Underdosing of Surfactant for Preterm Babies with Respiratory Distress Syndrome in Clinical Practice: A Retrospective Cohort Study

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Abstract

Objective To evaluate the initial doses of surfactant administered to preterm infants with respiratory distress syndrome.

Study Design This is a retrospective cohort study of 206 preterm infants admitted in four level III neonatal intensive care units of acute tertiary care hospitals in Spain between 2013 and 2015.

Results The mean initial dose of surfactant was 173.9 (37.3) mg/kg, and 47.5% of infants received a dose of 200 mg/kg ± 10% (180–220 mg/kg), 47% less than 180 mg/kg (–10%), and 5.4% more than 220 mg/kg (+10%). Very preterm infants (<28 weeks) received higher initial doses than more mature infants, but in all cases, the mean doses were below the recommended 200 mg/kg (by 9.2% in gestational age 23–28 weeks, by 15.9% in 29–32 weeks, and by 24.3% in >32 weeks).

Conclusion Administration of surfactant below the prescribed dose is a frequent error in clinical practice. Inadvertently rounding down doses seems a plausible explanation.

Keywords
- dosage
- preterm babies
- respiratory distress syndrome
- surfactant

Surfactant is the cornerstone of the treatment of respiratory distress syndrome (RDS) in preterm infants. Treatment with surfactant has been shown to reduce the risk of pulmonary morbidity (pneumothorax and pulmonary interstitial emphysema) and neonatal mortality.[1–3] Mechanical ventilation is considered the single most important risk factor for the development of bronchopulmonary dysplasia (BPD).[4] The clinical focus on avoiding mechanical ventilation and the care of infants of less than 26 weeks' gestation has spurred new approaches of surfactant administration.[5]

Animal-derived surfactants differ in their concentration of phospholipids and surfactant proteins, which may affect efficacy. There is evidence of the superiority of porcine (poractant alfa) versus bovine (beractant, bovactant) surfactants with respect to clinical outcomes, including mortality, the need for redosing, oxygen requirements, duration of oxygen treatment, and duration of mechanical ventilation.[6–10] A survival advantage for the high dose (200 mg/kg) of poractant alfa to treat RDS as compared with the low dose (100 mg/kg) and the 100 mg/kg/dose of beractant and 50 mg/kg/dose of bovactant

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has been reported.[10] Also, the 100 mg/kg/dose has been shown to be an independent predictor of surfactant redosing.[11] In this sense, the 2016 update of the European Consensus Guidelines on the Management of RDS[12] recommends the administration of poractant alfa in an initial dose of 200 mg/kg. Early surfactant administration reduces failure of continuous positive airway pressure (CPAP).[4] In a population-based study, failure of CPAP for initial respiratory management in preterm infants occurred in 43% of those at <29 weeks' gestation and was associated with adverse outcomes including death and other major morbidities.[13] Moreover, CPAP failure usually occurs because of unremitting RDS and is predicted by the need of a $FiO_2 \geq 0.3$ in the first hours of life.[14]

Despite clinical and pharmacokinetic data supporting the dose of poractant alfa of 200 mg/kg,[11,12,15] real-world studies have brought attention to the fact that the correct dose is not often given as clinicians may be tempted to administrate a rounded dose to the vial content.[16–18] To further explore everyday clinical practices in neonatal intensive care units (NICUs) regarding the optimal dosing of surfactant, in an effort to ensure high standards of newborn care, a retrospective cohort study was designed. The objective of the study was to evaluate the initial dose of surfactant used in preterm infants with RDS.

Materials and Methods

Study Design and Participants

A multicenter, retrospective cohort study was performed in four level III NICUs in Spain. The primary objective of the study was to evaluate the mean initial dose of surfactant administered to preterm infants diagnosed with RDS. Secondary objectives were (1) to assess the total number of doses of surfactant, (2) to determine the percentage of patients treated with the initial dose of poractant alfa of 200 mg/kg ± 10%, and (3) to describe adverse events and short-term respiratory outcomes.

Between January 1, 2013, and December 31, 2015, all preterm babies (gestational age < 37 weeks) with clinical symptoms of RDS receiving surfactant were eligible for the study. By protocol, in all four participating hospitals, the initial surfactant dose prescribed was 200 mg/kg in accordance with the recommendations of the 2013 European Consensus Guidelines on the Management of RDS.[19] The availability of a minimal dataset in clinical records, including gestational age, birth weight, FiO_2 before surfactant administration, and total actual dose of surfactant received in mg or mL as the initial treatment, was required for inclusion in the study. The study protocol complied with all the relevant national regulations and institutional policies, adhered to the tenets of the Declaration of Helsinki, and was approved by the Ethics Committee of Hospital Universitari Vall d'Hebron of Barcelona, Spain.

Definition of Study Variables

RDS was defined as clinical respiratory distress (tachypnea, nasal flaring, chest retractions, or grunting) that required invasive or noninvasive ventilatory support. The need for surfactant administration required $FiO_2 \geq 0.3$ to achieve O_2 saturation between 90 and 95%. Surfactant administration methods included intubation–surfactant–extubation (INSURE), less invasive surfactant administration (LISA), and endotracheal tube (ETT).

Statistical Analysis

According to the primary objective of the study and considering a theoretical standard deviation (SD) of 52.75 in the study population, a sample size of 167 infants was required to estimate, with a confidence interval (CI) of 95%, the mean dose of surfactant with a level of precision of 8 mg/kg. The required sample size of 167 was increased to 196, assuming a percentage of 15% loss due to lack of minimal data required.

Data extracted from patients' records were entered into an electronic database for analysis. All data were anonymized. Categorical variables are expressed as frequencies and percentages, and quantitative variables as mean and 95% CI, mean and SD, or median and interquartile range (IQR) (25th–75th percentile) as appropriate. Continuous data were compared using Student's *t*-test and the analysis of variance or the Mann–Whitney *U* test and the Kruskal–Wallis test, and categorical data with the chi-square (χ^2) test or Fisher's exact test according to the distribution and size of the variables. Analyses were performed for the overall study population and for the groups categorized by gestational age between 23 and 28 weeks, between 29 and 32 weeks, and >32 weeks. All tests of significance were two-sided and set at $p < 0.05$. The Statistical Analysis Systems software version 9.4 (SAS Institute, Cary, NC) was used for statistical analysis.

Results

A total of 219 infants was eligible during the study period, but 13 (5.9%) were excluded because inclusion criteria were not met ($n = 5$) or because of lack of minimal data required ($n = 8$). Therefore, the study population included 206 infants, 116 males and 90 females, with a mean (SD) gestational age of 28.8 (3.1) weeks, mean birth weight of 1,227.3 (582.6) g, and median Apgar scores at 1 minute and 5 minutes of 6 (IQR 4–7) and 8 (IQR 7–9), respectively. According to gestational age, there were 120 infants in the 23- to 28- week group, 56 in the 29- to 32-week group, and 30 in the >32-week group. Clinical findings before the administration of surfactant are shown in ►**Table 1**. Antenatal corticosteroid treatment was recorded in 84% of infants. In relation to the use of ventilatory support immediately after birth in the delivery room, noninvasive ventilation was used in 49% of neonates and invasive ventilation in 41.3%, and the remaining 9.7% did not require any type of ventilatory support. All patients required some type of ventilatory support during their stay in the NICU (invasive: 51.9%; noninvasive: 48.1%). Ventilatory failure requiring an increase in respiratory support was recorded in 42 (20.4%) infants, with mechanical ventilation used in 27 (64.3%) of them, mostly in infants initially treated with CPAP.

The mean FiO_2 value before the administration of surfactant was 0.47 (0.18). There were no significant differences in FiO_2 values according to gestational age, although higher

Table 1 Characteristics of the study population ($n = 206$) before the administration of surfactant

Variables	No. of patients (%)
Gender	
Male	116 (56.3)
Female	90 (43.7)
Antenatal corticosteroids	173 (84)
Gestational age, mean (SD)	28.8 (3.1)
23–28 wk	120 (58.3)
29–32 wk	56 (27.2)
>32 wk	30 (14.6)
Delivery-related data	
Cesarean section	152 (73.8)
Singleton	125 (60.7)
Multiple (twins, triplets)	81 (39.3)
Premature rupture of membranes	54 (26.2)
Chorioamnionitis	25 (12.1)
Cord prolapse	5 (2.4)
Fetal distress	27 (13.1)
Presence of meconium	5 (2.4)
Preeclampsia	30 (14.6)
Apgar score, mean (SD)	
1 min	6 (2)
5 min	8 (2)
Birth weight, g, mean (SD)	1,227.3 (582.6)
Length, cm, mean (SD)	37.3 (5.8)
Immediate ventilatory support (delivery room)	
Invasive	85 (41.3)
Mechanical ventilation	85 (41.3)
Noninvasive	
IPPV prongs/nasal mask	58 (28.1)
SNIPPV	2 (1)
CPAP	40 (19.4)
Other	1 (0.5)
None	20 (9.7)
Ventilatory support in the NICU	206 (100)
Invasive	107 (51.9)
Mechanical ventilation	107 (51.9)
Noninvasive	99 (48.1)
IPPV	16 (7.8)
CPAP	78 (37.9)
BIPAP	5 (2.4)
O_2 saturation, %, mean (SD)	89.7 (5.7)

Abbreviations: BIPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; IPPV, intermittent positive pressure ventilation; NICU, neonatal intensive care unit; SD, standard deviation; SNIPPV, synchronized nasal intermittent positive pressure ventilation.

values in infants in the >32-week group were found (►**Table 2**). The median time between birth and the administration of surfactant was 210 minutes (IQR: 60–497 minutes). The median time was significantly shorter for infants in the 23 to 28 gestational weeks as compared with those in the 29 to 32 and > 32 weeks ($p < 0.0001$) (►**Table 2**).

A total of 202 (98.1%) infants were treated with poractant alfa and the remaining 4 (1.9%) with beractant. Regarding the administration methods, ETT was used in 94.7% of the patients and LISA in only 5.3%. In the ETT group, the INSURE method (extubating in <1 hour) was used in 36.4% of babies and the remaining 63.6% were extubated for >1 hour after surfactant administration. Extubation > 1 hour was significantly more frequent in the 23- to 28-week group (74.8%) as compared with the 29- to 32-week (47.1%) and >32-week groups (48.3%) ($p = 0.0005$).

In relation to the primary objective of the study, the mean initial dose of poractant alfa was 173.9 (37.3) mg/kg (median: 186.2; IQR: 149.1–200 mg/kg). As shown in ►**Fig. 1**, there were differences in the doses of surfactant according to gestational age, with lower doses among infants in the >32-week group ($p < 0.001$). A total of 47.5% of infants received an initial surfactant dose of 200 mg/kg ± 10% (180–220 mg/kg), 47% received doses < 180 mg/kg (–10%), and 5.4% received doses > 220 mg/kg (+ 10%). Differences according to gestational age were also observed, with a significantly higher percentage of infants in the >32-week group treated with <180 mg/kg as compared with the 29- to 32-week and 23- to 28-week groups ($p = 0.006$) (►**Table 3**). Mean doses of surfactant administered according to birth weight are shown in ►**Fig. 2**.

The need of increasing respiratory support after surfactant therapy occurred in 18.4% of patients, with mechanical ventilation, intermittent positive pressure ventilation, and synchronized nasal intermittent positive pressure ventilation being the most commonly used rescue ventilation modes.

Redosing was needed in 57 patients (59 redosings) due to persistent high oxygen requirements in 86.2% of the cases. The median time between the initial dose and the first redosing was 16.3 hours (IQR: 10.5–27), and the total mean dose of surfactant retreatment was 121.2 (36.9) mg/kg. Need for intubation within the first 72 hours after surfactant administration was recorded in 27 (13.1%) patients.

A total of 168 (81.6%) patients were treated with caffeine citrate, 134 (79.8%) of them for the prophylaxis of apnea and 33 (19.6%) for the treatment of apnea.

Among all patients treated with at least one dose of surfactant, only one case of transient bradycardia (93 beats/minute) and oxygen desaturation (82%) possibly related to treatment was recorded.

Discussion

This study performed in routine daily practice provides evidence of administration of surfactant doses below the recommendations for treating babies with RDS. The mean first dose of poractant alfa was 173.9 (37.3) mg/kg, which is 13.5% lower than the theoretically prescribed and recommended dose of 200 mg/kg. Interestingly, we found statistically significant

Table 2 FiO_2 values and time from birth until the administration of surfactant in the overall study population and according to gestational age

	All patients ($n = 206$)	Gestational age			*p*-Value
		23–28 wk ($n = 120$)	29–32 wk ($n = 56$)	> 32 wk ($n = 30$)	
FiO_2, %					
Mean (SD)	0.47 (0.18)	0.47 (0.18)	0.44 (0.18)	0.52 (0.21)	0.137
Median (IQR)	0.40 (0.34–0.50)	0.40 (0.35–0.50)	0.40 (0.31–0.50)	0.47 (0.39–0.60)	
Time from birth to use of surfactant, minutes					
Mean (SD)	416.1 (566.6)	219.1 (322.9)	566.1 (594.4)	924.3 (873.1)	<0.001
Median (IQR)	210 (60–497)	100 (30–272)	301.5 (196–837)	669 (285–144)	

Abbreviations: IQR, interquartile range; SD, standard deviation.

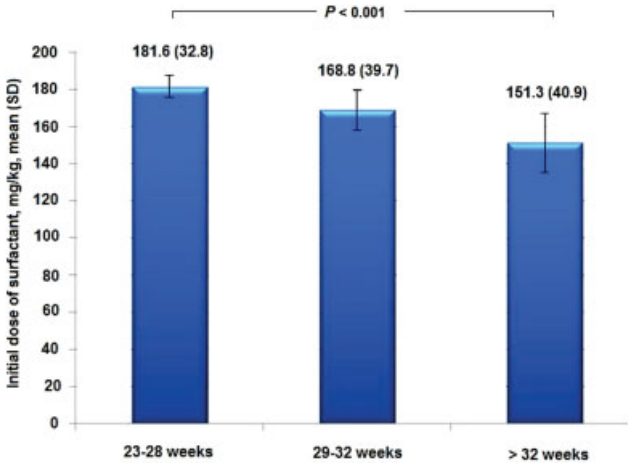

Fig. 1 Initial doses of surfactant (mg/kg) according to the gestational age.

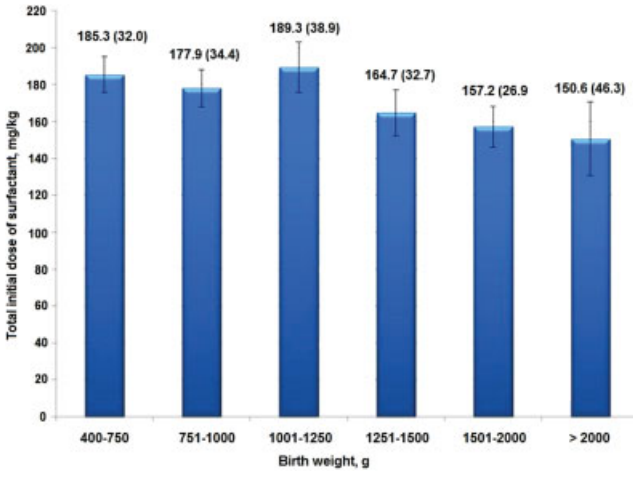

Fig. 2 Initial doses of surfactant (mg/kg) according to birth weight.

Table 3 Initial doses of surfactant in the overall study population and according to gestational age

Surfactant doses	All patients ($n = 202$)	Gestational age			*p*-Value
		23–28 wk ($n = 118$)	29–32 wk ($n = 56$)	>32 wk ($n = 28$)	
Median dose, mg/kg	186.2	190.1	171.1	166.4	
Target 200 ± 10%, mg/kg					0.026
>220	11 (5.4)	9 (7.6)	2 (3.6)	0	0.271
180–220	96 (47.5)	64 (54.2)	23 (41.1)	9 (32.1)	0.057
<180	95 (47)	45 (38.1)	31 (55.4)	19 (67.9	0.006
Mean (SD) dose, mg/kg					
>220	239 (22.9)				<0.001
180–220	197.7 (8.1)				
<180	142.2 (27.5)				

Abbreviation: SD, standard deviation.

differences in the doses of surfactant administered to patients among the three gestational age groups. In this respect, infants of lower gestational age at birth received higher initial doses of surfactant than infants of a more advanced gestational age, but in all cases, doses were below those prescribed. Extremely preterm infants (< 28 weeks) received a mean dose of 181.6 mg/kg, which was 9.2% below the recommended dose of 200 mg/kg. Infants of 29 to 32 weeks' gestational age and those >32 weeks' gestational age were given mean doses of 168.2 and 151.3 mg/kg, respectively, which were 15.9 and

24.3% inferior to the target dose. A further analysis according to the distribution of initial surfactant doses by percentiles was consistent with these findings.

Globally, 47.5% of infants received doses of surfactant $<$ 180 mg/kg (below the $\pm$ 10%) and were considered to be undertreated. Considering a median dose of 186.2 mg/kg, 38.1% of extremely preterm babies were undertreated ($<$180 mg/kg) as compared with 67.9% of moderate-late preterm babies. Also, overtreatment ($>$220 mg/kg) was more frequent in extremely preterm than in late preterm infants (37.6% versus 0%). Therefore, surfactant doses above or below the recommendations showed a clear relationship with gestational age.

The problem of inappropriateness of surfactant dosing for preterm neonates with RDS has been addressed in two previous studies only, both of which have drawn attention to the urgent need of making clinicians aware of errors in surfactant administration.[16,17] In a retrospective population-based cohort study of 455 infants, 25.4% were undertreated and 24.8% overtreated, with a tendency to overtreat extremely preterm and extremely low birth weight neonates and a trend to undertreat neonates $>$ 28 weeks' gestation, which, in turn, were more often subjected to surfactant redosing.[16] In a retrospective study of 119 infants with a median gestational age of 30 weeks and birth weight of 1,300 g, 51.2% received a dose lower than 150 mg/kg (mean dose 145.8 mg/kg), with rounding down as the most plausible explanation.[17] Also, in a retrospective analysis of 987 infants with a median gestational age of 29 weeks and birth weight of 1,190 g, the median first dose was 170 mg/kg, with 79.8%, 19.1, and 1.1% requiring one, two, and three doses, respectively.[18] In this study, 47.5% of infants received a dose of 200 mg/kg $\pm$ 10%, and the dose was lower than 180 mg/kg in 47% of patients. Dose rounding due to vial optimization to minimize costs has been suggested as a possible reason for inappropriate surfactant dosing.[16,17] In a European survey of surfactant replacement therapy in 338 preterm infants with a median gestational age of 27 weeks and birth weight of 860 g, the median first dose of poractant alfa was 168 mg/kg.[20] Moreover, in a Polish survey of 987 infants from 53 NICUs, the median first dose was 170 mg/kg,[18] also lower than the recommended 200 mg/kg dose.

In our study, when total mean doses were compared in the different birth weight groups, greater decreases were observed in the 1,251 to 1,500, 1,501 to 2,000, and $>$2,000 g groups for which more than one vial content of poractant alfa (Curosurf) should be used since the product is presented in 1.5- or 3-mL vials. However, the fact that 54.2% of neonates in the 23- to 28-week group received a dose of 200 mg/kg $\pm$ 10% as compared with 41.1% in the 29- to 32-week group and 32.1% in the $>$32-week group may also reflect greater concern for the clinical care of very premature infants. On the other hand, the time elapsed from birth to the administration of surfactant was significantly shorter in the 22- to 28-week group than in older infants. In a randomized, masked comparison trial of preterm infants ($n = 293$) with RDS treated with an initial dose of either 100 ($n = 96$) or 200 ($n = 99$) mg/kg of poractant alfa or 100 ($n = 98$) mg/kg of beractant, need of redosing was significantly lower in infants treated with an initial dose of 200 mg/kg.[6] Other outcomes including mortality up to 36 weeks in neonates born at $\leq$32 weeks were also significantly lower in the 200 mg/kg group as compared with 100 mg/kg of poractant alfa or 100 mg/kg of beractant.[6] Moreover, in a systematic review and meta-analysis of five randomized controlled trials involving 529 infants in which poractant alfa versus beractant for rescue treatment was compared, infants treated with poractant alfa at 100 mg/kg (low dose) or 200 mg/kg (high dose) exhibited statistically significant reductions in deaths, the need for redosing, oxygen requirements, duration of oxygen treatment, and duration of mechanical ventilation.[21] Further studies are needed to determine if treatment with surfactant doses below the recommendations, as seen in our study, is associated with worse respiratory outcomes.

A relevant finding of this study was an actual FiO_2 mean value of 0.47 before surfactant therapy, surprisingly higher than the recommended FiO_2 threshold level of 0.30 to 0.40 depending on gestational age.[12] Differences in FiO_2 values according to gestational age were observed, with higher levels in the $>$32-week group, although differences were not statistically significant. Also, CPAP was the most frequent noninvasive ventilation method (78.8%). However, noninvasive ventilation was associated with a higher percentage of ventilatory failure. In these cases, mechanical ventilation was the rescue ventilatory support most frequently used when CPAP failed and intubation within 72 hours of birth was required. In a study of CPAP failure in Australian and New Zealand Neonatal Network data from 2007 to 2013 in a cohort of 11,684 babies initially managed on CPAP only, failure was recorded in 43% of infants commencing on CPAP at 25 to 28 weeks' gestation and in 21% at 29 to 32 weeks.[13] CPAP failure was associated with a substantially higher rate of pneumothorax, and a heightened risk of death, BPD, and other morbidities compared with those managed successfully on CPAP.[13]

Results of this study should be interpreted taking into account some limitations, including variability of clinical practice among the participating NICUs, the retrospective design of the study based on data collected from medical records, and results obtained for the use of poractant alfa. Poractant alfa is the most common surfactant in Europe and was the main compound used and analyzed in this study.

In conclusion, underdosing of poractant alfa is an apparently inadvertent error in surfactant administration at the bedside. Preterm babies diagnosed with RDS requiring surfactant therapy may be at a risk of undertreatment. Specific actions to avoid unintentional underdosage of surfactant are urgently needed.

Authors' Contributions

The principal investigator H. B. had full access to the data in the study and takes responsibility for the integrity and accuracy of the data analysis. H. B. was responsible for the original conception and design of the study and drafted the final version of the manuscript. Coauthors S. R., M. D. E., and L. A. assisted in the implementation of the project, critical review of the manuscript at each step, and all data analysis, and participated in the manuscript approval of the final draft.

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Conflict of Interest
H.B. is a consultant of Chiesi España, S.A.U. L.A. has participated as a speaker in clinical workshops sponsored by Chiesi España, S.A.U. The remaining authors have no conflicts of interest to be disclosed.

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