IMAGE 1 Flow chart of the total study population. CPAP, continuous positive airway pressure; CPAP-F, CPAP failure (defined as need for mechanical ventilation within 72 h after birth); DR, delivery room; DRETT, delivery room endotracheal intubation; LISA, less invasive surfactant administration; LISA-S, LISA success (defined as no need for additional surfactant treatment and/or mechanical ventilation within 72 h after the first LISA); LISA-F, LISA failure (defined as need for additional surfactant treatment and/or mechanical ventilation within 72 h after the first LISA); LISA-R, LISA retreatment (defined as need for a second LISA to avoid mechanical ventilation within 72 h after birth)

Sixty-two patients (39.2%) received a second dose of surfactant, 31 via endotracheal tube, and 31 with LISA. Among the latter, further surfactant treatment and/or mechanical ventilation was avoided (repeat LISA successful, LISA-R) in 18 cases (58%). Despite the relatively low case number, we generated a similar logistic regression model as detailed above using the appropriate risk factors. However, none of the antenatal variables showed significant difference even at univariate level. In a multivariate logistic regression model, we could not identify significant predictors for the probability of the success of the LISA retreatment.

Table 4 provides a comparison of the mortality and morbidity indices of the two study groups. Preterm infants in the LISA-F group required significantly longer hospital care and had a higher incidence of adverse outcome indices except ROP than infants in the LISA-S group. Due to the low number of events, we could not reach statistically reliable conclusions on PVL, NEC, or mortality.

4 | DISCUSSION

Although early CPAP with LISA are effective in the treatment of RDS, a significant proportion of infants require repeat LISA or even mechanical ventilation in the first 3 days of life. Therefore, it is of interest to clinicians which clinical findings can predict early (before the first LISA) if further interventions may be required.

In this study we have investigated which factors predict the success of LISA in very preterm infants. Unlike the other reports already available about the topic,[11,15] we have defined LISA failure as the need of a repeat intervention (another LISA and/or mechanical ventilation in the first 72 h of life) rather than the need of mechanical ventilation only. The indications for surfactant treatment of very preterm infants have been clearly defined, supported by strong research evidence and included in international guidelines.[4,17] In contrast, the management of infants who continue to have significant respiratory distress after surfactant treatment with LISA is much less supported by evidence and shows much

TABLE 2 Descriptive statistics of the total study population

Birth weight, g (SD)	1025.38 (347.02)
Small for gestational age, *n* (%)	33 (20.75)
<750 g, *n* (%)	35 (22.15)
750–999 g, *n* (%)	50 (31.65)
999–1249 g, *n* (%)	26 (16.46)
>1250 g, *n* (%)	47 (29.75)
Gestational age, weeks (SD)	27.93 (2.26)
Gestational age, *n* (%)	
24–25 weeks	27 (17.09)
26–27 weeks	42 (26.58)
28–29 weeks	40 (25.00)
30–32 weeks	49 (31.01)
Male gender, *n* (%)	88 (55.35)
Vaginal delivery, *n* (%)	37 (23.27)
Multiple pregnancy, *n* (%)	63 (39.62)
Apgar score (SD)	
1 min	6.55 (1.46)
5 min	8.04 (0.80)
10 min	8.50 (0.67)
Temperature at admission, °C (SD)	36.07 (0.58)
Surfactant dose, mg/bw kg (SD)	198.54 (31.72)
Any antenatal steroid, *n* (%)	146.00 (92.41)
Median FiO_2 at the time of LISA (IQR)	0.35 (0.3)

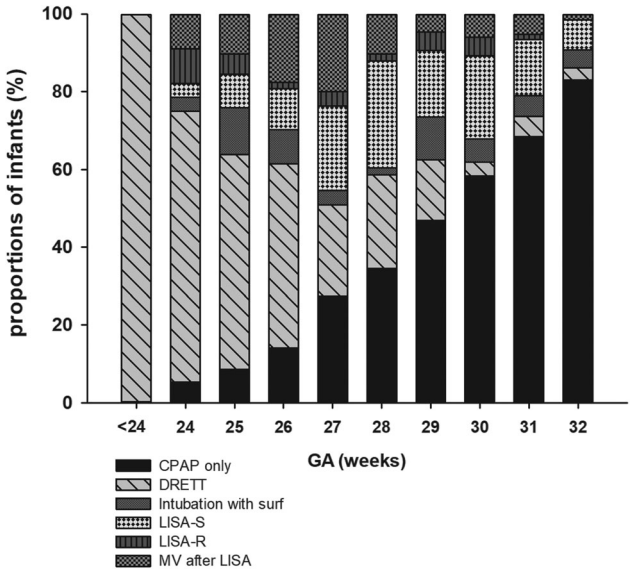

IMAGE 2 Overview of the respiratory support of all inborn preterm infants by gestational age. DRETT, delivery room endotracheal intubation; GA, gestational age; LISA, less invasive surfactant administration; LISA-S, LISA success (defined as no need for additional surfactant treatment and/or mechanical ventilation within 72 h after the first LISA); LISA-R, successful LISA retreatment (avoidance of mechanical ventilation by a second LISA within 72 h after birth); MV after LISA, mechanical ventilation after LISA

more variability among neonatal units. Depending on their setup and preference, some clinical teams may decide to intubate and ventilate these babies, while some units repeat the LISA once or even several times without intubating the baby and placing him or her on a ventilator. Therefore, to address this interesting question and to make our findings generalizable, we have put emphasis on predicting the success of the first LISA treatment.

Another novelty of our paper is that we assessed a larger number (39) of routinely available parameters as potential predictors for inclusion into our model than the previous reports.[11,15] We identified six independent predictors of the success of a single LISA: birth weight, maternal age, core temperature at the time of admission, highest RSS during the first hour of life or at the time of LISA, dose of poractant alfa (<200 mg/kg), and CRP levels (>10 mg/L) at 24 h of life. Three of these factors (hypothermia, high CRP, and low dose of surfactant) confirm the findings of the other reports.[11] The predictive power of our model is clearly indicated by the 0.85 AUC value of the ROC curve created by using the identified factors.

FiO_2 is the commonly used for assessment of RDS severity and as an indicator of the need for escalating treatment,[27,28] but its predictive value regarding the outcome of LISA is controversial. Janssen et al. found FiO_2 to be a potential predictor for outcome of LISA at univariate level, but it was not significant in their multivariate regression model. Although Kruczek et al.[15] found that FiO_2 before LISA was associated with the need for mechanical ventilation during the first 72 h, they noted that their cohort's median FiO_2 before LISA was 0.4, higher than the currently recommended treatment threshold. We also could not confirm the association between FiO_2 before surfactant administration and the outcome of LISA, but inclusion the CPAP pressure used by calculating the highest respiratory severity score during the first hour of life or before LISA added further strength to our predictive model.

We also observed correlation between outcome of LISA and hypothermia.[11] Preterm infants are prone to hypothermia; admission temperature is a strong predictor of both morbidity and mortality in every gestational age group.[29] Although the correlation between RDS and hypothermia is well known, their causal relationship is questionable because low admission temperature may also be the result of poor general condition, complicated transition, or the result of prolonged delivery room stabilization.[30,31]

We found that the initial dose of surfactant (poractant alfa) dose less than 200 mg/kg was associated with a higher risk of LISA-F. Multiple studies investigated the effect of the dose of poractant alfa, and <200 mg/kg found to be a risk factor for treatment failure not only with endotracheal intubation but also with the thin catheter method.[4,11,15,32] Accurate doses of surfactant seems to be crucial because surfactant reflux is a well-known side effect of LISA.[4] Moreover, in their bench study De Luca et al. reported a surfactant loss about two or three times higher using the thin catheter technique comparing endotracheal tube

TABLE 3 Comparison of pre- and postnatal risk factors between LISA-S and LISA-F groups

	LISA-S *n* = 86 (54.43%)	LISA-F *n* = 72 (45.57%)	*p*	95% CI Lower	95% CI Upper
Gestational age, weeks (SD)	28.62 (2.01)	27.11 (2.28)	<0.01	0.83	2.18
Birth weight, g (SD)	1134.07 (332.44)	895.56 (320.28)	<0.01	135.35	341.68
Maternal age (years), median (IQR)	29.26 (6.07)	31.13 (5.96)	0.05	−3.77	0.03
Apgar 1 min	6.78 (1.38)	6.28 (1.50)	0.03	0.05	0.96
Apgar 5 min	8.06 (0.83)	8.01 (0.76)	0.73	−0.21	0.30
Apgar 10 min	8.53 (0.65)	8.46 (0.71)	0.48	−0.14	0.29
Temperature at admission (°C), mean (SD)	36.24 (0.46)	35.88 (0.64)	<0.001	0.18	0.53
Time to caffeine loading (min), mean (SD)	72.23 (34.59)	83.65 (58.23)	0.13	−26.23	3.40
Time to 1st LISA (min), median (IQR)	135 (53)	120 (60)	0.02	34.37	329.97
Surfactant dose (mg/bwkg), mean (SD)	198.92 (30.76)	198.80 (33.05)	0.87	−9.22	10.86
ANS course started, *n* (%)	80 (93.02)	66.00 (91.67)	0.75		
ANS course finished, *n* (%)	56 (65.12)	43 (59.72)	0.49		
Moderate hypothermia at admission, n (%)	19 (22.10)	36 (50)	<0.01		
CRP level at 24–48 h after birth, mean (SD)	5.77 (16.01)	8.23 (9.61)	0.26	−6.73	1.82
GDM, *n* (%)	15 (17.45)	14 (19.44)	0.75		
Sedation during LISA, *n* (%)	10 (11.63)	13(18.06)	0.25		

Abbreviations: ANS, antenatal steroid prophylaxis; CRP, C-reactive protein; GDM, gestational diabetes mellitus; LISA, less invasive surfactant administration.

administration.[33] Despite these findings and current recommendations, both underdosing and dose rounding to full vials remains a significant issue in European countries.[32,34]

Increased CRP levels were in strong association with lower LISA-S rates, as also reported by others,[11] which is understandable since impaired surfactant response was reported in preterm infants with perinatal infection and inflammation.[35]

Unlike the study of Janssen et al.,[11] our study did not reveal any association between the outcome of LISA and ANS prophylaxis. The underlying reason may be the high steroid prophylaxis rates in both the LISA-S and LISA-F groups.

LISA success rates increased gradually with increasing gestational age until gestational week 28.[11] At gestational weeks 24 and 25, mechanical ventilation could be avoided in the first 72 h in nearly 60% of infants, which is higher than the rate published by others.[12,13] However, the need for mechanical ventilation in the first 72 h in preterm infants born at 26 weeks of gestation was significantly higher than in those born at 24–25 weeks. The likely explanation for this is inclusion bias: babies born below 26 weeks of gestation were more likely intubated already in delivery room.

Significantly shorter median time from birth to LISA was observed in the LISA-F group. The possible reason is that preterm infants who have failed the first LISA had more severe RDS and therefore they met the clinical criteria for surfactant administration earlier while being treated with early CPAP initially.

In our study, the surfactant retreatment rate was 39.1%. Of the 31 patients who underwent a second LISA, 18 (58%) succeeded on CPAP, lower than the rate reported by others (77%).[11] We used a higher FiO_2 threshold (≥0.4 vs. ≥0.3) as indication for second LISA, a possible explanation for this observation. Due to low sample size we could not identify any predictive factor of retreatment failure. Further adequately powered studies are needed to clarify both the retreatment FiO_2 threshold and the prediction of retreatment failure.

Compared to those with treatment failure, more favorable mortality and morbidity indices (except ROP) were observed in preterm infants in the LISA-S group, but our retrospective study cannot establish a causal relationship. Nonetheless, a successful LISA may predict of more favorable patient outcome. A prospective study would be needed to confirm this assumption.

Our study has some limitations. First, it is a retrospective study. Second, although there were strict indications for delivery room intubation, subjective opinion of the care provider may have overwritten them in some cases, which in turn could have affected the composition of the study population. Third, although our guideline of

TABLE 4 Comparison the incidence of neonatal morbidity between LISA-S and LISA-F groups

	LISA-S ($n = 86$)	LISA-F ($n = 72$)	p
PTX, *n*	0	5	<0.001
BPD,[22] *n*	34	55	<0.001
Severe BPD,[22] *n*	3	14	<0.001
Steroid treatment for BPD,[23] *n*	1	23	<0.001
IVH,[24] *n*	4	21	<0.001
Severe IVH, *n*	0	5	<0.001
PVL,[25] *n*	0	1	NA
ROP,[26] *n*	13	14	0.47
Severe ROP, *n*	0	6	<0.001
NEC, *n*	0	1	NA
Death, *n*	0	3	NA
Death or major morbidity, *n*	3	25	<0.001
Survival wo. major morbidity, *n*	82	48	<0.001
HFO ventilation, *n*	2	24	<0.001
Mechanical ventilation, mean hours (SD)	0.96 (4.27)	11.15 (13.98)	<0.001
LOHS, mean day (SD)	55.67 (21.15)	85.52 (43.297)	<0.001

Abbreviations: BPD, bronchopulmonary dysplasia; HFO, high-frequency oscillatory ventilation; IVH, intraventricular hemorrhage; LISA-F, LISA failure (defined as need for additional surfactant treatment and/or mechanical ventilation within 72 h after the first LISA); LISA-S, LISA success (defined as no need for additional surfactant treatment and/or mechanical ventilation within 72 h after the first LISA); LOHS, length of hospital stay; NEC, necrotizing enterocolitis requiring laparotomy; PTX, pneumothorax; severe IVH, stage ≥3 IVH; severe ROP, stage ≥3 ROP; death or major morbidity, defined as death or at least one of the following morbidities: severe BPD, severe IVH, severe ROP, NEC, PVL.

surfactant administration also defined strict criteria for treatment indication, time, and method, the attending neonatologist had the liberty to override them in individual cases based on the condition of the preterm infant.

In conclusion, failure of LISA is a relatively frequent event in preterm infants born before 33 weeks of gestation and is associated with adverse outcomes. Birth weight, maternal age, core temperature at the time of admission, highest RSS during the first hour of life or at the time of LISA, dose of poractant alfa, and level of CRP are independent predictors of outcome of the first LISA. Our predictive model can be used to identify infants where mechanical ventilation and/or surfactant re-treatment can likely be avoided with a single LISA.

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CONFLICT OF INTERESTS

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AUTHOR CONTRIBUTIONS

Andras Balajthy: conceptualization (equal); data curation (equal); formal analysis (equal); software (lead); writing—original draft (supporting). **Magdolna Riszter**: data curation (equal); supervision (equal). **Tamas Szabo**: supervision (supporting); validation (supporting); writing—review & editing (supporting). **Tamas Kovacs**: supervision (equal); writing—original draft (supporting). **Gusztav Belteki**: conceptualization (equal); methodology (equal); supervision (supporting); writing—original draft (supporting); writing—review & editing (lead). **Gyorgy Balla**: methodology (equal); supervision (lead); writing—original draft (equal).

DATA AVAILABILITY STATEMENT

The datasets analysed during the current study are not publicly available in accordance with the General Data Protection Regulation, but data sets may be available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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