Multi-centre randomised trial of invasive and less invasive surfactant delivery methods showed similar spirometry results at 5–9 years of age

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Funding information
Bundesministerium für Bildung und Forschung, Grant/Award Number: 01ER0805 and 01ER1501; Chiesi Farmaceutici; Federal Ministry of Education and Research; Chiesi

Abstract
Aim: We explored whether subnormal forced expiratory volume within 1s (FEV₃) at 5–9 years of age was lower in children born preterm who received less invasive surfactant administration (LISA) rather than surfactant via an endotracheal tube.

Methods: The multi-centre, randomised Nonintubated Surfactant Application trial enrolled 211 preterm infants born at 23–26 weeks of gestation from 13 level III neonatal intensive care units from April 2009 to March 2012. They received surfactant via LISA (n = 107) or after conventional endotracheal intubation (n = 104). The follow-up

Abbreviations: ARR, absolute risk reduction; CI, confidence interval; FEV₃, forced expiratory volume within one second; FVC, forced vital capacity; GMFCS, Gross Motor Function Classification System; IQR, interquartile range; LISA, less invasive surfactant administration; MABC-2, Movement Assessment Battery for Children, Second Edition; NICUs, neonatal intensive care units; SD, standard deviation; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence, Third Edition.

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1 | INTRODUCTION

Less invasive surfactant administration (LISA) delivers surfactant to spontaneously breathing preterm infants using a small diameter tube. Less invasive surfactant administration (LISA) delivers surfactant to spontaneously breathing preterm infants using a small diameter tube. One study found that it reduced the rate of mechanical ventilation when it was used in preterm infants born at 26 weeks of gestation or more. Other studies showed that LISA also reduced mechanical ventilation in the first 72 h in infants with a lower gestational age. However, many of these infants were subsequently intubated due to severe apnoea. Meta-analyses of randomised clinical trials indicated that LISA was superior to other ventilation strategies with regards to bronchopulmonary dysplasia and the composite endpoint of bronchopulmonary dysplasia or death. An updated version of the European Consensus Guidelines on the Management of Respiratory Distress Syndrome was issued in 2019. This stated that LISA was the preferred mode of surfactant administration for spontaneously breathing babies on continuous positive airway pressure. However, the guidelines added that clinicians needed to be experienced with the technique.

Long-term outcome data from randomised controlled trials on LISA are scarce. Follow-up data from the Avoiding Mechanical Ventilation trial reported no differences with regards to growth and Bayley scales of Infant Development (2nd Edition) at 2 years of age. However, no follow-up data from controlled LISA trials in children at age 5–9 years have been published.

The Nonintubated Surfactant Application was a multi-centre randomised trial of preterm infants born at 23–26 weeks of gestation who received surfactant replacement via LISA or endotracheal intubation. The 2-year neurocognitive follow-up data from this trial has been published. This study focused on the fact that the lung is the target organ of surfactant replacement therapy. Our aim was to test the hypothesis that children treated with LISA during the randomised control trial would have better lung function at 5–9 years of age than the control group who received surfactant via endotracheal intubation. We also determined the neurocognitive outcome as a safety measure.

2 | PATIENTS AND METHODS

This Nonintubated Surfactant Application randomised controlled trial was carried out in 13 level III neonatal intensive care units (NICUs). Most of these NICUs were located in the northern and western parts of Germany. Between April 2009 and March 2012, we enrolled 211 spontaneously breathing preterm infants born between 23 and 26 weeks of gestation. Infants were randomly assigned to a LISA or control group by in a 1:1 ratio using sealed opaque envelopes. Randomisation was stratified according to the study centre and gestational age: 23–24 versus 25–26 weeks. Multiple birth infants were assigned to the same group. Both groups received at least 100 mg/kg bodyweight surfactant. The 107 children in the LISA group received the surfactant via a 4 French catheter during spontaneous breathing, with continuous positive airway pressure. The 104 children in the control group received the surfactant via conventional endotracheal intubation and bolus administration, followed by mechanical ventilation. Repeated administrations of surfactant were permitted in both groups if the fraction of inspired oxygen levels exceeded 0.35. The trial was registered with the International Trial Registry (ISRCTN64011614).

assessments were carried out by a single team blinded to the group assignments. The main outcome was FEV \(_1\) < 80% of predicted values.

**Results:** Spirometry was successful in 102/121 children. The other children died or were lost to follow-up. Median FEV \(_1\) was 93% (interquartile range 80%–113%) of predicted values in the LISA group and 86% (interquartile range 77–102%) in the control group (\(p = 0.685\)). Rates of FEV \(_1\) < 80% were 11/57 (19%) and 15/45 (33%), respectively, which was an absolute risk reduction of 14% (95% confidence interval −3.1% to 31.2%, \(p = 0.235\)). There were no differences in other outcome measures.

**Conclusion:** The proportion of children aged 5–9 years with subnormal FEV \(_1\) was not significantly different between the groups.

**Key Notes**
- This randomised study enrolled 211 preterm infants born at 23–26 weeks of gestation from 13 level III neonatal intensive care units from April 2009 to March 2012.
- They received surfactant via less invasive surfactant administration (\(n = 107\)) or after conventional endotracheal intubation (\(n = 104\)).
- The proportion of children aged 5–9 years with subnormal forced expiratory volume within 1 s <80% of predicted values was not significantly different between the two groups.
The primary outcome was defined as survival without bronchopulmonary dysplasia at 36 weeks of postmenstrual age and was not significantly different between the LISA and control groups. The infants treated with LISA had lower rates of mechanical ventilation, a shorter duration of mechanical ventilation and a lower rate of pneumothorax and intraventricular haemorrhage grade III or IV. Of the 211 infants who were included in the study, 189 survived to discharge. 3

2.1 | Follow-up assessments

Between December 2014 and March 2019, the children were assessed once by the German Neonatal Network follow-up team. The follow-up team was blinded to which group the children were randomised to. In addition, they did not have any information on any interventions or complications during the children’s stays in the neonatal intensive care units. Identical instruments were used for all of the follow-up assessments, as the German Neonatal Network team took all the necessary equipment to the participating centres. Spirometry was carried out with an EasyOne spirometer (NDD Medizintechnik AG). The nostrils were closed with a gentle clip and a maximum of 10 attempts were assessed. The run with the highest quality was chosen for further analysis. Forced expiratory volume within 1s (FEV$_1$) and forced vital capacity (FVC) were recorded in litres. These were analysed as a percentage of predicted values, as FEV$_1$%, and FVC%, based on a European reference population. 9 We also calculated the FEV$_1$ and FVC z-scores, according to the Global Lung Function Initiative, and these were corrected for age, sex, height and ethnicity. 10 Cognitive impairment was measured by the German version of the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III). Motor impairment was determined with the Gross Motor Function Classification System (GMFCS) and the Movement Assessment Battery for Children, Second Edition (MABC-2). Height was measured with the Harpenden Portable Stadiometer (Holtain Ltd), and weight with ADE MAK T7336 scales (ADE GmbH).

2.2 | Endpoints

The target organ of surfactant therapy is the lung. Although spirometry has rarely been used as an endpoint in randomised controlled trials of preterm infants, 11, 12 a FEV$_1$ below 80% of the predicted value was defined as the main outcome of our study. This threshold has frequently been used in observational reports. 13 FEV$_1$ below 80%, or the inability to complete spirometry, was also defined as a combined endpoint. We analysed this endpoint, because younger children are not always able to complete spirometry, particularly if they have a neurocognitive delay. Further analyses included FEV$_1$% and FVC% data. Cognitive delay was defined as WPPSI-III scores of less than 85. Cerebral palsy was defined as a GMFCS scores above 1, blindness as visual acuity of <2%, and hearing impairment as the need for hearing aids.

2.3 | Ethics

The Nonintubated Surfactant Application follow-up study was approved by the ethics committee of the University of Lübeck (AZ 17–352).

2.4 | Statistics

The follow-up analysis was a two-group parallel study on an intention-to-treat basis, in keeping with the initial trial design. However, this was limited by the fact that only infants with follow-up assessments were available for the analysis. The main outcome was defined as a FEV$_1$ of less than 80%. All other analyses of outcome variables were exploratory and not adjusted for multiple comparisons. The main outcome and all the dichotomous secondary outcomes were tested using the Cochrane-Mantel–Haenszel test, with adjusted odds ratios. This was stratified by gestational age and 2×2 tables. Test results for the main outcome were adjusted using the data-estimated mean design effect of 1.29 to allow for clustering due to multiple births. 14 Linear regression was used for the FEV$_1$% and FVC% data and this was adjusted for gestational age.

The statistical analysis was performed using R version 3.5.2 (The R Foundation, Vienna, Austria). The R-function icc package irr (0.84.1) (The R Foundation) was used to obtain the intraclass correlation in order to obtain the mean design effect.

3 | RESULTS

The 13 centres randomised 211 infants: 22 (10.4%) died before discharge from the hospital and another seven children (3.3%) died after discharge. These 29 deaths were uniformly distributed across the LISA ($n = 15$) and the control ($n = 14$) groups. By 5–9 years of age, 61 children (28.9%) had been lost to follow up: 24 in the LISA group and 37 controls (Figure 1). This meant that we followed up 121 infants when they were in that age range.

The infants who died before, or after discharge, had a median birth weight of 564 grams, with an interquartile range (IQR) of 450–650 g, and a low median gestational age of 24.4 (IQR 24.1–24.9) weeks. The children who were lost to follow-up had a median birth weight of 680 g (IQR 560–860 g) and median gestational age of 25.3 weeks (IQR 24.6–26.3 weeks). These were not significantly different to the children who were followed up (Table 1). The 121/182 children who were followed up at 5–9 years of age comprised 12/21 (57%) born at 23 weeks of gestation, 28/38 (73%) born at 24 weeks, 48/68 (71%) born at 25 weeks and 33/55 (60%) born at 26 weeks. The characteristics of the 121 children who were followed up are shown in Table 1. Just under a third (22/68, 32%) of the remaining children in the LISA group were not able to complete spirometry or had a FEV$_1$ of less than 80%, compared to 23/53 (43%) in the control group. The absolute risk reduction in the LISA group was 11%, with a 95%
confidence interval (95% CI) from −6.3% to 28.4% (p = 0.297), based on a cluster-adjusted Cochrane–Mantel–Haenszel test that was stratified by gestational age.

The data on the 102 children with successful spirometry, 57 in the LISA group and 45 in the control group, are shown in Table 2. In the LISA group, 11/57 (19%) children had a FEV₁ of less than 80% of the predicted levels, compared to 15/45 (33%) children in the control group. This difference was not significant. When the control group was compared to the LISA group, the odds ratio for a FEV₁ of less than 80% was 2.16 (95% CI 0.76–6.08; p = 0.235) based on the Cochrane–Mantel–Haenszel test, stratified by gestational age. The lowest gestational age group, of 23–24 weeks, was not associated with worse FEV₁ % levels than older gestational ages (Figure 2). Additional pulmonary outcomes and neurocognitive outcome data are shown in Tables 2 and 3. These show that there were no differences between the children treated with LISA and the control children. The odds ratios for WPPSI-III scores of less than 85 were 1.94 (95% CI 0.8–4.8, p = 0.216) and for cerebral palsy they were 0.99 (95% CI 0.2–4.7, p = 0.991), as seen in Table 3.

4 | DISCUSSION

Our study reported outcome data from a randomised controlled trial, which compared preterm infants who received surfactant via LISA or an endotracheal tube. Spontaneously breathing preterm infants who were born from 23 to 26 weeks of gestation at 13 centres were followed up by the same German Neonatal Network team when they were 5–9 years of age. The data on the safety of the less invasive LISA procedure were reassuring.

No significant differences were observed between the preterm infants treated with LISA and the control children who received
GÖPEL et al. showed that surfactant via an endotracheal tube. This lack of significance was probably due to the small sample size. The mean difference in FEV$_1$% was 4% and the median difference was 7% (Table 2). A much larger paediatric trial compared drugs for cystic fibrosis and said that this kind of difference in percentages indicated a meaningful benefit.  

Randomised trials of preterm infants are often associated with small sample sizes and our study was no exception. This was due to the high mortality rate and the long gap before FEV$_1$ could be tested, two factors which have often been associated with considerable loss to follow-up.  

Few single centre studies have reported long-term outcome data on children treated with LISA and none have reported spirometry outcomes at the ages covered by our study. We compared the spirometry results of our study to published cohort data. The Extremely Preterm Infants in Sweden Study reported spirometry data for children who were born from 22–26 weeks of gestation when they reached 6.5 years of age. The FEV$_1$ in children born from 22 to 24 weeks was more than one standard deviation lower than the children born from 25 to 26 weeks. It is remarkable that our study found that children born at 23–24 weeks did not have different FEV$_1$% levels than those born at 25–26 weeks. The high FEV$_1$ levels in the LISA and control groups at 23–24 weeks indicates that other factors, in addition to the mode of surfactant administration, may be important for preserving optimal lung function in extremely immature infants.

Neurocognitive outcome data and rates of cerebral palsy in children born at a very low gestational age were published by the Extremely Preterm Infants in Sweden Study. GMFCS scores above 1 were reported in 3.9% of children born at 22–26 weeks and Wechsler Intelligence Scale for Children, fourth edition scores

| Pulmonary outcomes | LISA (n = 57) | Controls (n = 45) | ARR (95% CI) | p Value |
|-------------------|-------------|-----------------|-------------|---------|
| FEV$_1$ <80%, number (%) | 11 (19) | 15 (33) | 14.0 (−3.1 to 31.2) | 0.235$^a$ |
| FEV$_1$ in litres, median (IQR) | 0.92 (0.80–1.13) | 0.95 (0.73–1.08) | | |
| FVC in litres, median (IQR) | 1.00 (0.88–1.21) | 1.01 (0.77–1.20) | | |
| FEV$_1$ in % of predicted value, median (IQR) | 93 (84–100) | 86 (77–102) | | 0.685$^b$ |
| FVC in % of predicted value, median (IQR) | 84 (76–94) | 80 (71–94) | | 0.816$^b$ |
| FEV$_1$ z-score$^c$ median (IQR) | −1.35 (−0.71–−1.96) | −1.69 (−0.59–−2.41) | | |
| FVC z-score$^c$ median (IQR) | −1.45 (−0.67–−1.86) | −1.58 (−0.73–−2.48) | | |
| FEV$_1$/FVC, median (IQR) | 0.96 (0.87–1.00) | 0.97 (0.90–1.00) | | |

Abbreviations: ARR, absolute risk reduction; CI, confidence interval.

$^a$Cluster-adjusted Cochrane-Mantel–Haenszel test stratified by gestational age (mean design effect 1.29), all other p values in this table are descriptive.

$^b$Linear regression for randomisation group adjusted for gestational age.

$^c$z-scores were calculated according to Global Lung Function Initiative-standards$^{10}$
of less than −2SD in 29%.

The frequencies were similar in our study, at 5.8% for GMFCS scores above 1 and 27% for WPPSI-III scores of <85.

4.1 | Strengths and limitations

The major limitation of our study was the small sample size. The results of the OPTIMIST-A trial have now been published. This examined the effect of minimally invasive surfactant therapy versus sham treatment on death or bronchopulmonary dysplasia in preterm infants with respiratory distress. A number of randomised LISA trials are also under way. The follow-up assessments of infants who are enrolled in these trials will hopefully provide more information about the effects of LISA on long-term lung function. Another limitation of our study was the lack of information on children who were lost to follow up. However, the baseline data were not different between children with and without follow up. The major strength of our study was the long-term follow up, which included spirometry testing by a single team blinded to the children's group assignment.

5 | CONCLUSION

This study found that 46 of the 68 children who received LISA in this randomised controlled trial had normal FEV₁ levels at 5–9 years of age. We were not able to confirm our hypothesis that LISA increased the rate of normal FEV₁ at this age, but our trial was not powered for this particular endpoint. The spirometry and neurocognitive outcomes of the children treated with LISA were similar when they were compared to a control group who received surfactant via an endotracheal tube. They were also similar to other published cohort data. Our results indicate that LISA is a safe procedure with regards to long-term lung function and neurocognitive outcomes.

ACKNOWLEDGEMENTS

The authors are grateful to all the children and families who participated in this study.

FUNDING INFORMATION

This study was supported by Chiesi Farmaceutici SpA, Parma, Italy and the German Federal Ministry of Education and Research (BMBF 01ER0805 and BMBF 01ER1501). The sponsors had no influence on any aspect of the study or paper.

CONFLICT OF INTEREST

WG, CH, CR, CB, AK and EH have received payments for presentations and travel from Chiesi Farmaceutici SpA. The other authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Deidentified participant data is available upon reasonable request from the corresponding author.

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