





Respiratory distress syndrome in preterm infants of less than 32 weeks: What difference does giving 100 or 200 mg/kg of exogenous surfactant make?

Lucia Lanciotti MD^{1,2}  | Alessio Correani MSc, PhD¹  | Matteo Pasqualini MD¹ | Luca Antognoli MSc³ | Valentina G. Dell'Orto MD² | Chiara Giorgetti MD² | Sara Colombo MD² | Maria L. Palazzi MD² | Clementina Rondina MD²  | Ilaria Burattini MD²  | Virgilio P. Carnielli MD, PhD^{1,2}

¹Department of Odontostomatologic and Specialized Clinical Sciences, Polytechnic University of Marche, Ancona (AN), Italy

²Division of Neonatology, Mother and Child Department, G. Salesi University Hospital, Ospedali Riuniti, Ancona (AN), Italy

³Department of Industrial Engineering and Mathematical Sciences, Polytechnic University of Marche, Ancona (AN), Italy

Correspondence

Lucia Lanciotti, MD, Department of Odontostomatologic and Specialized Clinical Sciences, Polytechnic University of Marche, Via E. Toti 4, 60123 Ancona (AN), Italy.
Email: l.lanciotti@pm.univpm.it

Abstract

Background: Surfactant dosing and effective delivery could affect continuous positive airways pressure (CPAP)-failure. Nevertheless, information on exogenous surfactant dosing with current administration methods is limited.

Objective: To describe the effect of 100 or 200 mg/kg of surfactant as first-line treatment of respiratory distress syndrome in preterm infants of less than 32 weeks gestation.

Study Design: A retrospective single-center cohort study comparing two epochs, before and after switching from 100 to 200 mg/kg surfactant therapy.

Results: Six hundred and fifty-eight of the 1615 infants of less than 32 weeks were treated with surfactant: 282 received 100 mg/kg (S-100) and 376 received 200 mg/kg (S-200). There were no differences between S-100 and S-200 in perinatal data including prenatal corticosteroids, medication use, age at first surfactant administration and respiratory severity before surfactant.

The S-200 vs. S-100 had fewer retreatments (17.0% vs. 47.2%, $p < 0.001$) and a shorter duration of oxygen therapy and mechanical ventilation (315 vs. 339 h, $p = 0.018$; 37 vs. 118 h, $p = 0.000$, respectively). There was no difference in postnatal corticosteroid use (S-200 10.0% vs. S-100 11.0%, $p = 0.361$). Bronchopulmonary dysplasia (BPD) was significantly lower in S-200 vs. S-100 when comparing either the 4 and 6-year periods before and after the dose switch (29.4% vs. 15.7%, $p = 0.003$, and 18.7% vs. 27.3%, $p = 0.024$, respectively)

Conclusions: The switch from 100 to 200 mg/kg was associated with a marked reduction in the need for surfactant redosing, respiratory support, and BPD. This

Abbreviations: BPD, bronchopulmonary dysplasia; CPAP, continuous positive airways pressure; FiO₂, fraction of inspired oxygen; GA, gestational age; LISA, less invasive surfactant administration; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; S-100, group of infants receiving 100 mg/kg of surfactant; S-200, group of infants receiving 200 mg/kg of surfactant; SFR, saturation of oxygen to fraction of inspired oxygen ratio; SpO₂, saturation of oxygen.

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information could be important when designing a study in the modern era of less invasive administration as surfactant dosing and its effective delivery may affect the outcome.

KEYWORDS

preterm infants, respiratory distress syndrome, surfactant

1 | INTRODUCTION

Exogenous surfactant therapy represents a milestone in the treatment of neonatal respiratory distress syndrome (RDS) and is the most extensively studied drug in Neonatology.^{1–4}

However, relatively few studies have investigated the effect of surfactant dosage on respiratory outcomes.⁵

Hallyday et al.⁶ compared 200 vs. 100 mg/kg of poractant alfa as an initial treatment of RDS in preterm infants with a very low rate of prenatal steroids and found no differences in death and oxygen dependency.

In 2004, Ramanathan et al.⁷ reported that 200 mg/kg of poractant alfa as an initial dose for the treatment of RDS was associated with a significant reduction in mortality (3% vs. 11%; $p=0.046$) and in the need for second and additional doses.

In 2009, Cogo et al.⁸ reported better oxygenation and reduced need for retreatment in preterm infants receiving 200 rather than 100 mg/kg.

The use of 200 mg/kg poractant alfa was also recently associated with a lower incidence of bronchopulmonary dysplasia (BPD), BPD plus death, air leaks, lung hemorrhage, and the need for retreatment compared to 100 mg/kg of surfactant dosing.^{5,9}

During the last decade, there has been increased emphasis on less invasive surfactant administration (LISA) methods with the main purpose concerning the delivery of exogenous surfactant with a less invasive approach compared to standard methods and avoiding mechanical ventilation.¹⁰ In some of these studies, information on surfactant dosing and administration schemes is limited and it is not yet clear if the surfactant dose used may have affected the rather common postextubation continuous positive airways pressure (CPAP) failure, which thus caused a need for reintubation or redosing. The rate of reintubation with LISA methods appears to be significant, albeit rather variable.^{11–16} This finding has been suggested to be associated with the amount of surfactant administered.^{13,15}

After the work of Ramathan⁷ and Cogo,⁸ as of January 1, 2010, we decided to change our practice by switching from 100 to 200 mg/kg as the initial dose of exogenous surfactant. We thought that reporting our experience could be of interest for optimizing surfactant therapy in the modern era of LISA methods.

2 | MATERIALS AND METHODS

2.1 | Patients and study design

This was a retrospective cohort study conducted in the single level III neonatal intensive care unit (NICU) of the Marche region at the “G.

Salesi” Children’s Hospital (Ancona, Italy). Our institution serves as a regional referral center for all infants born in the Marche region with gestational age (GA) of less than 32 weeks.

Preterm infants with a GA between 24.0 and 31.6 weeks consecutively admitted in the NICU from January 1, 2004 to February 28, 2021 were included. Exclusion criteria were: (1) outborn (born in an I or II level regional hospital and then transferred to our center immediately after birth); (2) congenital malformations; (3) death before 72 h of life and (4) surfactant administration for indications of other than RDS (pulmonary hemorrhage and congenital pneumonia).

According to the initial surfactant dose, patients were divided into two groups: S-100 and S-200 which received 100 or 200 mg/kg of surfactant. The dose change occurred as of January 1, 2010.

This study was approved by the local ethics committee (Comitato Etico della Regione Marche; Prot N. 2021 487). Given the retrospective nature of this study, informed consent was not needed.

2.2 | Surfactant therapy

The diagnosis of RDS was based on clinical and radiological data.¹⁷ Porcine-derived surfactant (Curosurf®; Chiesi Farmaceutici SpA) was administered as an early rescue treatment for RDS when a fraction of inspired oxygen (FiO_2) ≥ 0.3 with 10% tolerance was needed to maintain an adequate saturation of oxygen (SpO_2) of 90%–92%. The recommended surfactant dosage was 100 mg/kg between 2004 and 2009, and 200 mg/kg between 2010 and 2021, while subsequent doses were always 100 mg/kg.¹⁸ These criteria remained unchanged during the study period and were based on local guidelines.

2.3 | Data collection

Clinical data were prospectively recorded using a dedicated software (Neotools®; Interactive).

SpO_2 by pulse oximeter (Masimo®) and FiO_2 , as indicated by ventilators or CPAP devices (depending on the ventilator support), were prospectively recorded on an hourly basis in the medical records throughout the hospital stay.

The SpO_2 to FiO_2 ratio (SFR) was used as a proxy for oxygen diffusion in the lungs. Both the SpO_2 and FiO_2 1 h before and 6 h after surfactant administration were used to calculate SFR before and after surfactant therapy, respectively.

SFR at 36 weeks was defined as the mean of the SFR values recorded during 24 h on the day that each infant reached 36 weeks postmenstrual age.

BPD was diagnosed according to the physiologic definition: infants receiving <30% oxygen or effective oxygen >30% with saturations >96% underwent a room-air challenge; outcomes were “no BPD” (saturations >90% during weaning and in room air for 30 min) or “BPD” (saturation <90%).¹⁹ Complications of prematurity were defined according to Vermont Oxford Network.²⁰

Neither the definitions of the medical conditions nor the indications for the use of the most common medications changed throughout the study period.

2.4 | Statistical analysis

Data were expressed as mean and standard deviation, median and interquartile range (IQR) or 25–75° percentile, and frequency, as appropriate. Independent *t*-test, χ^2 test or Mann–Whitney test were used to compare S-100 vs. S-200.

Multiple linear regression analysis was used to evaluate the association of SFR at 36 weeks with hypertension in pregnancy (yes/no), antenatal corticosteroids (yes/no), GA (weeks), male gender (yes/no), the diagnosis of small for gestational age <10th percentile (SGA, yes/no), time to first surfactant dose (hours), SFR before surfactant administration, early onset sepsis (yes/no), and 100 mg/kg as surfactant initial dose (yes/no).

Statistical significance was set at $p < 0.05$.

The statistical analysis was performed using SPSS 24.0 (IBM) and MATLAB 8.0 (The MathWorks, Inc.).

3 | RESULTS

From January 1, 2004 to February 28, 2021, 1615 preterm infants with a GA between 24.0 and 31.6 weeks were born in the Marche region and admitted to the NICU. The total number of surfactant doses administered was 1140.

Three hundred and twenty-six infants were excluded: 226 were outborn, 52 had congenital malformations, 37 died before 72 h of life, and 11 received surfactant for indications other than RDS.

Of the remaining 1289 infants, 658 were treated with 884 doses of surfactant (Figure 1).

Two hundred and eighty-two infants received 100 mg/kg (S-100), and 376 received 200 mg/kg (S-200) as the initial surfactant dose.

There were no differences in prenatal data and demographic characteristics between groups (Table 1).

SpO₂, FiO₂, and SFR before surfactant administration were similar between S-100 and S-200 (SpO₂: 92 [90–94] vs. 92 [90–93], $p = 0.807$; FiO₂: 40 [30–55] vs. 40 [30–50], $p = 0.402$; SFR: 232 [176–300] vs. 237 [180–303], $p = 0.398$), whereas SpO₂, FiO₂, and SFR at 6 h after surfactant administration were significantly better in S-200 compared to S-100 (SpO₂: 94 [92–96] vs. 93 [91–95], $p = 0.000$; FiO₂: 21 [21–25] vs. 24 [21–30], $p = 0.000$; SFR: 448 [376–457] vs. 384 [303–448], $p = 0.000$, respectively, Figure 2).

Postnatal age at the time of first surfactant administration did not differ between S-100 and S-200 (7.5 ± 9.0 vs. 6.9 ± 8.0 h of life respectively, $p = 0.411$).

The need for surfactant redosing in S-200 was 17.0% vs. 47.2% in S-100 ($p < 0.001$) (Figure 3). When redosing was needed, the time interval from the first to the second dose was significantly longer in the S-200 than S-100 (30.8 ± 22.1 vs. 23.4 ± 12.7 h, $p = 0.016$).

The common neonatal morbidities associated with preterm birth were not statistically different between groups. S-200 showed a significantly shorter duration of mechanical ventilation and oxygen therapy, though we observed a longer duration of CPAP than S-100 (Table 1). There was no difference in the use of postnatal corticosteroids between S-100 and S-200 (10.0% vs. 11.0%, $p = 0.361$) in the entire study period.

There was a lower incidence of BPD or death in S-200 than S-100 (27.9% vs. 35.1%, $p = 0.049$). Due to the long timespan of the study, we also compared two 6-year periods before and after the treatment change. We observed a significant reduction in BPD (27.3% vs. 18.7%, $p = 0.024$) and in BPD or death (35.1% vs. 26.7%, $p = 0.026$). The reduction of BPD remained statistically significant

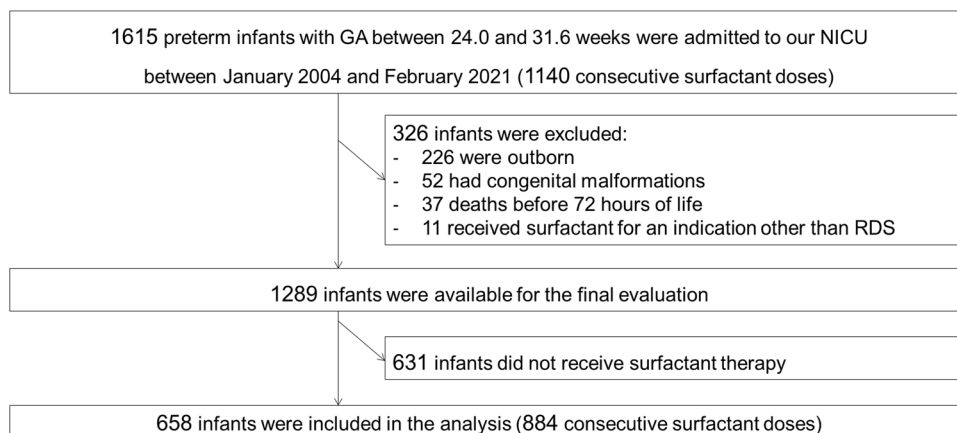


FIGURE 1 Flow chart of the study patients. GA, gestational age; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome.

TABLE 1 Clinical data of the 658 study patients

	S-100N = 282 (43%)	S-200N = 376 (57%)	p Value
Prenatal data and demographic characteristics			
GA, days	200 ± 14	199 ± 15	0.406
BW, (g)	1111 ± 369	1078 ± 358	0.249
Males, no. (%)	152 (54%)	203 (54%)	0.892
Singleton birth, no. (%)	186 (66%)	263 (70%)	0.245
Cesarean sections, no. (%)	257 (91%)	338 (90%)	0.781
Apgar score 5 min	8 [1]	8 [2]	0.358
SGA < 10th pct, no. (%)	48 (17%)	64 (17%)	0.929
SGA < 2 SDS, no. (%)	17 (6%)	26 (7%)	0.688
Antenatal corticosteroids therapy, no. (%)	257 (91%)	350 (93%)	0.354
Hypertension in pregnancy, no. (%)	76 (27%)	98 (26%)	0.772
Selected respiratory interventions			
Mechanical ventilation, hours	118 [208]	37 [198]	0.000
CPAP, hours	364 [674]	516 [738]	0.022
Oxygen therapy, hours	339 [1277]	315 [1002]	0.018
Corticosteroids for BPD, no. (%)	31 (11%)	37 (10%)	0.361
Neonatal morbidities associated to prematurity, no. (%)			
BPD	76 (27%)	83 (22%)	0.179
Death	24 (8%)	22 (6%)	0.212
BPD or death	100 (35%)	105 (28%)	0.049
Patent ductus arteriosus	167 (59%)	215 (57%)	0.648
Early onset sepsis	22 (8%)	26 (7%)	0.665
Late onset sepsis	48 (17%)	60 (16%)	0.628
Necrotizing enterocolitis grade II–III	14 (5%)	15 (4%)	0.435
Intraventricular hemorrhage >grade II	25 (9%)	26 (7%)	0.508
Periventricular leukomalacia >grade II	11 (4%)	11 (3%)	0.512
Retinopathy of prematurity >grade II	2 (1%)	1 (0%)	0.579

Note: Data are reported as mean ± SD, no. (%) or median [interquartile range]. Independent *t*-test, Mann–Whitney test and χ^2 test were used for the statistical analysis.

Abbreviations: BPD, bronchopulmonary dysplasia; BW, birth weight; CPAP, continuous positive airway pressure; GA, gestational age; SGA, small for gestational age.

even when comparing two 4-year periods before and after the surfactant dose switch (29.4% vs. 15.7%, $p = 0.003$).

Deaths in the first 72 h of life were 5% in S-100 and 2% in S-200 ($p = 0.006$) and those from birth to 36 weeks were 15% in S-100 vs. 8% in S-200 ($p = 0.004$).

The SFR at 36 weeks was positively associated with GA (B: +8.5 [95% CI: +6.2; +10.9], $p = 0.000$) and with the SFR before surfactant administration (B: +1.1 [95% CI: +0.5; +1.7], $p = 0.000$), while it was negatively associated with the male gender (B: –10.3 [95% CI: –19.5; –1.2], $p = 0.026$), with the diagnosis of SGA (B: –34.6 [95% CI: –47.7;

–21.6], $p = 0.000$) and with the use of the lower dose of 100 mg/kg of exogenous surfactant (B: –15.1 [95% CI: –24.3; –6.1], $p = 0.001$).

4 | DISCUSSION

This retrospective study on a large cohort of preterm infants of less than 32 weeks' gestation shows that 200 vs. 100 mg/kg of exogenous surfactant as the first dose for the treatment of RDS produced a marked clinical and statistical improvement in respiratory outcome.

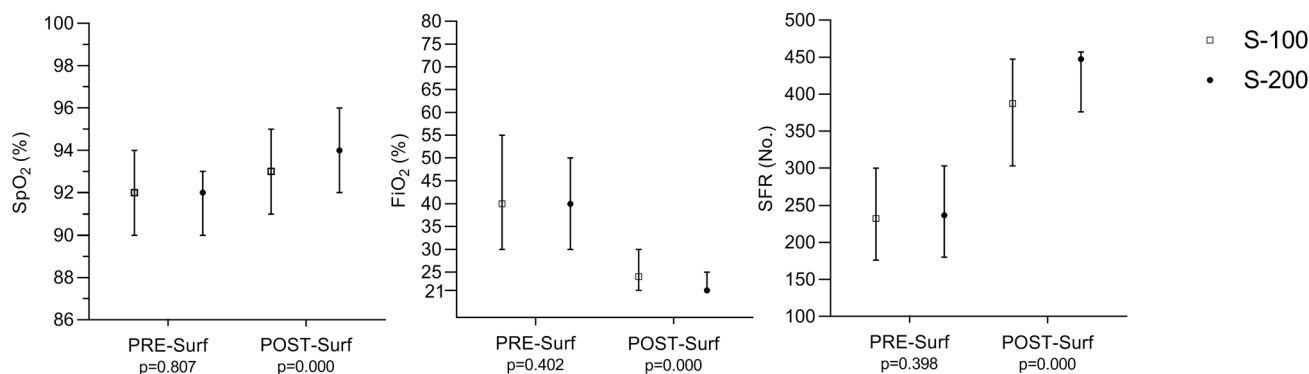


FIGURE 2 Respiratory severity before and after surfactant administration: S-100 vs. S-200 group. Data are given as median and interquartile ranges. Mann-Whitney test was used for the statistical analysis. FiO₂, fraction of inspired oxygen; SFR, saturation of oxygen to fraction of inspired oxygen ratio; SpO₂, saturation of oxygen; Surf, surfactant.

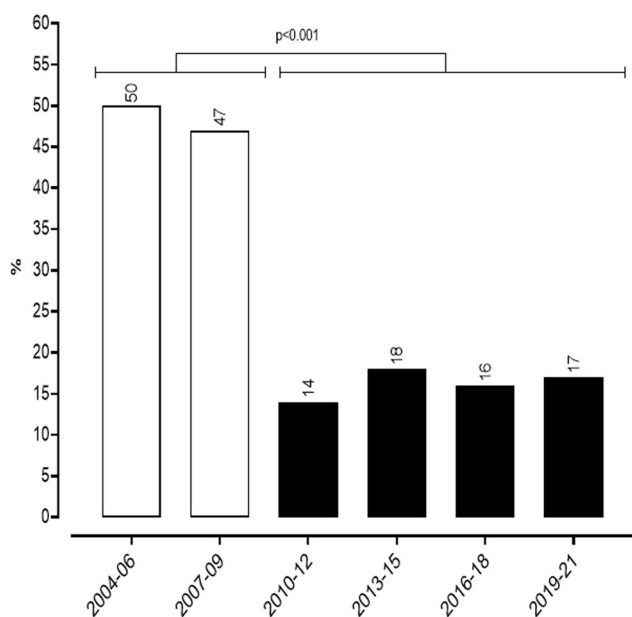


FIGURE 3 Rate of retreatment before and after the switch from 100 to 200 mg/kg of surfactant initial dose. χ^2 test was used for the statistical analysis.

The dose change was associated with fewer retreatments, a shorter duration of mechanical ventilation and oxygen therapy with improved SFR, and more importantly a reduction of BPD.

None of these findings are actually new; however, these data were obtained in a rather large number of preterm infants ($n = 658$) and through analyzing the response of 884 doses of exogenous surfactant (Figure 1). We thought that the immediate impact of this change in practice on surfactant redosing and its effect on respiratory outcomes deserved attention. Our results could be of interest in consideration of the variable surfactant dosing reported in the most recent studies of LISA and in the case of the “whole vial approach.”

We would like to discuss (1) the reduced need for surfactant redosing and speculate on the potential relevance of this finding in preventing CPAP failure in the current era of noninvasive surfactant

administration, (2) the improved gas exchange during the hospital stay, and the reduction in the incidence of BPD.

The finding of a reduced need for a second dose after a higher initial dose of exogenous surfactant is not new, as it was previously reported in the literature by us⁸ and by others.⁷ A longer interval from the first to the second dose after a higher dose of 200 vs. 100 mg/kg is also not new; however, in our opinion, this is significant as several centers still use 100 mg/kg as the initial dose. In the present paper, we reported a striking reduction in retreatments after we changed the initial dose from 100 to 200 mg/kg in 2010. This information is of clinical importance as the need for retreatment dropped markedly after the change in clinical practice (Figure 3), and it supports the hypothesis that a higher surfactant dose gives the infants “extra-mileage” while the endogenous biosynthesis slowly picks up.^{8,21}

We believe that a higher exogenous surfactant dose if retained by the very preterm lungs, would result in fewer retreatment and provide information in this direction in the present paper. This clinical observation is remarkably consistent with our previous finding that 200 mg/kg of exogenous surfactant was associated with a longer half-life than 100 mg/kg.⁸ We could speculate that a higher exogenous surfactant dose policy could reduce postextubation CPAP failure, especially in those infants who cannot adequately synthesize endogenous surfactant during the first days of life. This appears especially important in association with the use of LISA techniques where “some” surfactant might be lost to the lungs because of reflux from the airways.¹⁵

It is not yet clear why the rate of secondary intubation remains rather high in some studies after the first administration with a less invasive approach.¹² We strongly support the view that while optimizing respiratory support we should optimize surfactant dosing.

The optimal dose of exogenous surfactant to be used with LISA techniques remains largely unexplored. We believe that this information may help reduce post-LISA CPAP failures, which occur in several very preterm infants during the first 7–10 days of life.

The second finding of this study that we wish to discuss is the improved gas exchange immediately after the higher dose of surfactant and the reduction of BPD. This information is also not new, but the large number of infants studied and the very close change in outcome associated with the dose change makes these findings rather convincing. As we do not have at this stage a large enough randomized clinical trial, except for the study of Ramanathan et al.⁷ on this intervention, in very preterm infants with a high rate of antenatal corticosteroid treatment, we thought it was worth reporting our data. We would like to underscore that during the long timespan of the study, there were no significant changes in clinical practice (Table 1) and we could not detect differences between the groups (epochs) in the use of any medications, including antenatal and postnatal steroids. In addition, respiratory severity at surfactant administration and postnatal age at treatment was also very similar between groups. The shorter duration of oxygen therapy observed in S-200 than in S-100 patients and the reduction in the incidence of BPD strongly suggest that the higher surfactant dose was beneficial both in the short term and subsequently during hospital stay, as previously noted by others.⁷ Moreover, our study confirmed the finding of lower mortality in the S-200 group vs. S-100, as was reported by Ramanathan et al. in their RCT.⁷

The 200 mg/kg dose was associated with an improvement in gas exchange immediately after administration in comparison with the 100 mg/kg. All our infants were treated in a conventional way with intubation, surfactant administration, and extubation as soon as it was "deemed possible". Under these conditions, the higher dose gave better results than the lower dose. It is, however, well known that mechanical ventilation contributes to surfactant damage and catabolism, which thus reduces alveolar surfactant pool size.

It remains to be studied whether the 100 mg/kg could be adequate with less invasive administration methods that reduce lung and surfactant injury associated with mechanical ventilation.^{22,23} Our data cannot address this issue and further studies are required to clarify it. However, it is reassuring that the use of postnatal corticosteroids for facilitating extubation was rather low (about 10%) and that our BPD rate was in the range of 15%–20%.

Better oxygen diffusion in lungs at 36 weeks using 200 vs. 100 mg/kg surfactant dose was confirmed by a higher SFR in S-200 than S-100 after adjusting for other known risk factors of altered lung function/BPD, like hypertension in pregnancy, antenatal corticosteroids, GA, male gender, SGA diagnosis at birth, time to first surfactant dose (hours), SFR before surfactant administration (a proxy for RDS severity), and early onset sepsis.

This retrospective study has limitations and carries the risks of inherent biases, although data were collected according to pre-defined criteria. The study encompasses a long time period and different surfactant dosing corresponds to different epochs. However, there were no significant changes in clinical practice during the study period.

5 | CONCLUSION

This retrospective study reported the experience of a regionally-based cohort of 658 preterm infants with a GA between 24.0 and 31.6 weeks. We found that the switch from 100 to 200 mg/kg was associated with fewer surfactant retreatments, a reduction in the duration of invasive respiratory support, and BPD. We believe that our findings should be kept in mind when optimizing surfactant administration, even when using less invasive administration techniques. We speculate that higher doses of exogenous surfactant than those reported in recent publications on LISA could reduce the incidence of CPAP failure, reintubation rates, and possibly, BPD.

AUTHOR CONTRIBUTIONS

Lucia Lanciotti: Writing—original draft (lead); conceptualization (supporting); formal analysis (equal); writing—review and editing (equal). **Alessio Correani:** Formal analysis (lead); writing—review and editing (supporting). **Matteo Pasqualini, Valentina G. Dell'Orto, Chiara Giorgetti, Sara Colombo, Maria L. Palazzi, Clementina Rondina, and Ilaria Burattini:** Writing—review and editing (supporting). **Luca Antognoli:** formal analysis (lead). **Virgilio P. Carnielli:** Conceptualization (lead); writing—original draft (lead); formal analysis (equal); writing—review and editing (lead). All authors approved the final version as submitted.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Lucia Lanciotti  <https://orcid.org/0000-0001-7608-9804>

Alessio Correani  <https://orcid.org/0000-0001-5666-7806>

Clementina Rondina  <https://orcid.org/0000-0002-6345-0151>

Ilaria Burattini  <https://orcid.org/0000-0003-0239-2311>

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