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Article

Outcome at 7 Years of Age of Former Very Preterm Neonates Treated with Repeated Surfactant for Prolonged Respiratory Distress in the Neonatal Period

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Abstract: This study aimed evaluating 7 years' outcome in 118 very preterm newborn (VPN, gestational age=26±1.4wks) involved in a randomized controlled trial. They presented neonatal respiratory distress (RDS) requiring ventilation for 14±2 days post-natal age (PNA). Repeated instillation of 200mg/kg Poractant alfa (SURF) did not improve early bronchopulmonary dysplasia, but SURF infants needed less re-hospitalization than controls for respiratory problem at 1- and 2-years PNA. There was no growth difference at 7.1±0.3 years for 41 SURF vs. 36 controls (80% eligible children); 7.9% SURF vs. 28.6% controls presented asthma (p=0.021). Children underwent cognitive assessment (WISC IV) and pulmonary function testing (PFT) measuring spirometry, lung volumes and airway resistance. Spirometry showed differences (p<0.05) between SURF and controls (mean±standard deviation (median z-score)) for FEV1 (L/s) (1.188±0.690(-0.803) vs. 1.080±0.243 (-1.446)); FEV1 after betamimetics (1.244±0.183(-0.525) vs. 1.091±0.209(-1.342)); FVC (L) (1.402±0.217 (-0.406) vs. 1.265±0.267(-1.141)), and FVC after betamimetics 1.452±0.237 (-0.241) vs. 1.279±0.264 (-1.020)). PFT showed no difference in volumes or airway resistance. Global IQ median [Interquartile Range] was 89[82:99] vs. 89[76:98] with 61% children >85 in both groups. Former VPN presenting severe neonatal RDS treated with repeated Surfactant have improved lung function and less asthma at 7 years PNA. There were no differences in neurodevelopmental outcome.

Keywords: extreme prematurity; surfactant; outcome; children; longitudinal study; pulmonary function testing; neurodevelopment; asthma

1. Introduction

Advances in perinatal care have made it possible to improve significantly the survival of the most immature neonates. However, this improvement accounts for some of the increase in bronchopulmonary dysplasia (BPD) [1,2]. Indeed, despite good obstetric practice and regionalization [3], prenatal maturation by maternal corticosteroids [4,5] and the early use of surfactant replacement therapy [6,7], the improvement in neonatal survival is not associated with a lower risk of developing severe BPD, contributing to long-term morbidity such as chronic lung disease, asthma, impaired neurodevelopment, and increase resource utilisation [8,9]. BPD is a perinatal disease caused by

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multiple factors, for which diverse therapeutic approaches have been proposed [3,5,6,10,11]. These measures have limited somewhat the development of BPD, but are not enough effective or devoid of significant side effects in the long term.

Among the most effective measures, exogenous surfactant administration has become a standard of care for very premature neonates [7]. The modalities of optimal surfactant administration at birth are now well defined [3,7] with early instillation after continuous positive airway pressure from birth, and an early second dose in case of persistent respiratory distress (RDS) [12]. Most recent approaches using minimizing invasive ventilation without intubation allow lowering the risk associated to mechanical ventilation sequelae [6]. However, some very premature infants still present severe RDS with prolonged mechanical ventilation and high oxygen requirements. Repeated exogenous surfactant treatment in those neonates, presenting prolonged pulmonary disease dependent of the respirator and risking progression to severe BPD, should theoretically allow promoting pulmonary healing and growth [10,11,13,14]. Thus, we designed a double blind, randomized, multicentric controlled trial to evaluate the effects of one late repeated surfactant administration in very preterm infants, less than 33 weeks gestation, who still required mechanical ventilation at 14 days of age [15]. In this study, we observed that the 118 newborns involved presented a very high rate of associated infection. After surfactant instillation but not air, the FiO2 requirements dropped for up to 24 hours after instillation but there was only a trend for less severe bronchopulmonary dysplasia/death rates at 36 weeks' postmenstrual age (PMA) (27.1% vs 35.6%; P = 0.32). Nevertheless, significantly less surfactant-treated infants needed rehospitalization for respiratory problems within the first year after discharge in 91 of the 96 surviving infants (28.3%vs 51.1%; P = 0.03). Likewise, at two years of age, children hospitalized during their first year of life were more likely to be rehospitalised during their second year (OR 4.182, 95% CI 1.478–11.834) [16]. The aims of this preplanned longitudinal study were to evaluate the pulmonary and neurodevelopment outcome at 7 years of age of the infants involved in the multicenter controlled randomized trial in the neonatal period.

2. Materials and Methods

All surviving infants of the CURDYS trial [15] were eligible for this pre-planned 7 years longitudinal study. The investigating centers contacted the families by letter reminding the 7 years' follow-up visit and inviting them to call the units to make an appointment. In the event of no response, in accordance to the previously signed agreement, they were called by telephone.

The parents were first interviewed about the events that occurred since the 2 years visit. Then, they were proposed to respond to an auto-questionnaire evaluating their feelings on the impact of respiratory symptoms on their children and family's quality of life. This questionnaire was translated and adapted for the study from Powell et al. questionnaire with 31 questions rated from 0 (no impact) to 4 (severe impact) [17]. It evaluated 4 domains leading to a global score: diurnal symptoms, night symptoms, impact on child's quality of life, impact on family quality of life. The parents' education level was recorded and stratified into 4 groups as elementary or primary school, high school, baccalaureate degree and college degree achievement. The children underwent a complete physical examination by certified trained pediatricians who were not aware of the group they had been randomized to. The standardized physical examination recorded each child's weight, height, head circumference, heart rate and resting arterial blood pressure. The children also had a complete clinical neuro-motor examination corresponding to their age.

Pulmonary function testing (PFT) in children was performed using Jaeger MasterScreen PFT and Body System (CareFusion, Höchberg, Germany) by certified examiners who were also unaware of children's original condition. Spirometry used an electronic spirometer allowing visualization in real-time of the flow-volume loop (SPIRO-USB EOLYS®, SPCS2.4, 69160 Tassin, France). The necessary respiratory manoeuvres were explained to the child who learned performing forced acceleration using instructional software (Spirometry PC Software, MD Spiro® Anaheim, CA, USA). After learning, children performed at least three acceptable manoeuvres, according to ERS/ATS guidelines [18]. Examining the data from all of the usable flow-volume curves enabled to select the largest Forced

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Vital Capacity (FVC, L) and Forced Expiratory Volume in the first second (FEV1, L/s). In order to assess the change in respiratory function in response to bronchodilator administration, a bronchodilator responsiveness testing was also performed using four separated doses of 100µg of Salbutamol delivered at 30-s intervals and at least three additional acceptable spirometry manoeuvres were recorded 10 - 15 min after betamimetics (β+) administration. Static lung volumes, measured by the method of dilution of helium in a closed circuit, determined Functional Residual Capacity (FRC, L) Total Lung Capacity (TLC, L) and Vital Capacity (VC, L). Finally, the children had simply to inhale calmly through a mouthpiece for measurement of pressure and flow rate signals allowing calculation of respiratory impedance from which we extracted airway resistance determined by the loss of load in phase with the flow rate (sRaw, cmH20 / L.s).

Finally, the children took the latest version of the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) [19] for the evaluation of their neuropsychological and cognitive functions. Four indices, Verbal Comprehension index, Perceptual Reasoning index, Working Memory index and Processing Speed index were combined to determine the Full-Scale Intelligence Quotient of the children.

Descriptive data are presented as mean± standard deviation (SD) and median values with interquartile range [IQR]. Comparisons between groups were performed using Chi square test or Fisher's exact test for categorical variables when appropriate, and the Mann-Whitney U test for continuous variables. Results of spirometry are expressed as mean±SD and z-score, using the Global Lung Function Initiative reference (GLI-12) [20]. For all analyses, the alpha risk was set at 0.05, and the tests were two-sided. Statistical analyses were performed using SYSTAT 13 software (2009; Systat Software Inc., San Jose, California, USA).

3. Results

3.1. Patients and health resource utilization

From the 118 infants initially randomized by the 13 centers involved, 11 died in each group in the neonatal period. We were able to evaluate 77 out of the 96 surviving eligible infants (80%), 41 SURF and 36 controls. Table 1 presents the characteristics of the population. There was no difference between SURF and controls respectively, for passive smoking exposure 37 vs. 45% (p=0.484), the number of infants with at least one hospitalization since the 2 years visit (41.4 vs. 41.7%, p=0.986), the use of physiotherapy for respiratory purpose (14.6 vs. 25.0%, p=0.252) or motricity (14.6 vs. 19.4%, p=0.574).

Table 1. Characteristics of the population studied.

Characteristics[1]	Surfactant treated children	Controls
Gestational age, weeks	26.1±1.3	26.1±1.4
Post-natal age at evaluation, y	7.17±0.29	7.15±0.26
Maternal education level (%):		
. Elementary school	2.8	5.4
. High school	30.5	24.4
. Baccalaureate	25.0	35.1
. College	41.7	35.1
Paternal education level (%):		
. Elementary school	2.9	5.5
. High school	37.1	36.1
. Baccalaureate	22.9	27.8
. College	37.1	30.6
Gender (% male)	56	59
Weight, kg (z-score)	22.2±5.1 (-0.259±1.270)	21.4±5.3 (-0.465±1.292)
Height, m (z-score)	1.19±0.07 (-0.525±1.222)	1.18±0.06 (-0.722±1.031)
Head Circumference, cm	51.6 ±1.7	50.8±1.6

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Cerebral Palsy, %	5.0	2.8
Sleep problem, %	10.0	13.4
Deafness, %	12.5	11.1
Visual problem[2] %	46.3	52.8

[1] No differences were significant; [2] including glasses

3.2. Parents auto-questionnaire

The same proportion of parents agreed to respond to the auto-questionnaire (38/41 vs. 33/36 parents of SURF vs. controls respectively). Table 2 presents parents' responses to the questionnaire. Parents reported that 7.9% SURF vs. 28.6% controls (p=0.021) were diagnosed with asthma and presented symptoms requiring treatment.

Table 2. Parents' response to the auto-questionnaire.

Domain scores (min-max)[1]	Surfactant treated children	Controls
Wheezing anytime, %	63	76
Diurnal symptoms (0-16)[2]	7 [0; 12]	7.5 [0; 12]
Night symptoms (0-16)	1 [0; 2]	1 [0.25; 2]
Impact on Child's QoL (0-16)	2 [0; 5]	1 [0; 4]
Impact on Family's QoL (0-16)	1 [0; 3]	1 [0; 0.3]
Global score (0-64)	8 [0; 17]	9 [0; 19]

[1]Median [IQR]; No differences were significant. [2]Minimum-maximum values; QoL: quality of life.

3.3. Pulmonary function testing

Fifty-seven children [74%] underwent complete pulmonary function testing: 26 SURF and 31 controls. However, 2 more SURF and 1 control children were not able to perform the tests and 3 SURF were not able to understand the instructions. Table 3 presents the results of the evaluated children.

Table 3. Pulmonary Function testing comparison between the 2 groups.

Values (Mean±SD)	Surfactant treated children	Controls	P
FEV1[1]	**1.188±0.169**	**1.080±0.243**	**0.032**
FEV1 z-score	-0.803±1.045	-1.446±1.270	0.061
FEV1 post β[2]+	**1.244±0.183**	**1.091±0.209**	**0.030**
FEV1 post β+ z-score	-0.525±1.003	-1.342±1.133	0.056
FVC[3]	**1.402±0.217**	**1.265±0.267**	**0.049**
FVC z-score	**-0.406±0.217**	**-1.141±1.217**	**0.022**
FVC post β+	1.452±0.237	1.279±0.264	0.054
FVC post β+ z-score	**-0.241±0.907**	**-1.020±1.207**	**0.045**
FRC[4]	1.165±0.280	1.208±0.304	0.513
TLC[5]	2.179±0.358	2.137±0.343	0.974
VC[6]	1.385±0.210	1.270±0.293	0.142
sRaw[7]	10.233±3.564	11.604±8.945	0.312
sRaw post β+	7.459±2.505	8.666±5.079	0.760

[1]FEV1 (L/s): Forced Expiratory Volume in one second; [2]β+: betamimetics; [3]FVC (L): Forced Vital Capacity; [4]FRC (L): Functional Residual Capacity; [5]TLC (L): Total Lung Capacity; [6]VC (L): Vital Capacity; [7]sRaw: Airway resistances.

3.4. Neuro-psychological and cognitive evaluation

The majority of the evaluated children were in their normal school grade (87% vs. 94% in SURF vs Controls respectively) but 63 vs 44 % (p=0.095) required specialized assistance at school. There was no difference for the use of speech therapy (53.7 vs. 66.7%, p=0.246), the need for psychotherapy

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support (43.0 vs. 33.3%, p=0.343) or the recourse to a specialized institution (36.5 vs. 30.6%, p=0.577) for SURF vs control children respectively.

We were able to get 4 selected subtests, one for each scale, in order to determine the abbreviated representative IQ (aIQ) in 64 children (33 vs 31). Unfortunately, 3 more SURF and 4 control children were not able to pass the WISC-IV evaluation. Other children did not show up for neuropsychological evaluation. There was no significant difference between the 2 groups for the aIQ evaluation: 61% were above 85 in both groups, 18 vs 19% were between 85 and 70, and 21 vs 20% were below 70 in SURF vs. control children respectively. There was no difference for the different subtests between the 2 groups.

4. Discussion

This pre-planned longitudinal study shows that former very preterm neonates presenting prolonged severe neonatal RDS and treated with one repeated Surfactant dose at 14 days of age, have improved lung function with less obstructive indicators, and present less asthma symptoms at 7 years post-natal age. This is in line with the respiratory follow-up at 1 [15] and 2 years [16] of age which showed significantly less health resources utilization with less need of re-hospitalization for respiratory problems in the children who had received one repeated instillation of 200mg/kg Poractant alfa in the neonatal period, as compared to control infants. Parents' questionnaires evaluating their feelings on the impact of respiratory symptoms on children and family's quality of life showed a similar rather good tolerance in both groups. Finally, this study shows that despite there were no significant differences between the 2 groups in clinical, neurodevelopment and cognitive outcomes, about 20% of the surviving children may be regarded as neurologically severely impaired.

These results are consistent with the clinical status of the infants at discharge suggesting a difference in the severity of morbidity at the end of the neonatal hospitalization. Surfactant treated neonates had significantly less necrotizing enterocolitis and earlier full enteral feeding, and were discharged about 1 week earlier than controls [15]. In a study of 165 extremely low birth weight neonates, Katz et al. evaluated 25 infants (representing 20% of the infants with RDS in their study) who received a repeated course of surfactant therapy for severe persistent respiratory failure and surfactant slump. They found that 70% of them had significant improvement in their lung disease up to 48 hours after instillation [21], but no longer follow-up was evaluated. In a previous study, we showed that 42 VPN compared to 27 healthy term born children, non-asthmatic, non-atopic, had significant bronchoconstriction indicators on PFT at 7 years of age [22]. In addition, prematurity, chronic lung disease, the duration of mechanical ventilation or oxygen exposure and maternal smoking were significant determinants of exercise-induced bronchoconstriction [22]. In a review on the respiratory follow-up of prematurely born children, Bodgan et al. also found that former very premature infants are prone to long-term respiratory sequelae [23]. The reasons are mainly related to impaired lung development due to dysmaturity, infectious agents, mechanical ventilation and deficient control of breathing. The consequences are an increased risk of viral infections, recurrent wheezing, asthma and a decrease in airway flow. Therefore, the authors suggest that very prematurely born children should be followed in an organized fashion to undertake preventive strategies improving these vulnerable infants' prognosis [23]. These systematic follow-up organizations are now well developed in many countries via perinatal and follow-up networks [24]. Likewise, in a systematic review of studies on the outcomes of teenagers with BPD, Carrega et al. evaluated 31 studies up to march 2023 [25]. They found that teenagers with an history of BPD present more respiratory symptoms such as wheezing and respiratory exacerbations with an impairment in pulmonary function. There is a higher risk for special education needs but the quality of life seemed similar to that of non-BPD adolescents. The data from this review are consistent with the results of our study.

In a study about health related quality of life (HRQoL) in teenagers survivors of very premature birth, Bozzetto et al. compared 27 BPD patients to 27 asthmatic patients to 27 healthy controls using the Short Form 36 questionnaire [26,27]. Despite an impaired lung function at spirometry, BPD

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patients had a similar quality of life than controls, better than asthmatic patients. In a study on psychological functioning and HRQoL in adulthood after preterm birth, Dalziel et al. found in 126 young adults born prematurely compared to 66 born at term that adults born preterm had HRQoL consistent with those who were born at term [28]. However, BPD may be associated to impaired executive functioning [29] and the HRQoL may actually be related to the level of prematurity and the presence of neurosensory or cognitive limitations [30]. In a longitudinal study, Berdal et al. showed that VPN born adults reported lower HRQoL than term born controls at 32 years of age with a significant declined from 20 to 32 years of age especially for VPN born individuals with disabilities [31]. Therefore, one must be careful in evaluating HRQoL early in life and stay aware of difficulties appearing later in life that may benefit from appropriate support on a long-term basis.

Noteworthy, more than 40% of infants involved in the CURDYS trial were initially treated by probabilistic antibiotics, because of a high suspicion of materno-fetal infection. In addition, about 90% of them presented late-onset sepsis when the overall rate of infection ranged from 14% to 24% in the participating centers for infants below 33 weeks' gestation. This is consistent with Paananen et al. [32] who studied 128 very premature infants and found that infants with inflammation and high concentrations of inflammatory cytokines were at high risk of BPD. Thus, in addition to the neurological impairment associated to BPD [33] it is now recognized that the exposition of the immature brain to inflammation contributes to significant cerebral injury and adversely affects brain development leading to subsequent neurological impairment [34]. The role of inflammation in the development of BPD may also be responsible in part of the poor neurodevelopment outcome of the infants who had presented severe RDS and subsequent BPD in the neonatal period. In a study of 98 VPN children who had BPD compared to 75 VPN without BPD and 99 healthy term born children, Short et al. evaluated the cognitive and academic consequences of BPD at 8 years old [35]. As observed in our study, they showed that 54% vs. 37% of VPN without BPD and 25% of term born infants were more likely to require special education support. They showed the same rate as in our study of 20% of BPD children presenting a full-scale IQ < 70, compared to 11% for VPN without BDP or 3% in term born infants. They observed as in other studies a significant influence of maternal education level. In our study, there was no difference for maternal or parental education level between the 2 groups. Overall, the authors conclude that BPD and long duration of oxygen have long term adverse effects on cognitive and academic achievement. These findings highlight the need for learning, behavior and development support in BPD children to improve their learning abilities and attenuate their school difficulties.

Our study has limitations. The multicenter design may lead to some heterogeneity in the PFT method between centers despite standardized protocol. However, the use of z-score for all children may improve the generalization of the results. Secondly, despite we were able to follow 80% of the eligible survivors, the number of studied children is rather low and some results may lack of power. Finally, 6 children were not able to perform PFT and were not able to pass the WISC-IV evaluation because of insufficient understanding abilities. This worsens the actual results observed and reported. However, the children were equally distributed in both groups and an impact on the overall message is unlikely.

The CURDYS trial is consistent with new perspectives using surfactant not only for "physiologic" replacement, soon after birth, but repeated as a medication for infants with severe prolonged respiratory distress. Other strategies of treatment using surfactant as a vehicle showed promising results. After verifying the biochemical properties, Yeh et al. [36] showed that 128 infants treated with surfactant mixed with budesonide showed a significant reduction in the risk of BDP or death when compared to 134 controls (OR 0.58; 95% CI 0.44–0.77). This study is very interesting as we observed significant morbid association between respiratory distress and inflammation. Finally, the perspective of using human umbilical cord-derived mesenchymal stem cells combined with surfactant is under investigation and has shown promising results in animal studies [37].

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5. Conclusion

Beyond its importance as a physiological replacement soon after birth, the use of curative repeated surfactant therapy in infants presenting with severe prolonged respiratory distress improves lung function and lowers the risk of asthma on a long-term basis. However, it does not improve poor neurodevelopment that might also be related to inflammation. New perspectives of treatment combining surfactant and budesonide are promising.

Author Contributions: Conceptualization, JMH and IH; methodology JMH, HD and SD; validation, JMH, HD, SD and IH; formal analysis, JMH; data curation, JMH, SD and CB; writing—original draft preparation, JMH; writing—review and editing, all authors.; supervision, JMH; project administration and funding acquisition, JMH. All authors have read and agreed to the published version of the manuscript.

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Ethics Committee Statement: The *Comité de Protection des Personnes de Lorraine* approved the study (CPP number 09.07.02). The study was recorded in ClinicalTrial.gov registry (NCT01039285). The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Lorraine (protocol code 2009-012817-23, approved on September 10th 2009 and a substantial modification approved on May 6th 2010).

Informed Consent Statement: Written consent from the parents or legal guardian was obtained before randomization at the neonatal period of the study. Informed consent included the longitudinal follow-up at 1, 2 and 7 years of age.

Data Availability: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to the absence of accessible repository and a change in hospital responsibility in the middle of the study (a fusion between the Maternity Regionale University hospital and the CHRU of Nancy occurred in 2014).

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