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Management of neonatal respiratory distress syndrome by minimally invasive administration of surfactant: impact on the rate of infants treated with surfactant and evolution of practices, an observational study at the Montpellier University Hospital

Diane Gillot

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UNIVERSITÉ DE MONTPELLIER
FACULTÉ DE MÉDECINE MONTPELLIER-NIMES

THÈSE

Pour obtenir le titre de
DOCTEUR EN MÉDECINE

Présentée et soutenue publiquement
Par
Diane GILLOT

Le 30 septembre 2022

TITRE :

Prise en charge de la détresse respiratoire néonatale par administration mini-invasive de surfactant : impact sur le taux de recours au surfactant et évolution des pratiques, étude observationnelle au CHU de Montpellier

Directeur de thèse : Professeur Gilles CAMBONIE

JURY

Président : Professeur Gilles CAMBONIE

Assesseurs :

Docteur Christophe MILESI

Docteur Marie-Catherine RENOUX

Membre invité : Docteur Gaelle DE BARRY

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ABBREVIATIONS

BPD : bronchopulmonary dysplasia
BMI: body mass index (kg/m²)
CNGOF: college national des gynécologues et obstétriciens français
CMV: conventional mechanical ventilation
(n)CPAP: (nasal) continuous positive airway pressure
InSuRe: intubation, surfactant, extubation
IUGR: intra uterine growth restriction
IV: invasive ventilation
IVH: intraventricular hemorrhage
LISA: less invasive surfactant administration
LUS: lung ultrasound
MIST: minimally invasive surfactant therapy
MV: mechanical ventilation
NEC: necrotizing enterocolitis
NICU: neonatal intensive care unit
NIV: noninvasive ventilation
NO: nitric oxide
PDA: patent ductus arteriosus
PVL: periventricular leukomalacia
RDS: respiratory distress syndrome
TTN: transient tachypnea of the newborn
wGA: weeks gestational age

INTRODUCTION

The Respiratory Distress Syndrome (RDS) caused by surfactant deficiency is a common complication of premature birth that requires appropriate care to avoid early mortality and long-term morbidity. The current strategy to avoid severe RDS and its complications combines three key elements: prenatal administration of corticosteroids, early noninvasive respiratory support and early rescue surfactant administration. (1) The management of RDS influences the risk of developing Bronchopulmonary Dysplasia (BPD), which is the main respiratory complication of very premature birth. It is a chronic lung disease which results from an imbalance between lung injury and repair in the developing lung. BPD is strongly associated with the risk of developmental delay. (2)(3)

Surfactant administration reduces occurrence of pneumothoraces and decreases the risk of neonatal mortality and BPD. (4) For many years, surfactant administration required endotracheal intubation and invasive ventilation. The mechanical aggression of the lungs caused by invasive ventilation leads to an inflammatory response, resulting in an increased risk of BPD. (5) The InSuRe procedure (Intubate-Surfactant-Extubate) used to be the standard method to shorten the duration of mechanical ventilation. It consists in administering surfactant through an endotracheal tube with a brief duration of mechanical ventilation. However, it is still unclear if it can lead to pulmonary damages, and a significant proportion of neonates fails to be weaned off invasive ventilation after this procedure. (6)

During the last decade, a different method has become popular: Less Invasive Surfactant Administration (LISA), which consists in administering surfactant through a thin intratracheal catheter positioned by laryngoscopy in spontaneously breathing infants under nasal continuous positive airway pressure (nCPAP). This procedure has shown its superiority to methods requiring endotracheal intubation in preventing need for mechanical ventilation and reducing risks of BPD and in-hospital death, either compared with sustained or brief invasive ventilation or with CPAP alone. (7)(8) Besides its respiratory benefits, it also seems to decrease the risk of severe intraventricular hemorrhage (IVH). (9)

Most of the guidelines regarding the management of RDS are focused on very preterm infants, born before 32 weeks of gestational age (wGA). (1) RDS affects 80% of the infants born before 28 wGA and the risk of severe BPD remains high in this population, affecting up to 26% of the infants born between 23 and 26 wGA. (10) Therefore, surfactant treatment and the need to avoid lung aggression with invasive ventilation are clearly benefic in this population. (4) (5) On the other hand, risks of both RDS and BPD greatly decrease with gestational age: RDS affects only 10% of the infants born at 34 wGA and chronic lung disease is exceptional in the population of late preterm infants. (11)(10) Therefore, even though moderate and late preterm infants (born between 32 and 36⁺⁶ wGA) account for more than 80% of all premature births, the use of noninvasive ventilation and administration of surfactant is less defined in this population. (12)

A protocol for the administration of surfactant by the LISA method was implemented in our department in 2017. This mode of administration exempts from intubation followed by mechanical ventilation and is easy to perform. We asked ourselves whether the simplification of this procedure could have induced a drift of the practices resulting in a more frequent use of

surfactant in the treatment of RDS. We especially wanted to study changes in practices for the population of neonates born after 32 wGA, for the reasons mentioned above.

To explore this issue, we conducted a monocentric observational cohort study, comparing two distinct periods of 3 years, before and after the implementation of this protocol. Our main objective was to compare the percentage of infants treated with surfactant between these two periods. Our secondary objectives were to compare surfactant administration details, respiratory morbidity and other major neonatal complications between the two periods. We planned to perform all the analysis in the whole population and in three different subgroups of gestational age.

METHODS

This is a monocentric, retrospective, observational cohort study conducted in the NICU of the tertiary perinatal hospital of Montpellier, France.

1. Population studied

Live born neonates at 23⁺⁰ to 36⁺⁶ inborn in our hospital between 01/01/2013 and 12/31/2015 and between 01/01/2019 and 12/31/2021 and admitted to the NICU were eligible for inclusion. We included infants admitted to 3 different units: the neonatal intensive care units (type 3 and 2b beds) and the pediatric intensive care unit.

Exclusion criteria were the presence of major congenital malformations, chromosomal disorders, inherited metabolic diseases or other congenital diseases suggesting rapid post-natal death, and the absence of medical record.

2. Study objectives

The main objective of the study was to compare the rate of infants treated with surfactant before and after the implementation of less invasive surfactant administration.

LISA was introduced in our center from January 2016 and a written protocol was established in October 2017. To assure sufficient wash out, we recorded data from 2 distinct periods of 3 years: 2013-2015, during which we assumed most neonates received surfactant via an endotracheal tube with mechanical ventilation and 2019-2021, during which we assumed most of them received surfactant via a thin catheter without mechanical ventilation.

3. Data collection

Data was collected prospectively by clinicians in a database created in 2003 for neonates born before 33 weeks GA and/or with a birthweight lower than 1500g. The database uses a predetermined form, with detailed definition of each item. For neonates born between 33 and 36⁺⁶ wGA and with a birthweight of 1500g or more, we obtained data from the hospital reports and used a modified version of the same predetermined form. Specific details regarding surfactant administration were searched for in the patients' electronic records for all gestational ages.

Data collected included demographics, prenatal characteristics, labor and delivery information, maternal obstetric and neonatal outcomes, and data from neonatal intensive care units until discharge or death.

Maternal data included height and weight, body mass index (BMI), order of pregnancy, chorionicity, maternal medical disorders (pregnancy related hypertension defined as preeclampsia, eclampsia, gestational hypertension or chronic hypertension with superimposed preeclampsia; preexisting diabetes, gestational diabetes, chorioamnionitis), obstetrical complications, labor and delivery details. Prenatal corticosteroid use was recorded as followed: inexistant, complete and optimal (2 doses administered more than 24 hours and maximum 10 days before delivery), complete but out of date (if the last dose was administered more than 10

days before delivery), incomplete (1 dose or 2 doses with the last dose administered less than 24 hours before delivery). (13)

Neonatal data included gestational age, birth weight, sex, Apgar score, arterial blood lactate at the umbilical cord, temperature and glycemia at admission to the NICU. Intra uterine growth restriction was defined as birth weight Z score <-2DS as described by Olsen et al, and macrosomia as birth weight Z score >2DS. (14)

We recorded the number of infants treated with surfactant during the two periods and the following data for each infant: type of procedure, minute of life at which the surfactant was given, maximal inspired fraction of oxygen before surfactant administration, number of surfactant doses given per infant, use of sedation. We distinguished 3 types of procedure : (i) surfactant given via an endotracheal tube during mechanical ventilation, designated in this study as conventional administration, (ii) surfactant given via an endotracheal tube with a duration of mechanical ventilation of less than an hour, called InSuRe and (iii) surfactant given to spontaneously breathing infants on CPAP via a thin catheter placed in the trachea only for the time needed to give surfactant, called Less Invasive Surfactant Administration (LISA).

The local protocol for the administration of surfactant by the LISA method recommends the administration of a dose of 200mg/kg of Poractant alfa (CUROSURF®, Chiesi) after premedication with caffeine (loading dose of 20mg/kg) and administration of sedation (ketamine or propofol). The protocol was initially written for preterm neonates born between 25 and 30 wGA. It followed the 2013 Update of the European Consensus Guidelines: LISA was performed when the fraction of inspired oxygen increased over 30% for infants born before 26 wGA and over 40% for infants born after 26 wGA. LISA could be performed with a dedicated catheter in most cases (LISA Cath®) or with a thin catheter (5Fr sterile suction catheter or nasogastric tube), depending on the clinician preference.

Clinical definitions for respiratory disorders were determined as documented in the medical record by NICU clinicians. RDS was described with a pragmatic approach based on clinical assessment of work of breathing, oxygen requirement in the first hours of life and radiographic or lung ultrasound findings. Other outcomes included transient tachypnea of newborn, pneumonia and meconium aspiration syndrome.

Following data was recorded for each infant with respiratory disorder:

- Need and duration of noninvasive ventilation NIV (high-flow nasal cannula HFNC or nasal continuous positive airway pressure nCPAP), need and duration of invasive ventilation (IV) (conventional or high frequency oscillation), need of inhaled nitric oxide (NO).
- Time from birth to first NIV and time from birth to first IV. If NIV was started in the birth room, time from birth to first NIV was recorded as 0 hour. If IV was started in the birth room, time from birth to first IV was the precise time of intubation. In that case, time from birth to first NIV was the extubation time.
- Occurrence of pneumothorax and need for pleural drainage.

- Occurrence and severity of bronchopulmonary dysplasia (BPD). We defined BPD as the administration of oxygen for at least 28 days before a corrected GA of 36 weeks. If no oxygen was needed at that point, BPD was classified as mild, stage 1. If the need for oxygen was low ($F_i < 30\%$, low flow oxygen or high flow nasal cannula), BPD was classified as moderate, stage 2. If the need for oxygen was high ($F_i > 30\%$, low flow oxygen or high flow nasal cannula) or if a respiratory support with CPAP or IV was needed, BPD was classified as severe, stage 3.

For all infants, we recorded the occurrence of major in-hospital neonatal complications:

- Patent ductus arteriosus (PDA) that required pharmacological or surgical treatment.
- Severe neurological complications : stage 3 or 4 intraventricular hemorrhage (IVH), stage 3 or 4 periventricular leukomalacia (PVL) (classifications can be found in the *Appendix 1*). All the infants admitted to the NICU before 34 wGA had at least one cranial ultrasonogram assessment. Those born after 34 wGA without cranial ultrasonogram assessment were considered not to have severe cerebral lesions.
- Stage 2 or 3 necrotizing enterocolitis (NEC) according to Bell's definition (*Appendix 1*), bowel perforation
- Need and duration of central venous catheterization (umbilical or percutaneous venous catheter)
- Retinopathy of prematurity and need for treatment (laser or injection). All the infants admitted to the NICU before 31 wGA or with a birth weight of less than 1250g and all the infants with a birth weight of less than 2000g and additional risk factors had at least one fundoscopic examination. Those with no fundoscopic examination were considered not to have severe retinopathy of prematurity.
- Duration of hospitalization, mortality, survival without severe complications. Severe complications were defined as stage 3 BPD, stage 3 or 4 IVH, stage 3 or 4 PVL, stage 2 or 3 NEC, retinopathy treated by laser or injections.

Infants were discharged when they were in stable clinical condition and there was access to appropriate follow-up care. Some infants were transferred to secondary perinatal hospitals closer to their family home at the end of their stay. A home hospitalization service was opened during the study period and enabled earlier return home; in that case the discharge date was the date of discharge from our hospital.

4. Outcome measures

The primary outcome was the rate of infants treated with surfactant during the two periods. It was calculated both in the overall population and in the population of children who presented with respiratory distress at admission to the NICU.

Secondary outcomes were surfactant administration details, management and severity of respiratory failure, global evolution and other major neonatal in-hospital complications as described above.

All outcomes were analyzed in 3 different subgroups of gestational age: 23 to 26⁺⁶ wGA, 27 to 32⁺⁶ wGA and 33 to 36⁺⁶ wGA.

5. Statistical analysis

Descriptive analyses were conducted in full population and in 3 subgroups of gestational age, as detailed above. Qualitative variables were presented as frequencies and percentages of the different categories. Quantitative variables were presented as median and interquartile range (Q1-Q3) and/or as mean and standard deviation (SD) when normally distributed. The comparison between groups was carried out for qualitative variables using a chi-2 test, and when the conditions were not met, by Fisher's exact test. For quantitative variables, the comparison was made using the Student or Wilcoxon (Mann-Whitney) tests of comparison of means, depending on the distribution. The significance level was set at 5% for all the tests used. Statistical analysis was performed with SAS Enterprise Guide 7.13 software.

RESULTS

The number of infants assessed for eligibility and the number of infants whose data were analyzed are shown in *Figure 1*. A total of 1881 infants were born preterm and admitted to the NICU in our center during the 2 study periods. A total of 1875 had sufficient hospital records. Of these 1875, 94 presented exclusion criteria. At the end, 1781 infants were analyzed (95%). 826 (46%) of them were born between 2013 and 2015, 955 (54%) between 2019 and 2021.

Patients were excluded for the following reasons: for 6 infants, no hospital record was available; 94 had severe congenital diseases which could affect respiratory care (46 had severe digestive malformations, 14 had severe neurological diseases, 8 had severe cardiac malformations, the others had other diseases or malformations including hydrops fetalis, metabolic inherited diseases, diaphragmatic hernia).

The results for the subgroups of gestational age can be found in the *Tables 6, 7, 8 and 9* in the *Appendix 4*.

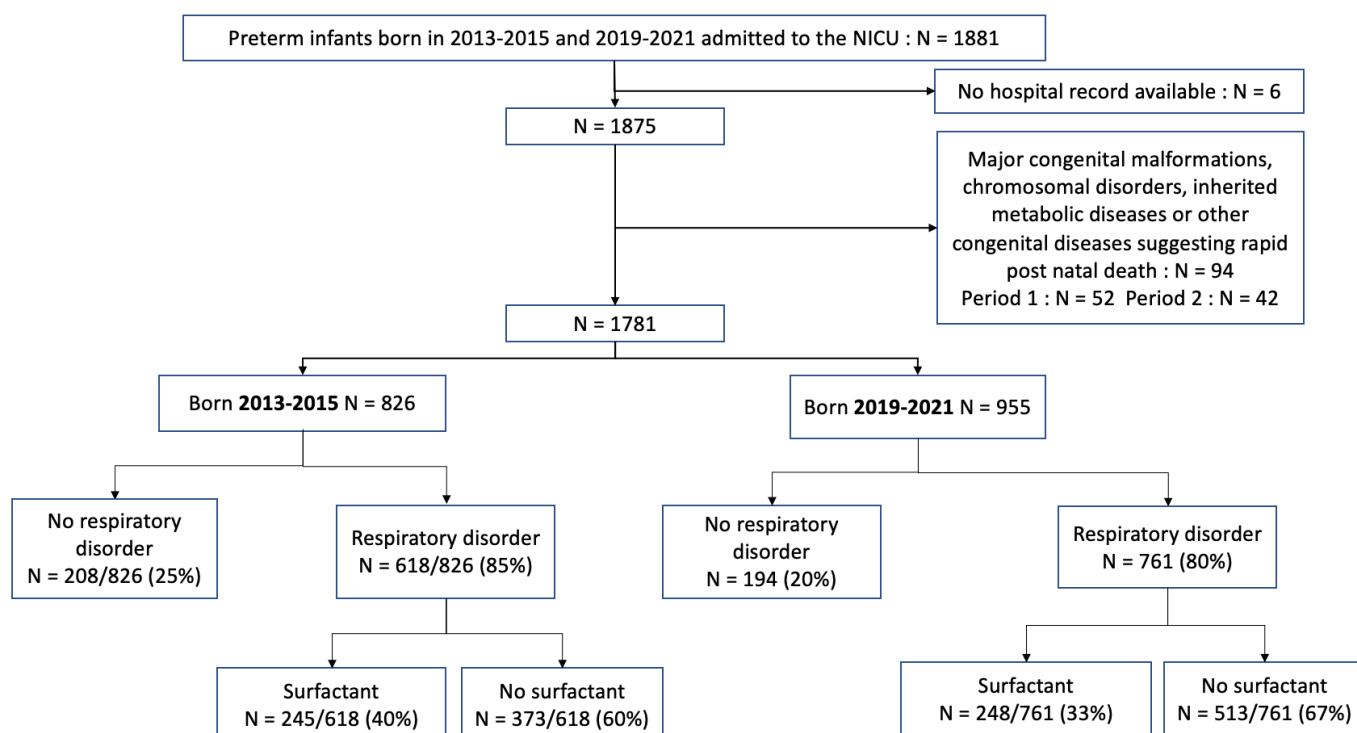


Figure 1: Flow chart

1. Maternal and neonatal characteristics

The baseline characteristics of the infants and their mothers are shown in Table 1.

<i>Table 1: Maternal and neonatal characteristics</i>	2013-2015	2019-2021	p	full population
Total population	826	955		
Mother				
Age, median (Q1-Q3), years	30 (27-35)	31 (27-36)	<0,001	31 (27-36)
Gravidity, mean (SD)	2,33 (1,67)	2,73 (2,1)	<0,001	2,5 (1,9)
Parity, mean (SD)	2,02 (1,3)	2,21 (1,38)	<0,001	2,1 (1,3)
Medically assisted procreation, n(%)	161/822 (19,6%)	179/949 (18,9%)	0,7	340/1771 (19,2%)
Singleton n(%)	527/826 (63,8%)	624/955 (65,3%)	0,3	1151/1781 (64,6%)
BMI, mean (SD)	23,9 (5,1)	24,4 (5,4)	0,22	24,3 (5,3)
BMI>30, n(%)	34/211 (16%)	123/870 (14%)	0,5	157/1081 (14,5%)
Gestation				
Gestational diabetes, n(%)	55/826 (6,7%)	118/955 (12,3%)	<0,001	243/1781 (13,6%)
Pre existing diabetes, n(%)	21/826 (2,5%)	32/955 (3,3%)	0,3	53/1781 (3%)
Hypertensive disorders, including pre-eclampsia, n(%)	165/821 (20,1%)	201/953 (21,1%)	0,6	366/1774 (20,6%)
Smoker during pregnancy, n(%)	140/735 (19%)	192/850 (22,6%)	0,08	332/1585 (21%)
Suspected chorioamnionitis, n(%)	49/826 (5,9%)	62/953 (6,4%)	0,7	110/1779 (6%)
Premature rupture of membranes, n(%)	222/818 (27%)	255/951 (26,8%)	0,9	477/1769 (27%)
If so, duration, median (Q1-Q3), days	4 (1,2-11)	4 (1,7-9)	0,9	4 (1,5-11)
Prenatal corticosteroid				
No prenatal corticosteroids	121/814 (14,9%)	170/950 (17,9%)	0,09	
Complete treatment, n(%)	505/814 (62%)	604/950 (63,6%)	0,5	1109/1764 (63%)
Complete and optimal, n(%)	393/814 (48,3%)	407/950 (42,8)		
Complete but out of date, n(%)	112/814 (13,8%)	197/950 (20,8%)		
Incomplete treatment, n(%)	188/814 (23,1%)	176/950 (18,5%)		
Delivery details				
Cephalic presentation, n(%)	530/791 (67%)	625/938 (66,6%)	0,1	1155/1729 (67%)
Caesarean, n(%)	562/826 (68%)	616/955 (64,5%)	0,2	1178/1781 (66%)
If caesarean, emergency caesarean, n(%)	225/562 (40,2%)	335/614 (54,6%)	<0,001	560/1174 (47,7%)
General anesthesia, n(%)	61/826 (7,4%)	106/955 (11,1%)	0,007	167/1781 (9,4%)
Newborn infant				
Female sex, n(%)	385/826 (46,6%)	438/955 (45,9%)	0,75	823/1781 (46,2%)
wGA, median (Q1-Q3)	32,5 (30-34)	32,5 (30-34)	0,67	32,6 (30-34)
Weight g, median (Q1-Q3)	1590 (1190-1990)	1620 (1214-2000)	0,5	1600 (1210-2000)
Zscore birth weight, median (Q1-Q3)	-0,3 (-1,2 - 0,3)	-0,3 (-1,1 - 0,3)	0,99	-0,3 (-1,1 - 0,3)
IUGR, n(%)	65/825 (7,8%)	79/955 (8,3%)	0,79	144/1780 (8%)
Macrosomia, n(%)	12/826 (1,5%)	13/955 (1,4%)	1	25/1781 (1,4%)
APGAR score, mean (SD)	8,6 (1,8)	8,6 (1,8)	0,8	8,6 (1,8)
APGAR score <7 at 5 min n(%)	97/826 (11,7%)	121/955 (12,7%)	0,55	218/1781 (12,2%)
Arterial blood lactate, mean (SD)	3,29 (2,05)	3,44 (2,53)	0,9	3,4 (2,4)
Admission to NICU				
Temperature at admission to NICU, °C, median (Q1-Q3)	36 (35,5-36,6)	36,7 (36,3-37)	<0,001	36,5 (35,9-36,9)
Glycemia at admission to NICU, g/l, median (Q1)Q3)	0,55 (0,43-0,7)	0,60(0,44-0,78)	0,002	0,57 (0,43-0,74)
Subgroups of gestational age				
wGA 23 - 26+6, n(%)	76/826 (9,2%)	85/955 (8,9%)	0,9	161/1781 (9%)
wGA 27 - 32+6, n(%)	383/826 (46%)	436/955 (46%)		820/1781 (46%)
wGA 33 - 36+6, n(%)	366/826 (44%)	434/955 (45%)		800/1781 (45%)

Mothers' age, gravidity and parity were statistically different between the 2 periods, but it was not clinically relevant.

Most of the pregnancies were singleton (63,8% in the first period and 65,3% in the second period). The most frequent complications were hypertensive disorders, premature rupture of membranes, and gestational diabetes, which was more frequent during the second period in the overall population and among all the subgroups of gestational age (6,7% vs 12,3%, $p < 0,001$). Most of the mothers had received a complete treatment with prenatal corticosteroids (62% during the first period, 63,6% during the second period). The percentage of birth by cesarean section remained stable (67% during the first period, 64,6% during the second period). There were more

emergency cesareans during the second period, in the overall population (54,6% vs 40,2%, $p < 0,001$) and in the subgroups of most premature births (65% vs 39% $p = 0,03$ in the subgroup 23-26⁺⁶ wGA and 61% vs 39% $p < 0,001$ in the subgroup 27-32⁺⁶ wGA), and more cesareans under general anesthesia in the same population.

Median gestational age was stable between the two periods, 32,5 wGA (30-34). There was no difference in median birth weight : 1590g in the first period and 1620g in the second period, $p = 0,5$. There was an 8% rate of Intra Uterine Growth Restriction (IUGR) during both periods. In the subgroup of 23-26⁺⁶, there were more infants with IUGR during the second period (9,4% vs 1,3%, $p = 0,036$), with a median weight significantly smaller (700g vs 752g).

APGAR score and mean arterial blood lactate were similar between the two periods.

Median temperature and median glycemia at admission to the NICU were higher in the second period (respectively: 36,7°C vs 36°C, $p < 0,001$ and 0,60 vs 0,55, $p = 0,002$). The difference in temperature at admission to the NICU was found in all the subgroups of gestational age.

9% of the infants were born between 23 and 26⁺⁶ wGA, 46% between 27 and 32⁺⁶ wGA and 45% between 33 and 36⁺⁶ wGA. The number of infants in each gestational age category can be found in the *Table 3*.

2. Surfactant administration

The surfactant administration rate and details regarding surfactant administration in the overall population are shown in *Table 2*. The complete data for all the subgroups can be found in *Appendix 4, Table 7*.

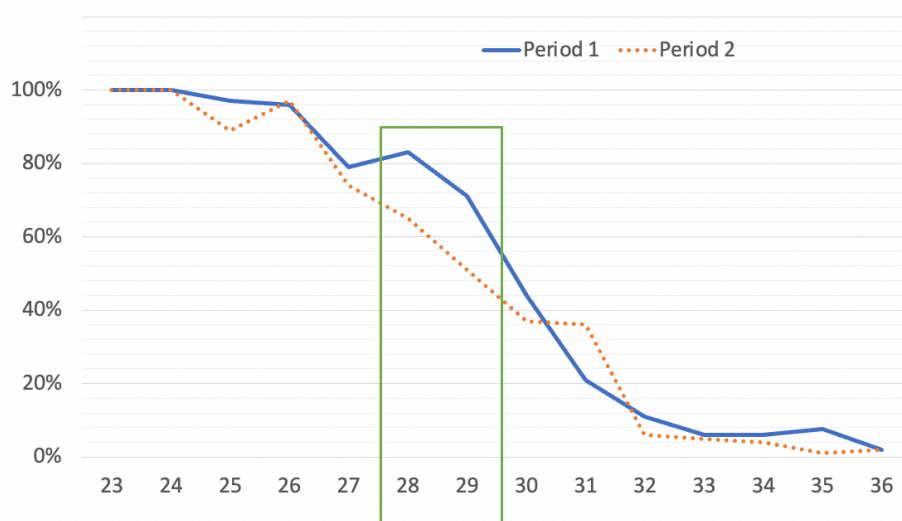
Surfactant was given to 493 out of 1781 infants in the overall population. The absolute number of infants treated with surfactant was similar during the 2 periods: 245 and 248. There was no statistically significant difference in the rate of infants that received surfactant in the overall population. However, if we consider only children with respiratory distress at admission to the NICU, there was a significant decrease in the rate of children treated with surfactant, from 40% in the first period to 33% in the second period, $p = 0,006$. In the subgroup analysis, this decrease was also found for children born between 27 and 32⁺⁶ wGA (37% vs 45%, $p = 0,03$), and for children born between 33 and 36⁺⁶ wGA but was not significant in this population (5.6% vs 10%, $p = 0,06$).

<i>Table 2 : Surfactant administration</i>	Full population		
	2013-2015	2019-2021	p
Total population	826	955	
Number of infants treated with surfactant, n(%)	245/826 (30%)	248/955 (26%)	0,08
Number of infants treated with surfactant if respiratory disorder, n(%)	245/618 (40%)	248/761 (33%)	0,006
Types of procedure			
Conventional administration, n(%)	197/239 (82,4%)	52/248 (21%)	<0,001
InSuRe, n(%)	40/239 (16,7%)	8/248 (3,2%)	
LISA, n(%)	2/239 (0,4%)	188/248 (75,8%)	
Others details			
More than 1 dose of surfactant, n(%)	29/245 (12%)	46/248 (19%)	0,04
Minutes of life, median (Q1-Q3)	28 (18-40)	30 (10-90)	0,63
FiO2 before surfactant administration, median (Q1-Q3)	50 (40-70)	42 (35-73)	0,07
Sedation before surfactant administration, n(%)	163/195 (83,6%)	169/201 (84%)	0,9

Surfactant administration rate by gestational age was different between the 2 periods (Table 3). The decrease in surfactant use was particularly marked for infants born at 28 and 29 wGA (table 3 and figure 2): 77% of the infants born at 28-29 wGA received surfactant in the first period versus 58% in the second period ($p<0,01$).

Gestational age, weeks	Period 1			Period 2			p=0,04	
	Surfactant	Total	%	Surfactant	Total	%		
23	1	1	100,00%	14	14	100,00%	p<0,01	
24	16	16	100,00%	17	17	100,00%		
25	30	31	96,77%	16	18	88,89%		
26	27	28	96,43%	35	36	97,22%		
27	27	34	79,41%	29	39	74,36%		
28	34	41	82,93%	36	55	65,45%		
29	35	49	71,43%	30	59	50,85%		
30	24	54	44,44%	25	67	37,31%		
31	16	77	20,78%	24	91	26,37%		
32	14	129	10,85%	8	125	6,40%		
33	8	133	6,02%	7	143	4,90%		
34	7	120	5,83%	5	129	3,88%		
35	5	66	7,58%	1	100	1,00%		
36	1	47	2,13%	1	62	1,61%		
28-29	69	90	76,67%	66	114	57,89%		p<0,01
Total	245	826	30%	248	955	26%		p=0,08

Figure 2: Surfactant administration rate by gestational age



The percentage of infants treated with surfactant each year can be found in the Appendix 4, Table 10. There was a drop in the number of infants treated with surfactant during the year 2020: 18% of the infants born in 2020 were treated with surfactant, compared with a mean of 30% during the other years studied, $p=0,06$.

During the first period, surfactant was administered via an endotracheal tube, using the INSURE procedure for 16,7% of the infants, or with sustained mechanical ventilation for 82,4%. During the second period, the most used method for surfactant administration was the Less Invasive Surfactant Administration procedure, in the overall population (75,8%) and in all the

subgroups of gestational age (respectively: 52% of the infants born between 24 and 26⁺⁶ wGA, 88% of the infants born between 27 and 32⁺⁶ wGA and 87% of the infants born between 33 and 36⁺⁶ wGA).

Most of the patients treated received a single dose, but there was a significant increase in the number of infants that needed a second dose during the second period (19% vs 12%, $p=0,04$). The median time for surfactant administration was similar between the 2 periods, (28 minutes in the first period versus 30 minutes in the second period), except for the subgroup of infants born between 33 and 36⁺⁶ wGA, for whom surfactant was administered later during the second period (300 minutes (240-360) vs 55 minutes (34-240), $p<0,001$). The median (Q1-Q3) for FiO₂ at the time of surfactant administration did not differ between the periods: 50% (40-70) in the first period and 42% (35-73) in the second period, $p=0,07$. Sedation was administered before surfactant for 84% of the infants, sedation rate was stable between the 2 periods in all the subgroups of gestational age. The most used drugs were propofol, ketamine and midazolam. Almost all the children who did not receive sedation were children who required emergency intubation for stabilization in the delivery room.

3. Management and severity of respiratory failure

There was no difference in the rate of infants presenting respiratory failure at admission to the NICU in the overall population (75% in the first period and 80% in the second period, $p=0,15$). In the subgroup 27-32⁺⁶ wGA, there was a higher rate of respiratory failure during the second period (94% vs 87%, $p<0,001$). For this reason, some data were analyzed both in the overall population and in the narrowed population of infants that presented respiratory failure at admission to the NICU.

30% of the infants received Invasive Ventilation during the first period, versus 12% during the second period ($p<0,001$). This decrease in the use of invasive ventilation was found in all subgroups of gestational age. Noninvasive ventilation was administered to 97% of the infants who presented with respiratory failure at the admission to NICU during the 2 periods, it was initiated at a median time of 10,6 hours of life in the first period and 3,2 hours of life in the second period ($p<0,001$), this was consistent among all the subgroups of gestational age. There was a more frequent use of high flow nasal canulae (HFNC) during the second period (77% vs 64%, $p=0,004$). The rate of infants treated with oxygen did not differ between the periods (44% of the infants in the first period, 41% in the second period). The median duration of oxygen therapy was longer during the second period, 4 days versus 3 days during the first period ($p<0,001$). This was also found in the subgroup of infants born between 27 and 32⁺⁶ wGA (2 days versus 1 day, $p<0,001$).

The age at spontaneous ventilation was 5 days higher during the second period: 34,6 wGA vs 33,9 wGA, $p<0,001$. This was found in all the subgroups.

In the overall population, there was no difference in the occurrence of early respiratory complications such as pulmonary hemorrhage (2% in both groups) or pneumothoraces (1,1% in the first period and 2% in the second period, $p=0,3$).

There was an increasing trend in the occurrence of BPD in the overall population, that did not reach statistical significance (9,7% during the first period and 12,9% during the second period, $p=0,053$). It increased noticeably in the subgroup 27-32⁺⁶ wGA, from 8,5% to 15%, $p=0,004$.

Results regarding the population of infants born between 33 and 36⁺⁶ wGA can be found in the *Appendix 4, Table 8*. The rate of IV dropped in this population as well, from 5,7% to 0,5%, $p<0,001$ (21 infants during the first period received IV in this subgroup, versus only 2 during the second period). Duration of NIV and use of HFNC also increased. Age at spontaneous ventilation was 2 days higher: 34,7 wGA during the second period and 34,4 wGA during the first period, $p=0,008$. A total of 13 infants had pneumothoraces: 3 occurred during the first period, none of which required exsufflation, drainage or invasive ventilation, and 10 occurred during the second period: 1 of them required exsufflation, 1 of them required drainage and 1 of them required both and invasive ventilation.

<i>Table 4 : Management and severity of respiratory failure</i>	<i>full population</i>		
	2013-2015	2019-2021	p
Total population	826	955	
Respiratory disorder			
No, n(%)	208/826 (25%)	194/955 (20%)	0,15
Yes, n(%)	618/826 (75%)	761/955 (80%)	
1. Respiratory distress syndrome	387/826 (46%)	490/955 (51%)	
2. Transient tachypnea of the newborn	216/826 (26%)	257/955 (27%)	
3. Meconium aspiration syndrome	0/826 (0%)	1/955 (0,1%)	
4. Pneumonia	3/826 (0,36%)	3/955 (0,3%)	
5. Others	12/826 (1,45%)	10/955 (1%)	
Invasive Ventilation			
IV invasive ventilation, n(%)	252/826 (31%)	115/955 (12%)	<0,001
Sequences of mechanical ventilation :			0,08
1 sequence, n(%)	200/252 (80%)	80/113 (70%)	
2 sequences, n(%)	41/252 (16%)	23/115 (20%)	
3 sequences or more, n(%)	9/252 (3,6%)	10/115 (4,5%)	
Time from birth to first IV in hours, median (Q1-Q3)	0,38 (0,27-0,65)	0,65 (0,1-47)	0,05
Duration of IV, median (Q1-Q3), days	1 (0,3-4,2)	4 (1-8)	<0,001
High frequency oscillation, n(%)	78/826 (9,4%)	69/955 (7,2%)	0,1
Duration of high frequency oscillation, days, median (Q1-Q3)	2 (1-6)	2 (1-5)	0,4
Non Invasive Ventilation			
NIV if initial diagnosis of respiratory disorder, n(%)	597/618 (97%)	736/761 (97%)	1
Time from birth to first NIV in hours, mean (ecart type)	10,6 (47)	3,2 (26)	<0,001
Duration of NIV, days, median (Q1-Q3)	5,8 (1-23)	9 (2-33)	<0,001
CPAP if initial diagnosis of respiratory disorder, n(%)	552/618 (89%)	705/761 (93%)	0,7
Duration of CPAP, days, median (Q1-Q3)	3 (1-10)	4 (1-22)	0,01
HFNC if initial diagnosis of respiratory disorder, n(%)	398/618 (64%)	585/761 (77%)	0,04
Duration of HFNC, days, median (Q1-Q3)	5 (2-17)	5 (2-13)	0,4
Other respiratory details	360/826 (44%)	388/955 (41%)	0,2
Need for oxygen, n(%)	360/826 (44%)	388/955 (41%)	0,2
Duration of oxygenotherapy, days, median (Q1-Q3)	3 (0,08-18,5)	4 (1-20)	0,002
Pulmonary hypertension treated with NO, n(%)	43/826 (5,2%)	52/955 (5,4%)	0,8
Age at spontaneous ventilation, wGA, median (Q1-Q3)	33,9 (32,9-35)	34,6 (33,4-35,6)	<0,001
Respiratory complications			
Bronchopulmonary dysplasia BPD, n(%)	75/770 (9,7%)	114/887 (12,9%)	0,053
Pulmonary hemorrhage, n(%)	17/825 (2%)	18/955 (2%)	0,8
Pneumothorax, n(%)	9/826 (1,1%)	19/955 (2%)	0,3
Drained pneumothorax, n(%)	5/826 (0%)	4/955 (0%)	1

4. Global evolution and major in-hospital complications

Nutritional management evolved during the study period. There was a decrease in the use of central venous catheter (CVC), in the overall population and in the subgroup of infants born between 33 and 36⁺⁶ wGA (32% vs 20%, p=0,005). Median duration of CVC was shorter during the second period (10 days in the first period vs 7 days in the second period, p<0,001), this was consistent among all the subgroups of gestational age. Initial post-natal weight loss was less pronounced during the second period. Z-score weight at discharge was significantly higher during the second period, this was found in the overall population and in the subgroups of infants born before 33 wGA.

Table 5: Global evolution and other major in-hospital complications	full population		
	2013-2015	2019-2021	p
Total population	826	955	
Hemodynamics			
Patent ductus arteriosus that required treatment, n(%)	95/826 (12%)	94/955 (10%)	0,1
Neurologic			
Intraventricular hemorrhage, stage 3 or 4, n(%)	28/826 (3,4%)	44/955 (4,6%)	0,4
Periventricular leukomalacia, stage 3 or 4, n(%)	4/826 (0,5%)	8/955 (0,8%)	0,4
Digestive			
Necrotizing enterocolitis, stage 2 or 3, n(%)	25/826 (3%)	22/955 (2,3%)	0,38
Bowel perforation, n(%)	3/836 (0,4%)	10/955 (1%)	0,1
Nutritional strategy			
Need for central venous catheterization, n(%)	535/826 (64%)	549/955 (57%)	0,001
Duration of central venous catheterization, days, median (Q1-Q3)	10 (7-16)	7 (6-12)	<0,001
Initial weight loss, %BW, median (Q1-Q3)	7 (4,7-9,8)	5,3 (2,8-8)	<0,001
Retinopathy of prematurity			
Fundoscopy anomaly	8/826 (1%)	8/955 (1%)	0,8
Retinopathy of prematurity treated with laser or injection	3/826 (0,004%)	4/955 (0,004%)	1
Discharge			
Duration of hospitalisation, days, median (Q1-Q3)	28 (15-46)	26 (12-46)	0,006
wGA at discharge, median (Q1-Q3)	37,1 (36-38,3)	37 (35,6-38,1)	0,1
Weight at discharge, grams, median (Q1-Q3)	2310 (2020-2655)	2339 (2030-2750)	0,1
Zscore weight at discharge, median (Q1-Q3)	-1,09 (-1,6--0,6)	-0,9 (-2,5--0,4)	<0,001
Zscore weight at discharge <-2DS, n(%)	91/772 (12%)	82/880 (9,3%)	0,1
Mortality, n(%)	36/826 (4,4%)	48/955 (5%)	0,6
Survival without severe complications, n(%)	745/826 (90%)	855/955 (90%)	0,7

Median length of stay was shorter in the second period in the overall population (26 vs 28 days, p=0,006). This was due to a major decrease in the duration of hospitalization in the subgroup of infants born between 33 and 36⁺⁶ wGA (13 vs 17 days, p<0,001). For the infants born before 33 wGA, duration of hospitalization remained stable.

There was no difference in the occurrence of severe neurological or digestive complications, nor in the occurrence of retinopathy of prematurity. Mortality and survival without severe complications were similar between the 2 groups.

DISCUSSION

There was a decrease in the use of surfactant among infants born between 27⁺⁰ and 36⁺⁶ wGA, which prevailed among children born at 28-29wGA. The implementation of a protocol for administration of surfactant by the LISA method has led to a clear change in practice; it has become the method of choice in all gestational age subgroups, including those that were not initially covered by our protocol. The administration of surfactant without endotracheal intubation resulted in a great decrease in the need for mechanical ventilation for preterm neonates admitted to our center, while maintaining a stable and high sedation rate during the procedure. Occurrence of BPD remained stable in the overall population, but it notably increased for infants born between 27 and 32⁺⁶ wGA. The overall management of prematurity underwent other important changes between the 2 study periods, which we cannot attribute solely to the implementation of this new method.

To our knowledge, this is the first study to explore changes in NICU practices following LISA implementation from this point of view, in particular the influence of this method on the decision to use surfactant in the treatment of RDS of the preterm newborn.

Limitations

In order to highlight the changes induced by the implementation of a protocol in our department, we only included neonates born in our institution. This was essential in order to assess the impact of a change framed by a service protocol in the management of preterm newborns during their first hours of life. However, this does not allow the extrapolation of our results to children requiring a transport in the first hours of life. Similarly, extrapolation to other centers where practices may differ from ours should be done with caution.

The retrospective design of our study and its duration of several years require very careful analysis of the results. Changes in practice besides the procedure for surfactant administration have occurred during this period. The updates of European recommendations on the management of RDS published in 2013, 2016 and 2019, have influenced the respiratory management of preterm neonates in our center (*Figure 3*). The suggested links between the introduction of the new protocol, its clinical application and patient outcomes are hypothetical.

Our 2 groups were comparable regarding most major risk factors for RDS : prenatal steroid treatment, cesarean section, male gender, APGAR at 5 min < 7, metabolic acidosis. (15) However, there was a significant difference in the median temperature at admission to NICU: a higher proportion of the infants was in the recommended range (36,5-37,5°C) during the second period. (1) This is not surprising as particular attention has been paid to the care of premature newborns in the delivery room within our department, especially regarding the risk of hypothermia, which is associated with poorer outcome and with increased risk of RDS. (16)

Other differences were found in the baseline characteristics, some of which could be cofounding factors as well. First, the increase in the rate of gestational diabetes, which is probably related to both an increase in obesity among young women in France over the last few years and

a progressive implementation of the new screening thresholds adopted in 2010 by the CNGOF. (17), (18). The evolution of the percentage of obesity in our study is not reliable as this data was missing for more than 70% of the mothers in the first period. Second, even though the rate of cesarean section was stable, there was a significant increase in emergency cesareans for the most premature births. This is probably a consequence of the increased intensity of perinatal care for extremely preterm babies that resulted from the advances in the field of neonatology over the past few decades. (10) The obstetric and pediatric approach has evolved towards a more and more active management of increasingly immature newborns. This is also reflected in our study by a higher proportion of newborns with IUGR as well as a significantly lower median weight in the second period in the 23-26⁺⁶ subgroup. These 3 elements, increased rate of gestational diabetes, increased rate of emergency cesarean delivery, and management of more immature and lower-weight neonates, are likely to favor the occurrence of respiratory disorders.

To limit the risk of bias related to these variations in maternal and neonatal characteristics, we compared the percentage of children treated with surfactant during the 2 periods both in the overall population and in the population of newborns with a respiratory disorder at admission to the NICU.

Finally, surfactant use decreased significantly during 2020 in relation to a lower proportion of very premature infants admitted to our service, for reasons we discuss below. This could have modified our results. For this reason, we compared surfactant rate between the two periods by gestational age as well.

Strengths

One of the main strengths of our study is the large number of patients included. We included all preterm neonates admitted to our NICUs over 2 periods of 3 years. Thus, all gestational ages are represented. We included all patients admitted to the NICU, whether or not they presented with respiratory distress, and regardless of the severity of respiratory distress. We only excluded 5% of all the eligible patients, they were all infants with severe diseases that significantly altered respiratory management in the first days of life and whose evolution was not relevant regarding our question.

Data collection was carried out prospectively for some of the children. Although retrospective, data collection for children born after 32 wGA and weighing more than 1.5 kg was highly accurate and complete thanks to standardized hospital reports. As all endpoints occurred during the first hospitalization, there was limited missing data.

The primary endpoint was single, well-defined and its assessment was simple and reliable. The increase we identified was confirmed in the subgroup analysis.

After the implementation of the protocol, LISA became the reference method in our department. This is reflected in the results of our study. Even though it was originally dedicated to infants born between 25 and 30 wGA, most children who received surfactant during the second period underwent the LISA procedure regardless of gestational age. The comparison of the two periods therefore allows us to evaluate the impact of this new method on the practices of our center, for all gestational ages.

Over the period 2013-2021, the proportion of preterm infants treated with surfactant has decreased. The absence of difference among the subgroup of infants born before 26 wGA was expected as RDS rate is extremely high in this population. Among infants born after 26 wGA, the more accurate assessment of the severity of RDS might have contributed to a reduction in the indications for surfactant therapy. This has been made possible by two important changes in the approach to RDS.

On the one hand, prophylactic surfactant administration has been abandoned in favor of selective administration, which consists in restricting surfactant indications to children with a dependence to oxygen despite effective ventilatory support by CPAP. Therefore, it avoids treating children with mild RDS who progress well under CPAP. Early rescue surfactant administration have been proven effective in high quality meta-analysis and repeated updates of the European recommendations during the period of our study have progressively restricted the indications for prophylactic surfactant. (19), (20) Since 2016, prophylactic surfactant administration is only recommended for infants who require intubation for stabilization in the delivery room (the updates of the European recommendations are summarized in the *Figure 3*).

	2010	2013	2016	2019
Surfactant preparation	Natural surfactant preparation : poractant alfa 200mg/kg			
Timing	Early rescue			
FiO2 threshold		FiO2>30% (≤26wGA) FiO2>40% (>26wGA)		FiO2>30%
Prophylaxis	Prophylaxis <26 wGA	Prophylaxis <26wGA if no antenatal steroids	Prophylaxis only for babies who require intubation for stabilization	
Procedure	INSURE		INSURE +/- LISA	LISA
Targeted saturation	85-93%		90-95%	
PEP	5 cm H2O	5-6 cm H2O	at least 6 cm H2O	

Figure 3: European Consensus Guidelines: 2010, 2013, 2016 and 2019 Updates

On the other hand, lung ultrasound (LUS) is increasingly used to assess the severity of RDS. It is a bedside technique which enables an easy and quick recognition of a normal aerated lung in contrast to an interstitial or alveolar pattern. (21) It does not use ionizing radiations and can be repeated to follow the progression of the disease and the response treatment. A prospective diagnostic accuracy study published in the JAMA pediatrics in 2015 showed that the LUS score (*Appendix 2*) is well correlated with oxygenation status in both term and preterm neonates and has good reliability to predict surfactant administration in preterm babies <34 wGA under CPAP, without differing its administration. (22) Even though this did not systematically appear in the hospital reports nor in the database, its use has become increasingly common in our department,

and we found multiple references to this method in the hospital records of the infants born during the second period. In our center, we use lung ultrasound as a diagnostic tool and to assess the severity of RDS, using the Lung Ultrasonography Score (LUS) described by Brat et al (*Appendix 2*). It is particularly useful when evaluation of symptoms and oxygen requirement do not allow easy decision making for surfactant treatment. However, even if it is increasingly used, its use is not systematic and varies depending on the clinician.

The decrease in surfactant administration rate prevailed in the 28-29 wGA population (*Table 3, Figure 2*). This is a pivotal population: infants born before 28wGA are at high risk of severe RDS and evolution towards DBP is a real threat, therefore it is rarely possible not to treat them with surfactant. On the opposite, among infants born at 30 wGA or more, surfactant administration rates were already quite low during the first period, so the margin of decrease was smaller. It is an interesting finding: in this population specifically, the observation period provided by the practice of selective surfactant administration combined with the use of lung ultrasound has led to a more precise targeting of indications for surfactant therapy. This restricted population of infants born at 28-29 wGA was not studied for overall outcome and respiratory complications as it was not planned in our study. However, the rate of bronchopulmonary dysplasia almost doubled in the 27-32⁺⁶ subgroup (*Appendix 3, Table 9*). There was no increase in the main risk factors for BPD in this population. It is possible that confounding factors not accounted for in our study explain this increase, but we cannot exclude that there may be a link between this decrease in the rate of children treated with surfactant and the increase in BPD.

Despite all the strategies in place to ensure optimal ventilatory management and decrease the risk of BPD, the increase in BPD rates associated with the care of increasingly immature and smaller newborns is a persistent issue. (23) Therefore, evolution of the BPD rate between the 2 periods of time in our study was expected, especially considering the lower weight of the most preterm newborns, which is one of the main risk factors for BPD in the literature. (5) Another factor that might have influenced the occurrence of BPD is the decreasing use of curative postnatal steroids in our department during the last 2 decades, because of concerns about adverse effects. We could not analyze with sufficient certainty the data regarding the degree of severity of BPD because it was extrapolated from the ventilation data for the patients of the first period and therefore was not completely reliable

Analysis of the rate of surfactant use each year showed a clear decrease over the year 2020: only 24% of preterm neonates admitted for respiratory distress were treated with surfactant during that year, compared with 34-43% during the other years studied. At the beginning of Covid-19 pandemic in 2020, a strict lockdown was established in France. This sudden change in lifestyle had consequences on perinatal epidemiology resulting in a slightly but significant decrease in the rates of preterm birth (-6%) (24), especially in areas weakly impacted by the Covid19 pandemic, which was the case of our region. In our department, it has led to a decrease in the proportion of very premature babies among the children admitted, which explains the lower consumption of surfactant. This is illustrated in the *Figure 4*. This constitutes a bias that could have masked an increase in surfactant use between the 2 study periods. The evolution of surfactant use by year is presented in *Appendix 4, Table 10*. It confirms the overall trend of decreasing in surfactant use over the years.

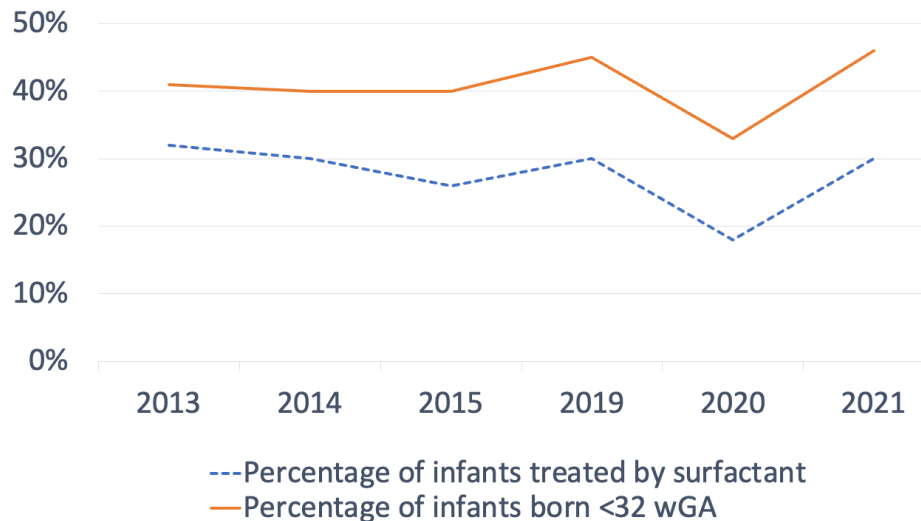


Figure 4: evolution of surfactant administration rate and gestational age over the years

Although there was a decrease in the percentage of children for whom an indication for surfactant treatment was retained, an increase in the total consumption of surfactant was reported by the pharmacy department of our hospital. This is related to 2 main factors.

First, the decrease in the average length of stay among infants born after 32 wGA in our department has allowed for more children to be cared for each year. It explains the difference in the total number of infants included between our two periods (826 in the first period and 955 in the second period). This shortened length of stay can be attributed to the opening of a home hospitalization service and to the strengthening of the collaboration with the secondary perinatal centers in the region, both of which allowed earlier discharge from our department.

Second, more children required a second dose of surfactant during the second period. This issue has been reported in the literature. Several hypotheses can explain this need for a second dose. On the one hand, it is possible that product loss is higher with this method. Thus, an experimental study conducted by De Luca published in 2013 showed that surfactant loss using thin catheters is around two to three times higher than using common endotracheal tubes: on average 20 mg of phospholipids (11% of the administered dose) are lost. (25) Surfactant reflux is also more frequent with LISA procedure compared to administration through an endotracheal tube. (7) Another possible explanation is the risk of apnea during the procedure, which can prevent or delay a homogeneous distribution of surfactant in the lungs.

According to our local protocol, sedation is mandatory before the LISA procedure. Indeed, it is well known that laryngoscopy is a stressful procedure, even with a thinner tube or catheter. However, it remains an open question in the literature and it is not performed in routine in many centers : according to a European declarative survey published in 2017, only half of the neonatologists use a sedative before the LISA procedure. (26). As sedation might compromise respiratory drive, it can interfere with surfactant distribution or lead to the need for intubation and mechanical ventilation until sedation is eliminated. This issue is still the subject of extensive research, and a meta-analysis was recently published in 2022. (27) It confirmed the effects of

sedative drugs on breathing and found an increased risk for nasal intermittent positive pressure ventilation and apnea, with a low/very low level of evidence. In our department, sedation is a standard practice, and this is reflected in the results of our study (*Table 2*). We did not evaluate the side effects of sedation as this was not the purpose of this study, but high acceptance of this method within our team suggests good feasibility. A study comparing ketamine and propofol before LISA was carried out in our department and published in 2021, it found a similar efficacy and tolerance between these 2 molecules. (28)

Ventilatory management of preterm neonates in our department has evolved profoundly between the two periods.

The most obvious consequence that can be attributed mainly to the generalization of the LISA method is the major decrease in the use of invasive ventilation. This is the main objective of this procedure.

The increase in the duration of non-invasive ventilation and the higher age at spontaneous ventilation are more surprising findings at first sight. However, these are consistent with the results of a previous study conducted in our department. This study published in 2020 by Habas and al described 15 years trends in respiratory care of extremely preterm infants. (29) The authors suggested that clinicians might continue NIV for nutritional purposes, with the idea that ventilatory support would decrease energy expenditure. Indeed, nutritional management has been one of the priorities of our department over the last decade. In the article mentioned above, the relationship between prolonged NIV and growth was supported by a positive influence of NIV on weight and head circumference growth. Moreover, during weaning, NIV may be perceived as helping and reducing the occurrence of apnea during active feeding. Finally, even if HFNC have been used in our center since 2009, its use increased between the 2 periods, as it became popular for the management of preterm neonates after being proved to be effective post extubation. (30)

In our subgroup of more mature infants born between 33 and 36⁺⁶ wGA, 10% of the infants with respiratory disorder at admission to the NICU were treated with surfactant during the first period. Our concern that the accessibility of the LISA method might lead to excessive surfactant administration in this population was not confirmed; on the contrary, it was even halved between the 2 periods. Invasive ventilation carries many inherent risks beyond those specific to prematurity, including self-extubation, obstruction of the tube, atelectasis, pneumothorax, subglottic stenosis. The application of the LISA method had beneficial consequences in this population as well, allowing a significant decrease in the rate of mechanical ventilation (IV 5,7% in the first period and 0,5% in the second period, $p < 0,001$).

There are no specific recommendations in this population which is poorly represented in high-level evidence meta-analyses. A systematic review of severe morbidity in infants born late preterm was published in 2011. It found that the risk for these infants to present with RDS is 17 times higher than for an infant born after 37 wGA, with a rate of RDS of 5,3%. In this review, the percentage of pneumothoraces in this population was 0,8%, 3,8% infants received surfactant and 2,5% required mechanical ventilation. (31) Despite the great number of infants affected by this

issue, the question of the benefit of surfactant treatment remains unanswered. A large prospective cohort study published in 2020 included 54 964 infants in the United States and compared the odds of mortality and morbidity between infants who were exposed vs unexposed to surfactant. They found no significant treatment effect. (31) Very few studies have investigated the benefits of administration of surfactant specifically by the LISA method in late preterm infants. A multicentric randomized controlled trial conducted in Canada and published in 2017 compared the efficacy of LISA as a mean of avoiding the composite outcome of exposure to mechanical ventilation and pneumothorax occurrence in 45 moderate and late preterm infants. LISA was associated with a significant reduction of MV exposure and pneumothorax occurrence (50 vs 90%). (32) However, because pneumothorax occurred after 24 hours life in 15 patients who did not meet the study inclusion criteria as they did not require 35% FiO₂ in the first 24 hours of life, the authors suggested that administration of LISA at a lower FiO₂ or after 24 hours of life may be useful in this population to avoid pneumothorax.

In that population, we observed a tendency towards an increase in the number and severity of pneumothoraces between the two periods. It is possible that this could have been avoided by surfactant therapy. This is an important issue, as pneumothorax occurrence is a major complication of RDS, that may require heavy resuscitation including mechanical ventilation, pulmonary drainage and recourse to vasopressors. In the study mentioned above published by Brat et al lung ultrasound was not as reliable in predicting surfactant requirement in children born after 34 weeks' gestation. (22) It is possible that the change in practice and the reduction in the use of surfactant in this population has favored the occurrence of pneumothoraces in this population. However, we cannot conclude on this, as our study was not designed for this purpose and lacks power to answer this question due to the small number of children involved.

Perspectives

The optimal procedure to administrate surfactant is still to be found. Although the administration of surfactant by the LISA method avoids the need for mechanical ventilation, this method requires laryngoscopy and is therefore still quite invasive. Tracheal instrumentation itself poses many challenges. It requires an experienced operator, requires administration of sedation in order to be performed quickly and to avoid discomfort and induces transient cardiovascular instability. Interesting perspectives of even less invasive methods that do not require laryngoscopy are currently under investigation. Nebulization is a very promising method in this sense. A recent study of preterm infants with mild RDS, randomized to CPAP with or without aerosolized poractant, showed greatly reduced requirement for intubation in the higher GA subgroup (32⁺⁰ to 33⁺⁶ weeks) in favor of nebulization (9% versus 77%). (33) Another device that could be interesting is the Laryngeal Mask Airway (LMA), which seems promising according to a meta-analysis published in 2021. It included infants as young as 28 wGA. (34) Although these methods still need to be investigated and haven't been compared with the LISA method yet, they appear promising.

The use of lung ultrasound to assess of the severity of RDS and to identify children most likely to benefit from surfactant therapy is becoming increasingly common in our department. As discussed above, this tool has probably played a role in reducing the use of surfactant. However, its use in practice is currently inconsistent and would benefit from a clearer framework. This is an issue we would like to explore further.

CONCLUSION

Despite the progress made during the last decades in the prevention and management of neonatal RDS, it remains an immediate postnatal complication for which adequate treatment is essential in order to avoid an increased risk of mortality and morbidity. The management of increasingly immature neonates with poorer prognosis has led to an increase in the prevalence of BPD.

The LISA method allowed the administration of surfactant to many children in our department during the study period, while avoiding the need for invasive ventilation. It was quickly adopted by the clinicians and became the standard method for all gestational ages. It could be performed while ensuring adequate sedation. We did not find a benefic effect as described in the literature on the occurrence of BPD, but there were confounding factors. Apart from LISA, many changes occurred between the 2 periods of the study, including the management of infants at higher risk of BPD and modifications in the respiratory management of preterm neonates.

Contrary to our initial hypothesis, the rate of surfactant use decreased over the last decade among children born after 26 wGA. Important changes in the management of RDS, such as selective surfactant administration as well as the use of lung ultrasound as a diagnostic tool have occurred during the study period. They allowed a more individualized evaluation and thus restricted surfactant therapy to infants most likely to benefit from it. However, among moderate and late preterm, the relevance of using lung ultrasound is less clear. The role of lung ultrasound in the assessment of RDS in our department would benefit from being more precisely defined.

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ANNEXES

Appendix 1: classifications

- Classification for intraventricular hemorrhage (35)

Papile's grading system	Volpe's grading system
CT scan findings	Echsonographic findings
Grade I: subependymal hemorrhage	Grade I: hemorrhage confined to the subependymal GM
Grade II: intraventricular hemorrhage without dilation	Grade II: hemorrhage within the lateral ventricle without ventricular dilation and/or hemorrhage occupying less than 50% of the ventricle
Grade III: intraventricular hemorrhage with ventricular dilation*	Grade III: hemorrhage with distention resulting in ventricular dilation and/or hemorrhage occupying more than 50% of the ventricle*
Grade IV: intraventricular hemorrhage with parenchymal hemorrhage	PVHI: ventricular hemorrhage that extends into the surrounding parenchyma

*Ventricular dilation taking as reference Levene's index values above 97 percentile

- Classification for periventricular leukomalacia (36)

Transient Flares	Periventricular Densities < 7 days
PVL grade 1a	Homogeneous periventricular densities \geq 7 days
PVL grade 1b	Inhomogeneous periventricular densities \geq 7 days
PVL grade 2	Periventricular densities, evolving into small localized cysts
PVL grade 3	Periventricular densities, evolving into extensive periventricular cystic lesions
PVL grade 4	Densities extending into the subcortical white matter, evolving into extensive periventricular and subcortical cysts

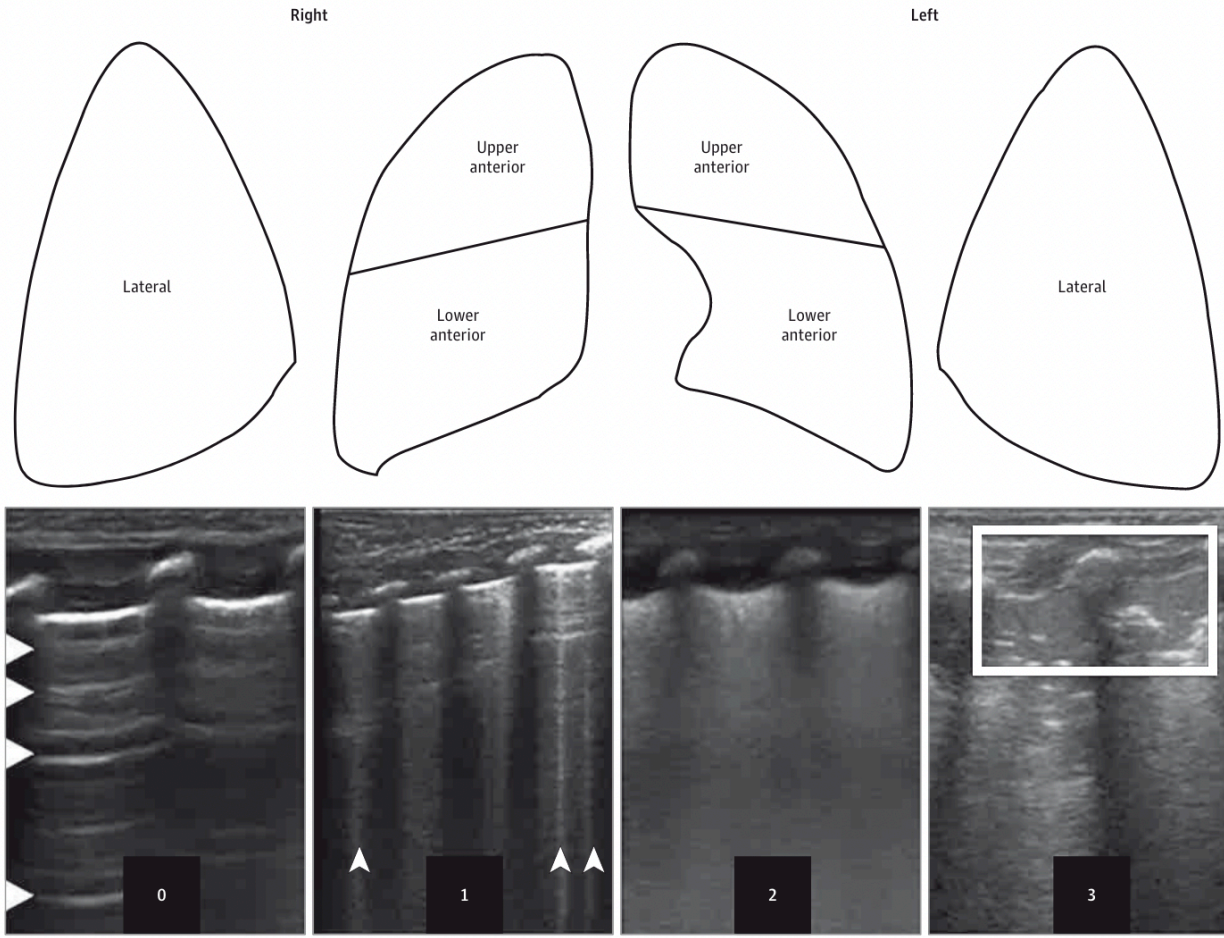
*Adapted from De Vries et al (2). PVL indicates periventricular leukomalacia.

- Bell's modified classification for necrotizing enterocolitis (37)

NEC staging according to modified Bell's Classification, radiologic signs and intestinal signs

Stage	Classification	Radiologic signs	Intestinal signs
IA	Suspected NEC	Normal or intestinal dilation, mild ileus	Elevated pre-gavage residuals, mild abdominal distention, emesis, guaiac-positive stool
IB	Suspected NEC	Same as above	Bright red blood from rectum
IIA	Definite NEC: mildly ill	Intestinal dilation, ileus, pneumatosis intestinalis	Same as above, plus absent bowel sounds, +/- abdominal tenderness
IIB	Definite NEC: moderately ill	Same as IIA, plus portal vein gas, with or without ascites	Same as above, plus absent bowel sounds, definite abdominal tenderness, +/- abdominal cellulitis or right lower quadrant mass
IIIA	Advanced NEC: severely ill, bowel intact	Same as IIB, plus definite ascites	Same as above, plus signs of generalized peritonitis, marked tenderness, and distention of abdomen
IIIB	Advanced NEC: severely ill, bowel perforated	Same as IIB, plus pneumoperitoneum	Same as IIIA

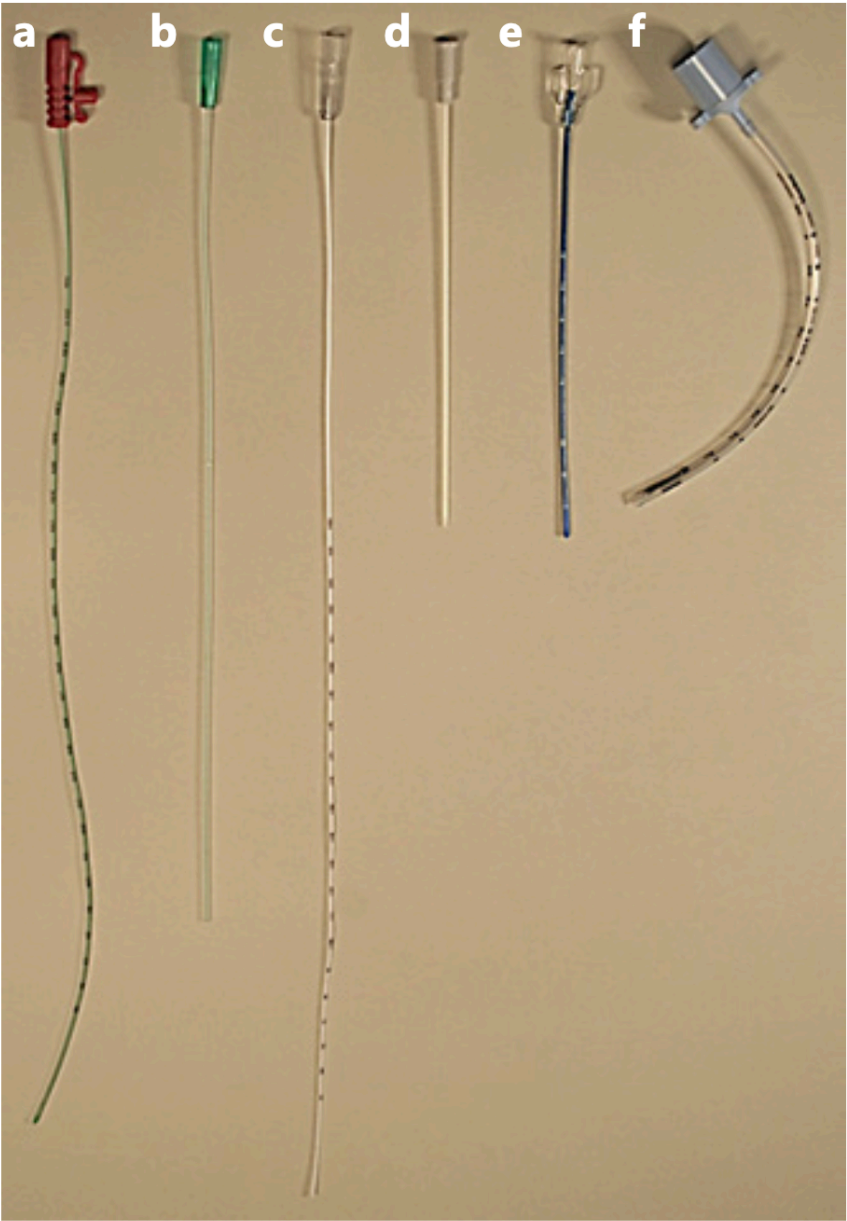
Appendix 2: Lung Ultrasound Score (22)



Each lung has been divided into 3 areas, as shown in the upper part of the figure. For each area, a score of 0 to 3 has been assigned. Score values correspond to 4 different patterns as shown in the ultrasonograms. Patterns were photographed during a longitudinal scan with a high-resolution linear probe (12-18 MHz; GE Logiq E9; GE Healthcare). Scores are given as follows, for

any lung area: 0 indicates A-pattern (defined by the presence of only A-lines [arrowheads]); 1, B-pattern (defined as the presence of ≥ 3 B-lines [arrowheads], well spaced); 2, severe B-pattern (defined as the presence of crowded and coalescent B lines with or without consolidations limited to subpleural space); and 3, extended consolidation (box).

Appendix 3: thin catheters used for surfactant administration with LISA procedure (38)



Appendix 4: supplementary Tables

	Table 6 : Maternal and neonatal characteristics, subgroups of gestational age								
	23 - 26+6 WGA		27 - 32+6 WGA		33 - 36+6 WGA				
	2013-2015	2019-2021	2013-2015	2019-2021	2013-2015	2019-2021	p		
Total population	76	85	384	436	366	433			
Mother									
Age, median (Q1-Q3), years	30 (25-35)	31 (29-35)	30 (27-34)	31 (27-36)	0.007	31 (27-35)	32 (28-36)	0.003	
Gravidity, mean (SD)	2.35 (1.65)	2.78 (2.03)	0.2	2.6	<0.001	2.4 (1.8)	2.9 (2.4)	0.01	
Parity, mean (SD)	1.88 (1.28)	2.07 (1.25)	0.2	1.9	0.001	2.2 (1.3)	2.3 (1.3)	0.2	
Medically assisted procreation, n(%)	22/76 (29%)	13/85 (15%)	0.054	78/382 (20%)	106/432 (35%)	0.2	61/366 (17%)	60/433 (14%)	0.3
Singleton n(%)	47/76 (62%)	62/85 (73%)	0.2	240/384 (63%)	288/436 (66%)	0.3	240/366 (66%)	274/433 (63%)	0.5
Gestation									
Gestational diabetes, n(%)	0/76 (0%)	8/85 (9.4%)	0.007	24/384 (6.3%)	64/436 (15%)	<0.001	52/366 (14%)	95/434 (22%)	0.006
Pre existing diabetes, n(%)	0/76 (0%)	1/85 (1%)	1	6/384 (1.6%)	6/436 (1.4%)	1	15/366 (4%)	25/434 (5.8%)	0.3
Hypertensive disorders, including pre-eclampsia, n(%)	9/76 (12%)	12/85 (14%)	0.8	97/384 (25%)	99/436 (23%)	0.4	59/366 (16%)	90/434 (21%)	0.1
Smoker during pregnancy, n(%)	12/66 (18%)	11/68 (16%)	0.8	69/343 (20%)	85/371 (23%)	0.4	59/326 (18%)	96/411 (23%)	0.08
Suspected chorioamnionitis, n(%)	18/76 (24%)	25/85 (29%)	0.5	22/384 (5.7%)	23/436 (5.3%)	0.9	9/366 (2.5%)	13/434 (3%)	0.7
Premature rupture of membranes, n(%)	34 (45%)	30 (35%)	0.3	100/384 (26%)	129/436 (30%)	0.3	88/366 (25%)	96/430 (22%)	0.5
If so, duration in days, median (Q1-Q3)	3 (1-7)	3 (1-6)	0.7	5 (2-16)	5 (2-15)	0.9	2 (1-8)	2.75 (1-6)	0.5
Prenatal corticosteroid									
Complete treatment, n(%)	55/76 (72%)	63/85 (74%)	0.9	252/384 (66%)	296/436 (68%)	0.1	198/366 (54%)	245/434 (57%)	0.3
Delivery details									
Cephalic presentation, n(%)	32/72 (44%)	47/83 (57%)	0.2	230/370 (62%)	262/428 (61%)	0.8	268/349 (77%)	317/428 (74%)	0.4
Caesarean, n(%)	41/76 (54%)	37/86 (44%)	0.2	285/384 (74%)	302/436 (69%)	0.1	236/366 (64%)	277/434 (64%)	0.9
If caesarean, emergency caesarean, n(%)	16/41 (39%)	24/37 (65%)	0.03	111/283 (39%)	183/302 (61%)	<0.001	98/236 (42%)	128/277 (47%)	0.3
General anaesthesia, n(%)	7/76 (9%)	14/85 (16%)	0.2	31/384 (8%)	60/436 (14%)	0.01	23/366 (6.3%)	32/434 (7.4%)	0.6
Newborn infant									
Female sex, n(%)	39/76 (51%)	48/85 (56%)	0.5	284/384 (48%)	218/436 (50%)	0.5	163/366 (45%)	172/434 (40%)	0.2
WGA, median (Q1-Q3)	25.5 (25-26.4)	25.6 (24.6-26.4)	0.5	31.1 (29.6-32.1)	30.9 (29.3-32)	0.3	34.3 (33.7-35.3)	34.4 (33.6-35.3)	0.3
Weight g, median (Q1-Q3)	752 (650-870)	700 (570-840)	0.03	1355 (1130-1650)	1365 (1130-1665)	0.9	2000 (1670-240)	2010 (1710-23)	0.7
Zscore birth weight, median (Q1-Q3)	0.02 (-0.6-0.5)	-0.25 (-0.8 -0.44)	0.1	-0.2 (-1.1-0.3)	-0.1 (-0.8-0.4)	0.09	-0.6 (-1.5-0.3)	-0.6 (-1.4 -0)	0.9
UGR, n(%)	1/76 (1.3%)	8/85 (9.4%)	0.04	19/384 (4.9%)	23/426 (5.3%)	0.9	45/366 (12%)	48/434 (11%)	0.6
Macrosomia, n(%)	0/76 (0%)	2/85 (2.4%)	0.5	3/384 (0.8%)	4/436 (1%)	1	9/366 (2.5%)	7/434 (1.6%)	0.5
APGAR score, mean (SD)	6.7 (2.5)	6.7 (2.5)	0.9	8.6 (1.8)	8.6 (1.8)	0.4	9 (1.3)	9 (1.4)	0.8
APGAR score <7 at 5 min n(%)	29/76 (38%)	35/85 (41%)	0.7	58/438 (11%)	58/436 (13%)	0.5	24/366 (6.6%)	28/434 (6.5%)	1
Arterial blood lactate, mean (SD)	3.7 (2.8)	3.8 (2.85)	0.7	2.7 (2-4)	2.8 (2-4.3)	0.7	3.2 (1.8)	3.1 (2)	0.3
Admission to NICU									
Temperature at admission to NICU °C, median (Q1-Q3)	35.7 (35.1-36.4)	36.4 (36-36.8)	<0.001	35.9 (35.4-36.5)	36.8 (36.5-37.1)	<0.001	36.2 (35.7-36.7)	36.6 (36.3-37)	<0.001
Glycemia at admission to NICU g/L, median (Q1-Q3)	0.7 (0.48-0.87)	0.75 (0.6-0.9)	0.2	0.54 (0.4-0.67)	0.6 (0.43-0.8)	<0.001	0.54 (0.44-0.7)	0.56 (0.43-0.7)	1

	Table 7 : Surfactant administration, subgroups of gestational age				
	2013-2015	2019-2021	2013-2015	2019-2021	
Total population	76	85	384	436	
Number of infants treated with surfactant, n(%)	74/76 (97%)	82/85 (96%)	150/384 (39%)	152/436 (35%)	
Number of infants treated with surfactant if respiratory disorder, n(%)	74/76 (97%)	82/85 (96%)	150/335 (45%)	152/411 (37%)	
Types of procedure					
Conventional administration, n(%)	68/69 (99%)	38/81 (47%)	117/149 (79%)	13/152 (8.6%)	
Insure, n(%)	0/69 (0%)	1/81 (1.2%)	31/149 (21%)	6/152 (3.9%)	
USA, n(%)	1/69 (1.4%)	42/82 (52%)	1/149 (0.67%)	133/152 (88%)	
Others details					
More than 1 dose of surfactant, n(%)	17/74 (23%)	29/82 (35%)	11/150 (7%)	17/135 (11%)	
Minutes of life, median (Q1-Q3)	19 (12-72)	22.5 (12-35)	0.1	32 (23-45)	30 (0-90)
FiO2 before surfactant administration, median (Q1-Q3)	61.7 (23)	60.8 (28)	0.5	50 (40-70)	40 (35-70)
Sedation before surfactant administration, n(%)	47/66 (71%)	48/68 (70%)	1	103/114 (90%)	109/120 (91%)

Table 9: Global evolution and other major in-hospital complications		23 - 26+6 WGA		27- 32+6 WGA		33 - 36+6 WGA		
		2013-2015	2019-2021	2013-2015	2019-2021	2013-2015	2019-2021	
Total population	76	85	384	436	366	434	p	
Hemodynamics								
Parent ductus arteriosus that required treatment, n(%)	51/76 (67%)	51/85 (60%)	0.15	44/384 (11%)	43/436 (10%)	0.5	0/366 (0%)	0/434 (0%)
Neurologic								
Intraventricular hemorrhage, stage 3 or 4, n(%)	17/76 (22%)	28/85 (33%)	0.3	9/384 (2.3%)	13/436 (3%)	0.7	2/346 (0.6%)	3/434 (0.7%)
Periventricular leukomalacia, stage 3 or 4, n(%)	1/76 (1.3%)	0/85 (0%)	0.2	3/384 (0.8%)	8/436 (1.8%)	0.4	2/366 (0.6%)	1/434 (0.2%)
Digestive								
Necrotizing enterocolitis, stage 2 or 3, n(%)	5/76 (6.6%)	8/85 (9.4%)	0.6	17/384 (4.4%)	11/436 (2.5%)	0.2	3/366 (0.8%)	3/434 (0.7%)
Bowel perforation, n(%)	3/76 (3.9%)	7/85 (8.2%)	0.3	0/384 (0%)	3/436 (0.7%)	0.3	0/366 (0%)	3/434 (0%)
Nutritional strategy								
Need for central venous catheterization, n(%)	76/76 (100%)	85/85 (100%)	1	340/384 (89%)	373/436 (86%)	0.8	119/366 (32%)	91/434 (20%)
Duration of central venous catheterization, days, median (Q1-Q3)	21 (1.5-32)	17 (10-28)	0.04	10 (8-14)	7 (6-11)	<0.001	6 (4-10)	6 (5-7)
Initial weight loss, %BW, median (Q1-Q3)	6.9 (2:10)	4.3 (0.5-9.5)	0.2	8.1 (5.7-10.5)	5 (2.4-7.6)	<0.001	6 (4-8)	6 (3.7-8.1)
Retinopathy of prematurity								
Fundoscopic anomaly	7/76 (9%)	6/85 (7%)	0.8	1/384 (0.3%)	2/436 (0.5%)	1	0/366 (0%)	0/434 (0%)
Retinopathy of prematurity treated with laser or injection	3/76 (4%)	4/85 (4.7%)	0.8	0/384 (0%)	0/436 (0%)	0/366 (0%)	0/434 (0%)	
Discharge								
Duration of hospitalisation, days, median (Q1-Q3)	85 (68-98)	84 (39-101)	0.9	44 (22)	43 (21)	0.8	17 (10-26)	13 (8-22)
WGA at discharge, median (Q1-Q3)	38 (35.5-39.4)	38.9 (37.7-41.1)	0.007	37.1 (35.3-38.4)	36.9 (34.7-38.4)	0.2	37 (36.1-38)	36.7 (35.7-37.9)
Weight at discharge, grams, median (Q1-Q3)	2490 (2000-2800)	2900 (2430-3310)	<0.001	2335 (1995-2670)	2385 (1976-2810)	0.06	2280 (2055-2600)	2260 (2030-2555)
Zscore weight at discharge, median (Q1-Q3)	-1.1 (-1.5 - -0.7)	-0.8 (-1.3 - -0.2)	0.02	-1.1 (-1.6 - -0.6)	-0.8 (-1.3 - -0.3)	<0.001	-1.1 (-1.8 - -0.6)	-1.1 (-1.7 - -0.6)
Zscore weight at discharge <2DS, n(%)	3/53 (5.7%)	2/51 (3.9%)	1	130/366 (8.2%)	38/420 (9%)	0.7	58/353 (16%)	42/409 (10%)
Mortality, n(%)	23/76 (30%)	34/85 (40%)	0.3	13/382 (3.4%)	14/436 (3.2%)	1	0/366 (0%)	0/434 (0%)
Survival without severe complications, n(%)	40/76 (53%)	32/85 (38%)	0.06	344/384 (90%)	397/436 (91%)	0.5	361/366 (99%)	426/434 (98%)

Table 10: Number and percentage of infants treated with surfactant each year

	Infants treated by surfactant, n	Total number of infants, n	% surfactant / total	Respiratory failure, n	% surfactant / respiratory failure
2013	91	284	32%	211	43%
2014	82	269	30%	193	43%
2015	72	273	26%	214	34%
Total period 1	245	826	30%	628	40%
2019	90	301	30%	245	37%
2020	60	328	18%	247	24%
2021	98	326	30%	269	36%
Total period 2	248	955	26%	761	33%

SERMENT D'HIPPOCRATE

En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure, au nom de l'Être suprême, d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine.

Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.

Admise dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Respectueuse et reconnaissante envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.
Que je sois couverte d'opprobre et méprisée de mes confrères si j'y manque.

RÉSUMÉ / ABSTRACT

Prise en charge de la détresse respiratoire néonatale par administration mini-invasive de surfactant : impact sur le taux de recours au surfactant et évolution des pratiques, étude observationnelle au CHU de Montpellier

Introduction : L'administration de surfactant par méthode mini-invasive pourrait limiter le recours à la ventilation invasive et diminuer le risque de mortalité et de dysplasie bronchopulmonaire (DBP). Peu d'études ont documenté l'influence de cette procédure sur le taux d'utilisation du surfactant chez le nouveau-né prématuré.

Méthodes : L'objectif principal était de comparer le taux de traitement par surfactant des nouveau-nés prématurés sur deux périodes distinctes de 3 ans (2013-2015 et 2019-2021), avant et après mise en place d'un protocole encadrant l'administration mini-invasive de surfactant (2017). L'objectif secondaire était de comparer la prise en charge respiratoire et globale pendant ces deux périodes.

Résultats : 1781 nouveau-nés [32.6 (30-34) SA, 1600 (1210-2000) g] ont été inclus, 9% à 23-26SA, 46% à 27-32SA et 45% à 33-36SA. L'administration de surfactant par méthode mini-invasive est devenue majoritaire (76% vs 0,4%, $p < 0,001$), pour tous les âges gestationnels. Le recours au surfactant a diminué (33% vs 40%, $p < 0,01$), en particulier aux termes 28-29 SA (57,9% vs 76,7%, $p < 0,01$). Le taux de sédation est resté stable (84%). Plus d'enfants ont nécessité une deuxième dose (19% vs 12%, $p < 0,001$). Le recours à la ventilation invasive a diminué (12% vs 31%, $p < 0,001$) mais le taux de DBP a augmenté dans le sous-groupe 27-32 SA (15% vs 8,5%, $p < 0,01$).

Conclusion : L'administration mini invasive de surfactant est devenue majoritaire pour l'ensemble des prématurés, elle s'est accompagnée d'une réduction du recours au surfactant et à la ventilation invasive, sans démontrer de bénéfice sur le risque de DBP.

Mots clés : prématurité, surfactant, détresse respiratoire néonatale, surfactant sans ventilation, SSV, MIST

Management of neonatal respiratory distress syndrome by minimally invasive administration of surfactant: impact on the rate of infants treated with surfactant and evolution of practices, an observational study at the Montpellier University Hospital

Introduction: Less invasive surfactant administration (LISA) may reduce the need for invasive ventilation and decrease the risk of mortality and bronchopulmonary dysplasia (BPD). Few studies have documented the influence of this procedure on the rate of surfactant use in preterm neonates.

Methods: The primary objective was to compare the rate of surfactant therapy for preterm neonates over two distinct periods of 3 years (2013-2015 and 2019-2021), before and after the implementation of a protocol for LISA (2017). The secondary objective was to compare respiratory and overall management between these two periods.

Results: 1781 neonates [32.6 (30-34) wGA, 1600 (1210-2000) g] were included, 9% at 23-26 wGA, 46% at 27-32 wGA and 45% at 33-36 wGA. LISA became the standard method (76% vs 0.4%, $p < 0.001$), for all gestational ages. Surfactant use decreased (33% vs 40%, $p < 0.01$), especially at 28-29 wGA (57,9% vs 76,7%, $p < 0.01$). Sedation rate remained stable (84%). More children required a second dose (19% vs 12%, $p < 0.001$). The use of invasive ventilation decreased (12% vs 31%, $p < 0.001$) but the BPD rate increased in the 27-32 wGA subgroup (15% vs 8.5%, $p < 0.01$).

Conclusion: LISA has become the standard method for surfactant administration for all preterm infants, with a reduction in the use of surfactant and invasive ventilation, without demonstrating a benefit on BPD risk.

Key words: prematurity, surfactant, neonatal respiratory distress syndrome, less invasive surfactant administration, minimally invasive surfactant therapy, MIST