Original Paper

Neonatology

Neonatology 2011;100:71–77
DOI: 10.1159/000322004

Received: July 6, 2010
Accepted after revision: October 3, 2010
Published online: January 11, 2011

Surfactant Replacement Therapy in Preterm Infants: A European Survey

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source: https://doi.org/10.48350/8422 | downloaded: 12.10.2024

Key Words
Surfactant · Preterm infant · Mechanical ventilation · Best practice guidelines

Abstract
Background: Exogenous surfactant is an undisputed treatment for neonatal respiratory distress syndrome but its efficacy is highly dependent on the treatment strategy. International guidelines have published recommendations on the optimal surfactant replacement strategy. ***Objective:*** To determine how evidence-based guidelines on surfactant replacement therapy are implemented in daily clinical practice. ***Methods:*** Data on surfactant replacement therapy, including preparation, dosing and timing, were collected in 173 European neonatal intensive care units (NICUs) by questionnaire and in a cohort of preterm infants mechanically ventilated on two separate predefined dates in these units. ***Results:*** All NICUs used animal-derived surfactant in the treatment of respiratory distress syndrome, with Poractant being most widely used (86%). The most frequently used first dose was 100 mg/kg (58%) and 200 mg/kg (39%) and all NICUs allowed for repeat dosing. 39% of the NICUs claimed to use prophylactic treatment (<15 min of life). Data on surfactant treatment were collected in 338 infants, with a median gestational age of 27 weeks and a birth weight of 860 g. All infants were treated with animal-derived surfactant. The median first dose was 168 mg/kg in the Poractant group compared with 100 mg/kg in the Beractant and Bovactant groups. Prophylactic treatment was used in 23% of the infants and 28% of the infants received surfactant >2 h after birth. 43% of the infants received multiple doses. ***Conclusions:*** With the exception of surfactant timing, guidelines on surfactant replacement therapy seem to be implemented in daily clinical practice in European NICUs.

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Introduction

Exogenous surfactant is an undisputed treatment for neonatal respiratory distress syndrome (RDS) that optimizes gas exchange, reduces the risk of air leaks and, most importantly, reduces mortality [1]. However, the efficacy of exogenous surfactant is highly dependent on the treatment strategy, including timing of administration,

Participating centers of the European study on neonatal respiratory care are listed in the Appendix.

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1661–7800/11/1001–0071$38.00/0

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Table 1. Participating countries and centers

Country	Number of centers
Austria	5
Belgium	9
Czech Republic	4
Denmark	2
Finland	2
France	10
Germany	36
Greece	8
Ireland	1
Italy	21
Lithuania	2
Netherlands	10
Norway	9
Portugal	14
Romania	6
Serbia Montenegro	1
Slovenia	1
Spain	3
Sweden	9
Switzerland	6
United Kingdom	14
Total	173

the surfactant preparation, and the dosage regimen [2–5]. International guidelines have summarized the available evidence from randomized controlled trials on surfactant therapy and published recommendations on the optimal surfactant replacement strategy [6–8].

The basic idea is that these guidelines assist the clinician in determining best practices and to promote clinical implementation of the available evidence on surfactant replacement therapy. However, studies investigating surfactant treatment practices in preterm infants are scarce and it is therefore unknown if and how the guidelines on surfactant treatment have been translated into routine practice.

To improve our knowledge on current surfactant policies, we performed an international survey in 173 European neonatal intensive care units (NICUs).

Methods

Between April 2007 and May 2008, we performed a collaborative study on respiratory care of newborn infants in 21 European countries. Using personal contacts in the different European countries we were able to retrieve the contact information of 440 NICUs. For 96 NICUs the contact information proved to be incorrect and from the remaining 344 NICUs, 268 replied of which 208 agreed to participate. A total of 35 NICUs failed to respond to additional e-mails, leaving a total of 173 NICUs that participated in this study (table 1). As part of this study we collected data on surfactant treatment practices by asking each participating NICU to complete a questionnaire on local surfactant policies. In addition, each NICU was asked to collect data on surfactant treatment in all patients that were endotracheally ventilated at any time point between 09:00 and 16:00 h on two predefined dates. These dates were determined by one of the principle investigators (A.H.v.K.) and set per country. Each date was communicated to a local investigator several weeks in advance and, if data collection was not feasible, a new date was set as close as possible to the predefined national date. Only the preterm infants (<37 weeks' gestation) from this cohort were included in the present study. The study protocol was reviewed by the institutional review board of each hospital. All patient data were collected anonymously.

Surfactant Policies

We collected the following information on surfactant policies: surfactant preparations used in the unit, the use of prophylactic treatment including the criteria, the use of rescue treatment including the criteria, the amount of surfactant administered during the first dose and the repeat doses, and the number of repeat doses. We defined prophylactic treatment as endotracheal intubation and subsequent surfactant administration independent of the respiratory condition. Rescue surfactant treatment was defined as endotracheal intubation and subsequent administration of exogenous surfactant in infants with established RDS based on clinical signs and/or chest radiograph.

Patient Data on Surfactant Use

We collected the following data on surfactant use in preterm infants: the number of surfactant doses and for each dose the timing of administration, the actual dose and the surfactant preparation.

Demographic Data

In addition to the surfactant data, we also collected patient and hospital characteristics including level of neonatal care, number of neonatal intensive care beds, average bed occupancy, yearly average of endotracheally ventilated patients with a corrected age of <30 days, and the percentage of doctors with official neonatology training or >5 years working experience in a NICU.

Data Collection and Statistical Analysis

The local investigator completed the questionnaire on surfactant policies via a secured website specially designed for the study. Patient data were collected on a case record form and thereafter entered on the website. Instructions on data collection and the use of the web-based database were sent to the investigators personally by e-mail and they were available on the website. Two of the principal investigators checked the database for inconsistencies and missing data. If necessary the local investigator was contacted in an attempt to correct or complete the data.

Data are presented as median with interquartile ranges (IQR) and analyzed using the Wilcoxon signed ranks test. A p value <0.05 was considered significant.

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Table 2. Hospital characteristics

Neonatal intensive care units, n	173
Level 2, n (%)	21 (12)
Level 3, n (%)	152 (88)
Number of intensive care beds, n (%)	
<10	19 (11)
10–20	60 (35)
>20	94 (54)
Average bed occupancy, % (IQR)	85 (75–92)
Doctors with neonatal training, % (IQR)	80 (55–100)
Ventilated patients per year, n (%)[a]	
<50	30 (18)
50–100[a]	70 (40)
>100	73 (42)

IQR = Interquartile range.
[a] n = 172, 1 neonatal intensive care unit recently opened.

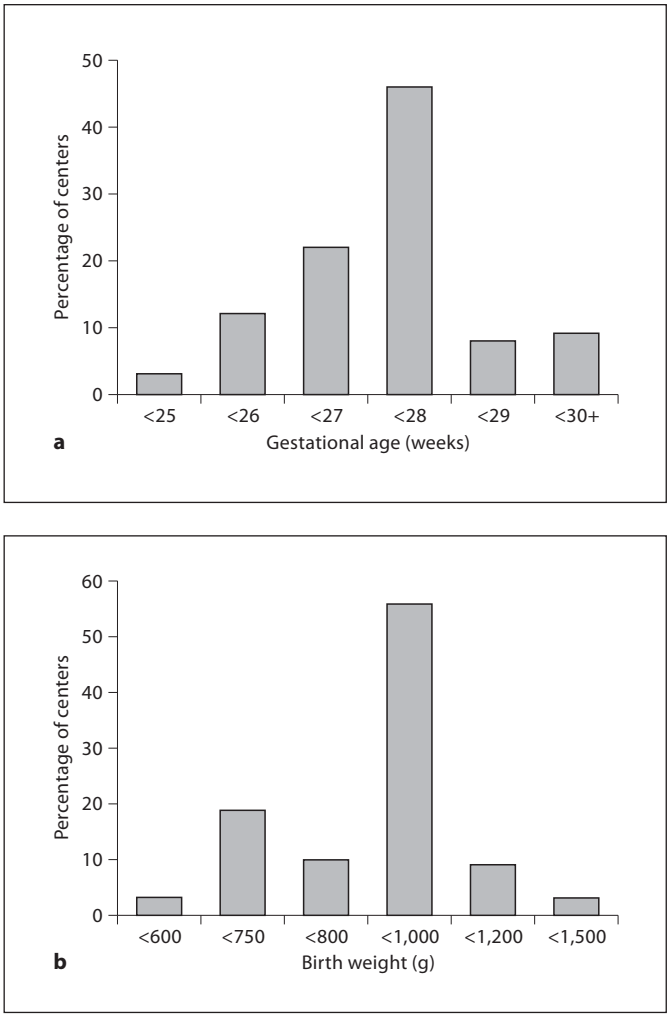

Fig. 1. Distribution of gestational age (**a**) and birth weight (**b**) criteria for prophylactic surfactant treatment in the 173 European NICUs.

Results

Table 2 shows the characteristics of the 173 NICUs that participated in this study.

Surfactant Policies

All but 2 NICUs used exogenous surfactant in the treatment of RDS. 134 (78%) of the NICUs used one surfactant preparation, 34 (20%) two, and 3 (2%) more than two preparations. Poractant was used in 148 (86%), Beractant in 41 (24%) and Bovactant in 25 (15%) of the NICUs.

Prophylactic surfactant treatment was used in 67 (39%) of the NICUs. Gestational age and birth weight were the criteria used to select patients for prophylactic treatment (fig. 1). In 17 additional NICUs, preterm infants were treated with exogenous surfactant in the delivery room if they had a gestational age of ≤28 weeks and showed clinical signs of RDS or needed intubation for other reasons.

In 150 NICUs (88%) the FiO_2 was used as the indicator for rescue surfactant treatment. The median FiO_2 above which surfactant was administered was 0.40 (IQR 0.35–0.40). In many NICUs the FiO_2 was combined with other variables, such as mean airway pressure (36%), signs of RDS on the chest radiograph (15%), the product of FiO_2 and mean airway pressure (12%) and oxygenation index (9%).

The most frequently used first surfactant dose was either 100 mg/kg (58%) or 200 mg/kg (39%). The 200-mg/kg dose was only administered when using Poractant.

In respectively 27, 54, 13 and 5% of the NICUs, preterm infants were allowed to receive 1, 2, 3 or 4 repeat surfactant doses. In 43% of the NICUs the repeat doses were different from the first dose, with the most common doses being 50 mg/kg (22%) and 100 mg/kg (75%).

Patient Data

A total of 460 preterm infants were endotracheally ventilated on the two dates and 338 (73%) were treated with exogenous surfactant. The median gestational age and birth weight of these infants was, respectively, 27.0 weeks (IQR 25.3–29.0) and 860 g (IQR 700–1,200).

In 77 (23%) of the infants, surfactant was administered prophylactically (<15 min after birth) and this subgroup

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had a median gestational age of 25.6 weeks (IQR 24.3–27.4) and a median birth weight 750 g (IQR 625–910). The percentage of infants with a gestational age <28 weeks or a birth weight <1.000 g who received prophylactic treatment was 24% in both subgroups.

In 261 (77%) infants, surfactant was administered after 15 min of life, with a median time of 120 min (IQR 60–240). The median gestational age and birth weight in this subgroup was, respectively, 27.4 weeks (IQR 25.9–29.6) and 900 g (IQR 730–1300). In 95 (28%) of the infants, surfactant was administered >2 h after birth.

Poractant was used in 259 (77%) infants, Beractant in 63 (18%) and Bovactant in 16 (5%) and the median first dose for each of these preparations was, respectively, 168 (131–197), 100 (98–106), and 100 (84–119) mg/kg.

A second dose was administered in 145 (43%) of the infants at a median age of 17 h (IQR 11–27). Infants treated with Poractant as a first dose needed a second dose in 42% of the cases. The median second dose of Poractant was lower (125 mg/kg) compared with the first dose. Infants initially treated with Beractant needed a second dose in 41% of the case and the median second dose (100 mg/kg) was comparable with the first dose. A second dose of Bovactant was needed in 63% of the infants receiving this same preparation as their first dose. The median second dose (63 mg/kg) tended to be lower compared with the first dose. The timing of the second dose was comparable in all three surfactant preparations. Only 36 (11%) of the infants received more than two surfactant doses.

Discussion

This report describes surfactant treatment practices in a large number of NICUs all across Europe. The data on which this report is based were obtained via a questionnaire and from a cohort of ventilated preterm patients, allowing us to assess how the surfactant policies were applied in daily clinical practice.

Based on studies showing an improved efficacy of prophylactic versus (late) rescue surfactant treatment [2], international guidelines have recommended to use or at least consider prophylactic treatment for extremely preterm infants (<27 weeks) [6–8]. The present study shows that prophylactic treatment is used in 39% of the European NICUs. Most of these NICUs used prophylactic surfactant treatment in patients with a gestational age <28 weeks or a birth weight <1,000 g. Data obtained from the patient cohort showed that 23% of the preterm infants received their first surfactant dose within the first 15 min after birth, a time point often used to define prophylactic surfactant treatment [8]. Consistent with the surfactant policies, the IQRs of gestational age and birth weight in this subgroup indicated that prophylactic treatment was mainly reserved for the extremely preterm infants.

Randomized studies have also shown that early rescue treatment is superior to late surfactant treatment [3]. Guidelines have therefore stated that preterm infants with established RDS should be treated as soon as possible, preferably within 2 h, after birth [6–8]. The majority of NICUs in the present study used the FiO_2 as the main determinant to define established RDS, often combined with other variables. The patient analysis showed that the first rescue dose was administered after a median time of 2 h after birth. The proportion of infants receiving the first surfactant dose >2 h after birth was 28%.

Horbar et al. [9] studied the timing of surfactant treatment in a large cohort of preterm infants (23–29 weeks) born between 1998 and 2000 in the United States or Canada. They reported a median time of surfactant treatment of 50 min, prophylactic surfactant treatment in 27% of the infants, and a proportion of 21% of infants receiving their first surfactant dose >2 h after birth. These results are strikingly similar to findings of the present study, suggesting that the timing of surfactant treatment has not much changed over time and is quite similar across continents.

Due to limitations in the available evidence, the surfactant guidelines are much less firm and consistent in their recommendations on what surfactant preparations should be used and what is the optimal dosage regimen [6–8]. Most of the guidelines recommend the use of animal-derived surfactants because there is sufficient evidence that these preparations are superior to first-generation protein-free synthetic surfactants in reducing air leaks and mortality in preterm infants with RDS [4]. The present study shows that European NICUs only use animal-derived surfactants and that Poractant is the most widely used product. Of note, synthetic surfactants are no longer widely available in Europe.

Most NICUs used either 100 or 200 mg/kg as the first surfactant dose. The fact that 200 mg/kg was only used in combination with Poractant seems to suggest that the decision to use a high surfactant dose is mainly based on the recommendations issued by the manufacturer. Most NICUs allow for multiple dosing but often used a repeat surfactant dose lower than the first dose. The data obtained from surfactant-treated patients were consistent with these surfactant policies, showing the median first

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dose was highest in those infants treated with Poractant. Almost half of the patients received a second dose and this proportion was not different between the two most frequently used preparations, i.e. Poractant and Beractant. As expected and in accordance with the recommendations, the second dose of Poractant was lower than the first dose. Only 10% of the surfactant-treated infants required more than two doses.

This study has some limitations. First, this study only included NICUs situated in Europe. Some of the results may be different when analyzing surfactant practices in other parts of the world. Second, patient inclusion was based on the need for invasive mechanical ventilation and not on the need for surfactant treatment. This means that not all surfactant-treated infants were included in the patient cohort and this might explain some of the small discrepancies between the surfactant policies and the actual practices. Finally, the survey did not collect data on the use of the InSurE policy. During this procedure, preterm infants are briefly intubated for surfactant administration and thereafter immediately extubated [10].

Despite these limitations this study provides, for the first time, valuable information on how recommendations from international guidelines on surfactant replacement therapy are implemented in daily practices. It shows that, in contrast to the surfactant preparation and dosing, the timing of surfactant treatment differs considerably from the recommendations in the guidelines, with only 29% of the NICUs using prophylactic surfactant treatment and 28% of the patients treated with late rescue surfactant. There may be several reasons for these observed differences. First, most of the studies on surfactant timing were conducted in the 1980s when the use of antenatal steroids was much lower than today. Considering the fact that antenatal steroids have a profound effect on RDS severity, it might well be that clinicians are less convinced of a clinically relevant treatment effect of prophylactic surfactant administration. Secondly, until recently there were no trials comparing prophylactic to early rescue surfactant treatment [11]. Being in equipoise, clinicians may have opted for early rescue treatment once RDS had been established, thereby reducing unnecessary treatment with surfactant. Finally, there has been a growing interest and use of early nasal continuous positive airway pressure in the delivery room, thereby avoiding intubation and mechanical ventilation. As shown by a recent study, this approach leads to less and later surfactant treatment [12].

In conclusion, the present study shows that, consistent with international guidelines, most NICUs in Europe use animal-derived surfactant products in a dose of either 100 or 200 mg/kg, allowing for multiple doses. However, the recommended use of prophylactic surfactant treatment in extremely preterm infants has been adopted in only 39% of the NICUs and 28% of the patients receive rescue treatment >2 h after birth.

Acknowledgement

We would like to thank J.W. Theeuwes for database construction and management.

Disclosure Statement

The authors have no potential conflict of interests to declare.

Appendix

The following hospitals and investigators participated in the European study on neonatal respiratory care: University Hospital Gasthuisberg, Leuven, Belgium: A. Debeer; Centre de Pédiatrie Gatien de Clocheville, Tours, France: A. Chemin, K. Norbert; Institut de Puériculture, Paris, France: F. Autret; Ipokratio, Kalamaria, Greece: A. Andreou; Erasmus MC-Sophia Children's Hospital, Rotterdam, Netherlands: A. Kroon; Mother and Child Health Institute, Belgrade, Serbia: A. Minić; University Hospital Vienna, Vienna, Austria: J. Schwindt; University Medical Center Utrecht, Wilhelmina Children's Hospital, Utrecht, Netherlands: H. Brouwers; Antwerp University Hospital, Antwerp, Belgium: P. van Reempts; Children's Hospital University of Ulm, Ulm, Germany: H. Hummler; Emma Children's Hospital, Academic Medical Center, Amsterdam, Netherlands: M. van Veenendaal; Hipokration General Hospital, Thessaloniki, Greece: K. Sarafidis; Leiden University Medical Centre, Leiden, Netherlands: E. Lopriore; Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Milan, Italy: F. Mosca; The John Radcliffe, Oxford, UK: K. McCormick; Universitätsklinikum Mannheim, Mannheim, Germany: T. Schaible; University Medical Center Groningen, Groningen, Netherlands: A. Jaarsma; Bambino Gesù Chidren's Hospital, Rome, Italy: V. Polimeni; General Faculty Hospital Prague, Prague, Czech Republic: R. Plavka, L. Pazderova; Groupe Hospitalier Cochin – Saint Vincent de Paul, Paris, France: J. Patkai, G. Moriette; Hospital de Cruces, Barakaldo, Spain: A. Valls I Soler; Norfolk & Norwich University Hospital, Norwich, UK: P. Clarke; Ospedale Spedali Civili, Brescia, Italy: C. Migliori; Universitätsklinikum Freiburg, Freiburg, Germany: R. Hentschel; University General Hospital, Alexandroupolis, Greece: J. Sigalas; Asklepios Klinik St. Augustin, Sankt Augustin, Germany: M. Ehlen, C. Fremerey; Centre Hospitalier Régional d'Orléans, Orleans, France: M. Roujou-Gris; Clinical Hospital of Obstetrics and Gynecology 'Cuza-Voda', Lasi, Romania: M. Stamatin; Great Ormond Street Hospital, London, UK: Q. Mok; Marienhospital

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