

Surfactant retreatment in very preterm infants with respiratory distress syndrome: an observational cohort study

Carlo Dani^{1,2}, Marina Lo Nigro¹, Chiara Poggi², Iuri Corsini^{1,2}, Simone Pratesi^{1,2}

¹Department of Neurosciences, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy; ²Division of Neonatology, Careggi University Hospital, Florence, Italy

Contributions: (I) Conception and design: C Dani; (II) Administrative support: None; (III) Provision of study materials or patients: M Lo Nigro, C Poggi, I Corsini, S Pratesi; (IV) Collection and assembly of data: M Lo Nigro, C Poggi, I Corsini, S Pratesi; (V) Data analysis and interpretation: C Dani; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Carlo Dani, MD. Division of Neonatology, Careggi University Hospital, University of Florence, Largo Brambilla 3, 50134 Florence, Italy; Department of Neurosciences, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy. Email: carlo.dani@unifi.it.

Background: Data on surfactant retreatment in preterm infants with respiratory distress syndrome (RDS) are limited, and international guidelines do not provide specific recommendations on this issue. The objective of this study was to evaluate the effectiveness of surfactant retreatment in very preterm infants (VPI).

Methods: We retrospectively studied 140 VPI born at 23⁺⁰–29⁺⁶ weeks of gestation from January 2018 to June 2024 requiring surfactant treatment. Peripheral oxygen saturation/fraction of inspired oxygen (SpO₂/FiO₂) and arterial/alveolar partial pressure of oxygen (a/APO₂) ratios were calculated prior to and following administration of the first and second doses of surfactant. Demographic and clinical features of infants receiving a single dose were compared with those of infants requiring multiple doses.

Results: Fifty-four (39%) infants received one dose of surfactant and 86 (61%) multiple doses. SpO₂/FiO₂ and a/APO₂ ratios improved significantly after administration of both the first and second doses of surfactant. Logistic regression analysis demonstrated that the SpO₂/FiO₂ ratio before the first dose of surfactant (odds ratio 0.994, 95% CI: 0.989–0.999, P=0.047) was inversely correlated with the need for a second dose of surfactant.

Conclusions: The first and second doses of surfactant were effective in improving SpO₂/FiO₂ and a/APO₂ ratios in VPI with RDS. Low SpO₂/FiO₂ ratios prior to the first surfactant dose may identify infants likely to require multiple surfactant doses. These results support the importance of further studies aimed at standardizing the treatment with multiple doses of surfactant.

Keywords: Surfactant; retreatment; respiratory distress syndrome (RDS); preterm infant

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Introduction

Surfactant treatment and noninvasive or invasive respiratory support are essential for the treatment of respiratory distress syndrome (RDS) in preterm infants. Evidence from previous studies indicates that surfactant therapy is associated with reduced mortality and a lower risk of pneumothorax in preterm infants with RDS (1) while early noninvasive respiratory support (2) combined with surfactant treatment (3,4) reduces mechanical ventilation

and the risk of bronchopulmonary dysplasia (BPD) (4–6).

The effects of multiple versus single doses of surfactant have also been studied and were found to reduce the risk of pneumothorax, with a trend toward decreased mortality (7). However, these studies are quite dated, and their results are influenced by the low frequency of prenatal corticosteroid treatment and a fixed schedule of surfactant treatment, which limits their current usefulness. More recent data on a large population (n=8,024) have shown that 25% of

extremely preterm infants required more than one dose of surfactant and that, as expected, these patients were sicker and had worse outcome than infants who received a single dose (8). Ferri *et al.* reported similar results, finding that the surfactant retreatment rate was 15% in a cohort of 605 very low birth weight infants and confirmed that these patients had a worse outcome and a higher risk of BPD (9). Other studies have investigated predictors of multiple surfactant doses. Lower gestational age (10), lower birth weight (11), small for gestational age status (10,12), and maternal hypertensive disorders (10) were reported to be associated with surfactant retreatment.

Although extremely preterm infants often require more than one dose of surfactant (7-9,13,14), evidence on the effectiveness of surfactant retreatment in preterm infants with RDS remains limited, largely due to the limited available literature, inconsistent findings, and the predominantly single-center design of previous investigations (10-12). This situation is reflected in international guidelines which do not provide specific recommendations for retreatment with surfactant (15-17), limiting themselves to suggesting repetition of the dose when the surfactant is inactivated by an infectious process, meconium or blood or when there is evidence of ongoing moderate to severe RDS (13,16).

In light of these observations, the present study aimed to assess the short-term effectiveness of surfactant retreatment in very preterm infants (VPI). To achieve this objective, we evaluated changes in oxygenation indices and the severity

of respiratory failure after surfactant administration in a population of VPI requiring multiple doses for RDS. We present this article in accordance with the STROBE reporting checklist (available at <https://tp.amegroups.com/article/view/10.21037/tp-2025-aw-794/rc>).

Methods

This retrospective study included preterm infants with a gestational age of 23⁺⁰ to 29⁺⁶ weeks, born between January 2018 and June 2024 in the level III neonatal intensive care unit (NICU) at Careggi University Hospital, Florence. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the National Ethics Committee for Clinical Trials in Paediatrics of the Italian Medicines Agency (ID 0024705-25/02/2025). Informed consent was waived in this retrospective study.

Patients

Infants included in the study were affected by RDS requiring respiratory support and surfactant treatment. RDS was defined by clinical signs of respiratory distress, oxygen dependency during the first day of life, typical chest X-ray features (reduced lung aeration, reticulogranular pattern, and air bronchograms), and without other causes of respiratory failure (18). Exclusion criteria were major congenital malformations, chromosomal abnormalities, or inborn errors of metabolism.

Respiratory management

Patients were resuscitated in the delivery room according to the American Academy of Pediatrics and American Heart Association (AAP/AHA) guidelines (19). In synthesis, continuous positive airway pressure (CPAP) was used for spontaneously breathing neonates with respiratory distress and a heart rate ≥ 100 bpm, whereas intubation and mechanical ventilation (MV) were required for apnea or gasping, heart rate < 100 bpm, ineffective ventilation, need for chest compressions, or failure of CPAP (19). In the NICU, noninvasive respiratory support was provided using nasal continuous positive airway pressure (NCPAP), bi-level NCPAP, or nasal intermittent positive pressure ventilation (NIPPV). Transition to MV was initiated in infants with pH < 7.20 with partial pressure of arterial carbon dioxide (PaCO_2) > 65 mmHg, partial pressure of arterial oxygen

Highlight box

Key findings

- The first and second doses of surfactant were effective in improving respiratory function in very preterm infants with respiratory distress syndrome.

What is known and what is new?

- Evidence regarding the retreatment with surfactant in very preterm infants is largely incomplete.
- International guidelines do not report specific recommendations on the retreatment with surfactant of very preterm infants.

What is the implication, and what should change now?

- We reported that the second dose of surfactant was effective in improving $\text{SpO}_2/\text{FiO}_2$ and a/APO_2 ratios in very preterm infants with respiratory distress syndrome.
- Low values of $\text{SpO}_2/\text{FiO}_2$ ratio before the first dose of surfactant can predict the need for multiple doses of surfactant.

(PaO_2) <50 mmHg with fraction of inspired oxygen (FiO_2) >0.50 , or when apnea episodes (>4 per hour, or >2 requiring positive ventilation) despite NCPAP ($5\text{--}7$ cmH_2O) and oxygenation occurred.

MV was provided through patient-triggered ventilation, with or without volume guarantee, or via high-frequency ventilation. Ventilatory parameters were adjusted to keep PaCO_2 between 55 and 65 mmHg and oxygen saturation (SpO_2) between 90% and 95%.

Surfactant (Curosurf®, Chiesi Farmaceutici Spa, Parma, Italy; 200 mg/kg) was administered to infants requiring MV or when $\text{FiO}_2 >0.30$ (17) was necessary to achieve the target SpO_2 , in both the delivery room and the NICU. Additional surfactant administrations (100 mg/kg) were given based on the same criteria used for the initial dose. Surfactant was administered to non-intubated patients using either less invasive surfactant administration (LISA) or the Intubation-Surfactant-Extubation (InSURE) technique.

Collected data

Data recorded for each infant included gestational age, birth weight, Apgar score at 5 min, need and duration of noninvasive and invasive ventilation, occurrence of sepsis, BPD, intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC) >2 grade, duration of hospitalization, and death.

We recorded the $\text{SpO}_2/\text{FiO}_2$ ratio 1 h before (T_0) and 1 (T_1), 3 (T_3), 6 (T_6), and 12 h (T_{12}) after the first and second doses of surfactant. We also calculated the arterial/alveolar partial pressure of oxygen (a/APO_2) ratio 1 h before (T_0) and 1 h after (T_1) the first and second doses of surfactant with the following formula: $[\text{PaO}_2 / (\text{FiO}_2 \times 713) - 1.25 \times \text{PaCO}_2]$. Calculation of the a/APO_2 ratio was discontinued because no subsequent serial blood gas analyses were available.

We acknowledge that $\text{SpO}_2/\text{FiO}_2$ and a/APO_2 ratio may be influenced by ventilator settings, including mean airway pressure (MAP). However, MAP reflects disease severity and ventilatory support rather than representing an independent confounder. Moreover, $\text{SpO}_2/\text{FiO}_2$ and a/APO_2 ratios are validated and widely used biomarkers for monitoring oxygenation in preterm infants (20), where frequent arterial blood sampling is neither feasible nor ethically justified. Thus, they remain appropriate for assessing respiratory status in our study.

Sepsis was diagnosed based on clinical and laboratory findings—including total neutrophil count, C-reactive

protein, and procalcitonin—and confirmed by at least one positive blood or cerebrospinal fluid culture. BPD was defined as oxygen-dependency at 36 weeks of post-conceptual age (21). The adapted classification of Papile *et al.* (22) was used to grade the severity of IVH. NEC was diagnosed according to Bell's criteria (23). ROP was assessed in accordance with the International Classification of ROP (24).

The maternal variables examined included antenatal steroids, type of delivery, hypertensive disorders, and clinical chorioamnionitis (defined as the presence of fever with one or more of the following: maternal leukocytosis $>15,000/\text{mm}^3$, uterine tenderness, fetal tachycardia, or foul-smelling amniotic fluid).

Primary and secondary endpoint

The primary endpoint was the evaluation of changes in the $\text{SpO}_2/\text{FiO}_2$ ratio and a/APO_2 following the second dose of surfactant as indicators of RDS severity. Secondary endpoints included changes of these ratios after the first dose of surfactant, as well as the assessment of potential predictors for the need for multiple surfactant doses and for a positive response to the second dose.

Statistical analysis

Clinical characteristics of infants were reported as mean and standard deviation, rate and percentage, or median and interquartile range (IQR). Infants who showed an increase in $\text{SpO}_2/\text{FiO}_2$ ratio $<10\%$ after the second dose of surfactant were considered non-responding. Missing data were imputed using mean values based on available information. Statistical analyses were conducted using Student's *t*-test for normally distributed continuous variables, the two-sample Wilcoxon rank-sum test for non-normally distributed continuous variables, and the χ^2 test for categorical variables. The $\text{SpO}_2/\text{FiO}_2$ ratio was expressed as mean $\pm$ standard deviation, and changes over time were evaluated using repeated-measures analysis of variance (ANOVA). A *P* value <0.05 was considered statistically significant. Logistic regression analysis examined independent predictors of repeated surfactant administration: variables that were different at univariate analysis ($P < 0.200$) between infants requiring single or multiple doses of surfactant were considered. Therefore, a multivariable logistic regression analysis evaluated the effect of gestational age, birth weight, need for MV, and the $\text{SpO}_2/\text{FiO}_2$ ratio before surfactant

treatment on the risk for multiple doses of surfactant. We also planned logistic regression analysis to evaluate possible factors predicting the effectiveness of the second dose of surfactant. However, since no differences were found in the univariate analysis between responding and non-responding infants, this analysis was not performed.

Receiver operating characteristic (ROC) curve analysis was used to assess the predictive value of the $\text{SpO}_2/\text{FiO}_2$ ratio before the first surfactant dose for subsequent administration of a second dose. The test's discriminative ability between infants who required multiple surfactant doses and those who did not is indicated by the area under the ROC curve (AUC).

Results

A total of 266 VPI were born at our center during the study period, and 140 (53%) were treated with surfactant. Among them, 54 (39%) received one dose of surfactant, 86 (61%) received >1 dose, and 47 (34%) received >2 doses.

Infants administered multiple doses were treated earlier, had a lower gestational age, birth weight and $\text{SpO}_2/\text{FiO}_2$ ratio before and 1 h after the first dose of surfactant, more frequent and longer MV, and a higher mortality and occurrence of IVH than infants who required one dose of surfactant (Table 1).

The first dose of surfactant was given at the median age of 109 (42–180) min of life and the second at 960 (513–1,860) min, when FiO_2 was 0.53 ± 0.22 and 0.54 ± 0.22 , respectively (Table 2). The $\text{SpO}_2/\text{FiO}_2$ ratio and a/APO_2 significantly increased after both the first and second doses of surfactant (Table 2, Figure 1).

Logistic regression analysis demonstrated that the $\text{SpO}_2/\text{FiO}_2$ ratio before the first dose of surfactant [odds ratio (OR) 0.994, 95% CI: 0.989–0.999, $P=0.047$] was inversely correlated with the need for a second dose of surfactant. In ROC analysis, the $\text{SpO}_2/\text{FiO}_2$ ratio prior to the first surfactant dose significantly predicted subsequent administration of additional doses ($P<0.001$), with an AUC of 0.679 (95% CI: 0.589–0.769). The optimal prognostic cut-off was an $\text{SpO}_2/\text{FiO}_2$ ratio of 221, with a sensitivity of 69% and specificity of 60% (Figure 2).

Responding and non-responding infants with respect to the second dose of surfactant had similar clinical characteristics, except for the $\text{SpO}_2/\text{FiO}_2$ ratio after 1 h from surfactant which was higher (174 ± 81 vs. 295 ± 88 , $P<0.001$) in responding infants (Table 3). Therefore, logistic regression analysis was not performed.

Discussion

In this study, the effectiveness of the first and second surfactant doses in VPI with RDS was assessed. Significant increases in both $\text{SpO}_2/\text{FiO}_2$ and a/APO_2 ratios were observed following each administration.

The improvement in the $\text{SpO}_2/\text{FiO}_2$ ratio is clinically relevant because oxygen dependency reflects RDS severity. Recently, this ratio has been suggested as a noninvasive alternative to the $\text{PaO}_2/\text{FiO}_2$ ratio in acute respiratory failure, with the benefit of allowing continuous monitoring. This result suggests that, as expected, surfactant treatment is followed by the improvement of respiratory failure, probably due to the recruitment of surfactant-deficient areas and the consequent increase in alveolar surface area for gas exchange. The increase in a/APO_2 ratio confirmed the beneficial effects of surfactant on respiratory function. Indeed, its value reflects the degree of ventilation/perfusion mismatch and shunting, as greater stability has been observed in patients with large shunts (25). Consequently, this ratio is particularly relevant in VPI, which frequently experience both ventilation/perfusion mismatch (e.g., severe RDS, persistent pulmonary hypertension) and shunts (e.g., hemodynamically significant patent ductus arteriosus) (26). Our results confirmed previous findings (10–12) on the acute beneficial effects of the first dose of surfactant on pulmonary function and gas exchange. Cogo *et al.* studied 125 preterm infants with gestational age ≤ 32 weeks with RDS and found that the $\text{PaO}_2/\text{FiO}_2$ ratio and oxygenation index (OI) significantly increased 1 h after the first surfactant dose in infants who required single or multiple surfactant doses (11). Lanciotti *et al.* studied 662 preterm infants with gestational age ≤ 32 weeks treated with surfactant and found that the $\text{SpO}_2/\text{FiO}_2$ ratio increased 6 h after the first dose of surfactant in infants who required single or multiple surfactant doses (10). Greiner *et al.* studied 156 preterm infants with gestational age ≤ 32 weeks and reported that FiO_2 decreased and OI increased after the first surfactant dose (exact timing is not detailed) in infants who required single or multiple surfactant doses (14). It is interesting that our study and previous ones demonstrated that the $\text{PaO}_2/\text{FiO}_2$ (11) and $\text{SpO}_2/\text{FiO}_2$ ratios (10) before and after the first dose of surfactant were lower in infants who required additional doses of surfactant. Since the $\text{PaO}_2/\text{FiO}_2$ (11) and $\text{SpO}_2/\text{FiO}_2$ ratios are biomarkers of RDS severity, these findings suggest that infants with severe RDS respond poorly to surfactant treatment and are at higher risk of redosing. In line with this, logistic regression

Table 1 Baseline clinical characteristics of the infants and their mothers who received single or multiple doses of surfactant

Characteristics	Single dose (n=54)	Multiple doses (n=86)	P
Infants			
Gestational age (weeks)	27.3±1.6	25.8±1.9	<0.001
Birth weight (g)	969±235	803±233	<0.001
<10 th percentile	5 (8)	10 (11)	0.87
Apgar score at 5 min	8 (7–8)	8 (7–8)	0.11
Surfactant in the delivery room	7 (13)	10 (12)	0.84
Age at first surfactant dose (min)	109 (42–180)	109 (42–180)	<0.001
SpO ₂ /FiO ₂ before surfactant	258±236	188±70	<0.001
SpO ₂ /FiO ₂ after 1 h from 1 st surfactant dose	363±74	260±103	<0.001
Noninvasive ventilation	54 (100)	86 (100)	>0.99
Duration of noninvasive ventilation (h)	41±33	53±51	0.13
Mechanical ventilation	11 (20)	42 (48)	0.001
Mechanical ventilation in the delivery room	10 (19)	25 (29)	0.16
Duration of mechanical ventilation (h)	4±10	21±28	<0.001
Early onset sepsis	1 (2)	7 (8)	0.24
Late onset sepsis	17 (31)	40 (47)	0.11
Bronchopulmonary dysplasia	23 (42)	52 (60)	0.06
Necrotizing enterocolitis	2 (4)	6 (7)	0.66
Intraventricular hemorrhage	9 (16)	35 (41)	0.005
Retinopathy of prematurity	7 (13)	23 (27)	0.09
Duration of hospital stay (days)	92±46	95±62	0.76
Death	1 (2)	22 (26)	<0.001
Mothers			
Antenatal steroids	43 (80)	62 (72)	0.56
Cesarean section	39 (72)	45 (53)	0.03
Gestational diabetes	7 (13)	15 (17)	0.64
Hypertensive disorders of pregnancy	11 (20)	17 (20)	0.93
Chorioamnionitis	8 (15)	21 (24)	0.25

Data are presented as mean ± standard deviation, median (interquartile range), or n (%). FiO₂, fraction of inspired oxygen; SpO₂, peripheral oxygen saturation.

analysis confirmed in our and Lanciotti's study (10) that the SpO₂/FiO₂ ratio value before the first dose of surfactant is inversely related to the risk of subsequent doses. ROC analysis further revealed that the SpO₂/FiO₂ ratio before the first surfactant administration significantly predicted the requirement for subsequent doses, with the optimal

threshold identified at 221; however, both sensitivity (69%) and specificity (60%) remained modest. For the first time, we documented that the second dose of surfactant was also followed by increases in SpO₂/FiO₂ and a/APO₂ ratios in VPI. The effectiveness of the therapy indicates that in the subgroup of infants treated with multiple doses of surfactant

Table 2 Changes of SpO₂/FiO₂ and a/APO₂ before and after the first and second doses of surfactant

Variable	1 st dose of surfactant (n=140)	2 nd dose of surfactant (n=86)
Age at surfactant (min)	109 (42–180)	960 (513–1,860)
FiO ₂ before surfactant	0.53±0.22	0.54±0.22
SpO ₂ /FiO ₂		
SpO ₂ /FiO ₂ before surfactant	212±162	188±70
SpO ₂ /FiO ₂ after 1 h from surfactant	320±102	260±103
SpO ₂ /FiO ₂ after 3 h from surfactant	345±105	267±113
SpO ₂ /FiO ₂ after 6 h from surfactant	363±97	272±111
SpO ₂ /FiO ₂ after 12 h from surfactant	366±98	279±109
P (time effect)	<0.001	<0.001
a/APO ₂		
a/APO ₂ before surfactant	0.44±0.20	0.34±0.18
a/APO ₂ after 1 h from surfactant	0.51±0.27	0.42±0.16
P (time effect)	0.01	0.002

Data are presented as mean ± standard deviation or median (interquartile range). a/APO₂, arterial/alveolar partial pressure of oxygen; FiO₂, fraction of inspired oxygen; SpO₂, peripheral oxygen saturation.

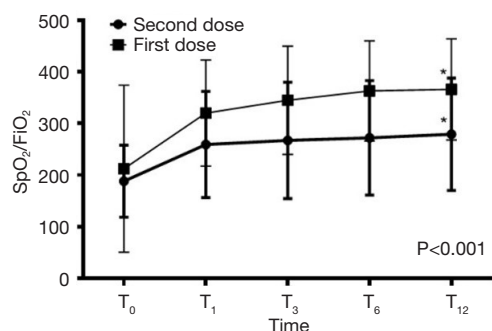


Figure 1 Changes of SpO₂/FiO₂ before and after the first and second doses of surfactant. *, P<0.05. FiO₂, fraction of inspired oxygen; SpO₂, peripheral oxygen saturation.

there was a persistent deficiency. Thus, although it was reported that the pool size of surfactant in preterm infants is 5–10 mg/kg with slow kinetics and prolonged half-life (47–106 h) (27), it is evident that some patients require large amounts of exogenous surfactant to correct their deficit despite the treatment with positive pressure noninvasive or invasive support. Furthermore, studies in animal models have shown that the second dose of surfactant distributes both to areas that initially received surfactant and to areas that remain surfactant-deficient, resulting in a significant

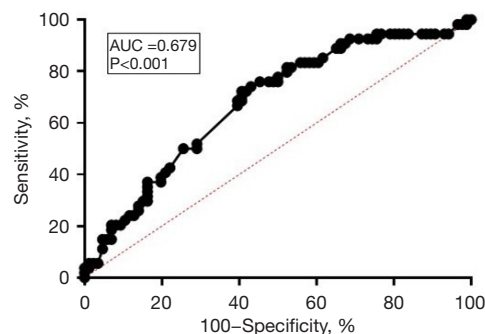


Figure 2 ROC curve analysis for the SpO₂/FiO₂ ratio 1 h before the first dose of surfactant. The plotted curve indicated a value of 221 as the best predictive threshold with a sensitivity of 69% and a specificity of 60%. The ROC curve distinguishes infants requiring single or multiple doses of surfactant. AUC, area under the curve; FiO₂, fraction of inspired oxygen; ROC, receiver operating curve; SpO₂, peripheral oxygen saturation.

increase in PaO₂, which may be partially attributable to additional alveolar recruitment after the second dose (28).

We did not find any clinical predictors of response to the second surfactant dose. This could depend on several factors, including the small size of our population, the lack of strict criteria for surfactant redosing in our study, and possible hemodynamic confounding factors that we could

Table 3 Clinical characteristics of infants who responded to the second dose of surfactant or did not

Characteristics	No responders (n=25)	Responders (n=61)	P
Infants			
Gestational age (weeks)	25.7±2.0	25.8±1.8	0.82
Birth weight (g)	803±246	803±229	>0.99
<10 th percentile	3 (12)	7 (11)	0.95
Apgar score at 5 min	8 (7–8)	8 (7–8)	0.74
Noninvasive ventilation	25 (100)	61 (100)	>0.99
Duration (h)	56±45	52±53	0.74
Mechanical ventilation	11 (44)	31 (51)	0.40
Duration (h)	27±36	18±24	0.18
SpO ₂ /FiO ₂ before surfactant	188±88	188±62	>0.99
SpO ₂ /FiO ₂ after 1 h from surfactant	174±81	295±88 [†]	<0.001
Early onset sepsis	3 (12)	4 (7)	0.40
Late onset sepsis	12 (48)	28 (46)	0.86
Bronchopulmonary dysplasia	15 (60)	37 (61)	0.96
Necrotizing enterocolitis	2 (8)	4 (7)	0.81
Intraventricular hemorrhage	11 (44)	24 (39)	0.69
Retinopathy of prematurity	9 (36)	14 (23)	0.21
Duration of hospital stay (days)	103±64	91±61	0.42
Death	7 (28)	15 (25)	0.74
Mothers			
Antenatal steroids	18 (72)	44 (72)	0.99
Cesarean section	14 (56)	31 (51)	0.66
Gestational diabetes	3 (12)	12 (20)	0.40
Hypertensive disorders of pregnancy	5 (20)	12 (20)	0.97
Chorioamnionitis	5 (20)	16 (26)	0.54

Data are presented as mean ± standard deviation, n (%), or median (interquartile range). [†], P<0.001 vs. SpO₂/FiO₂ before surfactant. FiO₂, fraction of inspired oxygen; SpO₂, peripheral oxygen saturation.

not consider in our analysis.

However, we believe that our findings are clinically relevant also because lung ultrasound has been increasingly used in recent years to guide decisions regarding the administration of the first dose of surfactant (29–31) and, more recently, also of the second dose (32). Therefore, the availability of data supporting the beneficial effects of multiple doses of surfactant may help to further optimize the high accuracy of lung ultrasound in predicting the need for surfactant in VPI with RDS.

The retrospective design and limited population size of our study constrain its ability to conduct a thorough analysis of factors associated with repeated surfactant administrations. This may explain why we did not observe this correlation, unlike previous studies in VPI (8–10), which reported that infants born to mothers with hypertensive disorders of pregnancy or who are small for gestational age are more likely to receive multiple surfactant doses. A further limitation is that we arbitrarily defined non-responder infants as those who showed an

increase in the SpO₂/FiO₂ ratio of <10% after the second dose of surfactant. Although the absence of improvement in oxygenation indices after surfactant administration is commonly used to identify non-responder patients, the exact percentage change in the SpO₂/FiO₂ ratio has not been specified in the literature.

Conclusions

We found that the first and second doses of surfactant were effective in improving the SpO₂/FiO₂ and a/APO₂ ratios in VPI with RDS. We demonstrated that lower SpO₂/FiO₂ ratio values before the first dose of surfactant are correlated with an increased risk of requiring multiple doses of surfactant. These data may contribute to a better understanding of the effects of surfactant retreatment in VPI and promote the importance of further studies aimed at standardizing the treatment with multiple doses of surfactant.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://tp.amegroups.com/article/view/10.21037/tp-2025-aw-794/rc>

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Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the National Ethics Committee for Clinical Trials in Paediatrics of the Italian Medicines Agency (ID 0024705-25/02/2025). Informed consent was waived in this retrospective study.

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