

Original Investigation

Nonintubated Surfactant Application vs Conventional Therapy in Extremely Preterm Infants

A Randomized Clinical Trial

Angela Kribs, MD; Claudia Roll, MD; Wolfgang Göpel, MD; Christian Wieg, MD; Peter Groneck, MD; Reinhard Laux, MD; Norbert Teig, MD; Thomas Hoehn, MD; Wolfgang Böhm, MD; Lars Welzing, MD; Matthias Vochem, MD; Marc Hoppenz, MD; Christoph Bühner, MD; Katrin Mehler, MD; Hartmut Stützer, PhD; Jeremy Franklin, PhD; Andreas Stöhr, PhD; Egbert Herting, MD; Bernhard Roth, MD; for the NINSAPP Trial Investigators

IMPORTANCE Treatment of respiratory distress syndrome in premature infants with continuous positive airway pressure (CPAP) preserves surfactant and keeps the lung open but is insufficient in severe surfactant deficiency. Traditional surfactant administration is related to short periods of positive pressure ventilation and implies the risk of lung injury. CPAP with surfactant but without any positive pressure ventilation may work synergistically. This randomized trial investigated a less invasive surfactant application protocol (LISA).

OBJECTIVE To test the hypothesis that LISA increases survival without bronchopulmonary dysplasia (BPD) at 36 weeks' gestational age in extremely preterm infants.

DESIGN, SETTING, AND PARTICIPANTS The Nonintubated Surfactant Application trial was a multicenter, randomized, clinical, parallel-group study conducted between April 15, 2009, and March 25, 2012, in 13 level III neonatal intensive care units in Germany. The final follow-up date was June 21, 2012. Participants included 211 of 558 eligible (37.8%) spontaneously breathing preterm infants born between 23.0 and 26.8 weeks' gestational age with signs of respiratory distress syndrome. In an intention-to-treat design, infants were randomly assigned to receive surfactant either via a thin endotracheal catheter during CPAP-assisted spontaneous breathing (intervention group) or after conventional endotracheal intubation during mechanical ventilation (control group). Analysis was conducted from September 6, 2012, to June 20, 2013.

INTERVENTION LISA via a thin catheter.

MAIN OUTCOMES AND MEASURES Survival without BPD at 36 weeks' gestational age.

RESULTS Of 211 infants who were randomized, 104 were randomized to the control group and 107 to the LISA group. Of the infants who received LISA, 72 (67.3%) survived without BPD compared with 61 (58.7%) of those in the control group. The reduction in absolute risk was 8.6% (95% CI, -5.0% to 21.9%; $P = .20$). Intervention group infants were less frequently intubated (80 infants [74.8%] vs 103 [99.0%]; $P < .001$) and required fewer days of mechanical ventilation. Significant reductions were seen in pneumothorax (5 of 105 intervention group infants [4.8%] vs 13 of 103 [12.6%]; $P = .04$) and severe intraventricular hemorrhage (11 infants [10.3%] vs 23 [22.1%]; $P = .02$), and the combined survival without severe adverse events was increased in the intervention group (54 infants [50.5%] vs 37 [35.6%]; $P = .02$; absolute risk reduction, 14.9; 95% CI, 1.4 to 28.2).

CONCLUSIONS AND RELEVANCE LISA did not increase survival without BPD but was associated with increased survival without major complications. Because major complications are related to lifelong disabilities, LISA may be a promising therapy for extremely preterm infants.

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Nonintubated Surfactant Application Trial Investigators are listed at the end of this article.

Corresponding Author: Angela Kribs, MD, Department of Neonatology, Children's Hospital University of Cologne, Kerpener Strasse 62, 50937 Cologne, Germany (angela.kribs@uk-koeln.de).

Continuous positive airway pressure (CPAP) as a first-line respiratory intervention in extremely low-gestational-age (GA) neonates who have respiratory distress syndrome has been shown¹⁻⁴ to be at least as efficient as intubation, surfactant treatment, and mechanical ventilation. *CPAP failure*, defined as the need for mechanical ventilation, should be avoided because it is associated with increased mortality and morbidity compared with CPAP success.⁵

Intratracheal surfactant administration is the only specific treatment for respiratory distress syndrome and usually requires endotracheal intubation and mechanical ventilation. Because animal data⁶ suggest that even very short periods of positive pressure ventilation are harmful to the immature lung, several methods of surfactant administration without mechanical ventilation have been investigated.⁷

One of these alternative methods is less invasive surfactant application (LISA) via a thin endotracheal catheter during spontaneous breathing with CPAP. Use of LISA allows administration of surfactant while avoiding positive pressure ventilation. Observational studies⁸⁻¹⁰ have fostered expectations of a positive effect of LISA on mortality, BPD, the need for mechanical ventilation, and the duration of oxygen supplementation. Recently, 2 prospective randomized clinical trials, Avoidance of Mechanical Ventilation (AMV)¹¹ and Take Care,¹² were designed to compare LISA with some method of standard therapy. In the AMV study,¹¹ infants who received LISA were less frequently intubated, had fewer days of mechanical ventilation, and needed less oxygen at 28 days. The Take Care investigators¹² observed significantly less BPD in the group of infants who received LISA compared with surfactant administration via short intubation. In both studies, infants were relatively mature (mean GA, 28 weeks).

The present study was designed to evaluate whether LISA is applicable to preterm infants of 23 to 26 weeks' GA. We tested the hypothesis that LISA increases survival without BPD at 36 weeks' GA compared with conventional treatment.

Methods

Study Design and Patients

The Nonintubated Surfactant Application (NINSAPP) trial was a multicenter, randomized, clinical parallel-group study conducted at 13 level III neonatal intensive care units in Germany between April 15, 2009, and June 21, 2012. The study was performed in accordance with Good Clinical Practice guidelines.¹³ The ethics committee of each participating center approved the study, and an independent data and safety monitoring committee reviewed the data 2 times per year. The protocol of the trial is presented in the [Supplement](#). Infants with GA between 23 weeks 0 days and 26 weeks 6 days were eligible. Inclusion criteria were spontaneous breathing, age 10 to 120 minutes, and signs of respiratory distress (fraction of inspired oxygen [FiO_2] >0.3 for saturation of peripheral oxygen [SpO_2] >83%, and/or Silverman score¹⁴ ≥ 5); written informed consent had to be given by legal guardians prior to birth or immediately thereafter, but in any case before randomization. Infants were excluded if they had a prenatally diagnosed severe

At a Glance

- Less invasive surfactant application (LISA) during continuous positive airway pressure (CPAP)-assisted spontaneous breathing is applicable to a subgroup of extremely preterm infants with a gestational age of 23 weeks to 26 weeks 6 days.
- In the presented study, LISA failed to improve the primary outcome of "survival without bronchopulmonary dysplasia."
- LISA improved the important secondary outcome of "survival without major complications."
- Further investigation of the LISA approach is mandatory.

underlying disease, had primary cardiopulmonary failure, or were enrolled in any other interventional trial.

Randomization

Infants were randomly assigned to receive surfactant by LISA during CPAP (intervention group) or by endotracheal intubation during mechanical ventilation (control group). Random allocation was designed in a 1:1 ratio with variable block sizes by an independent statistician (H.S.) and implemented using serially numbered opaque, sealed envelopes. The procedure was stratified according to the study center and GA (23-24 weeks vs 25-26 weeks). Multiple-birth infants, once eligible for inclusion, were assigned to the same group.

Study Intervention

For LISA, surfactant was administered to infants in the intervention group according to the following protocol. A 4F end-hole catheter was marked with a wax pencil approximately 1.5 cm above one end. A syringe was connected, and this syringe and the catheter were prefilled with at least 1.25 mL/kg of body weight (100 mg/kg) of the surfactant preparation. While the infant was breathing via nasal CPAP, a laryngoscope was introduced to provide a glottal view. The tube was grasped with a Magill forceps at an angle of approximately 120° and the infant was intubated up to the mark; the tube was fixed in this position and the laryngoscope was removed. The infant's mouth was closed, and the surfactant was instilled by hand during 30 to 120 seconds by mini-boluses. In cases of apnea or bradycardia, positive pressure ventilation was performed until recovery. Blinding of the procedure was not possible. Documentation of data was also not blinded.

After surfactant administration, CPAP therapy was continued. During the first 96 hours of the infant's life, CPAP was withdrawn only if the infant showed no signs of dyspnea and was well oxygenated when ventilated with a CPAP pressure level of 5 millibars or less and an FiO_2 level of 0.21. The CPAP level was titrated within a range of 5 and 8 millibars to achieve the lowest Silverman score and FiO_2 level. This level was regarded as optimal.

Intubation criteria in the intervention group during the first 96 hours of life were FiO_2 of greater than 0.45 for more than 2 hours during CPAP to obtain a Po_2 of greater than 45 mm Hg, respiratory acidosis with pH less than 7.15, or severe apnea during CPAP despite respiratory analeptic therapy.

Infants assigned to the control group were intubated, mechanical ventilation was initiated, and surfactant was admin-

istered via the endotracheal tube. Sedation and analgesia for intubation were not used routinely.

Mechanical ventilation was performed following standards established at the various study sites. Centers were advised to start weaning the infant from mechanical ventilation as soon as possible. Extubation criteria were predefined as FiO_2 of less than 0.3 and mean airway pressure of less than 10 cm H_2O . Reintubation criteria for both groups were the same as those for the intubation criteria for the intervention group during the infant's first 96 hours of life. Use of nasal or pharyngeal CPAP was allowed for weaning.

Infants in both groups received poractant alfa (Chiesi Farmaceutici SpA), at doses of at least 1.25 mL/kg of body weight (100 mg of surfactant/kg), up to the full vial content (1.5 mL containing 120 mg of surfactant). Repeated administrations of surfactant were permitted in both groups when the FiO_2 level exceeded 0.35.

All infants breathing spontaneously and those planned to be extubated soon received either theophylline or caffeine. All other concomitant medical therapies were applied according to site-specific standards. Participating centers agreed to follow the German national guidelines (www.awmf.org) that were valid at the time the study was conceptualized.

Primary and Secondary Outcomes

The primary outcome of the trial was survival without BPD at 36 weeks' GA as determined by a standardized test.¹⁵ Infants receiving mechanical ventilation or CPAP, or those with a supplemental oxygen concentration exceeding 0.30 received a BPD diagnosis without additional testing. Infants with a supplemental oxygen concentration of less than 0.30 underwent a timed stepwise reduction to room air. Those in whom the reduction failed received a BPD diagnosis.

The most important prespecified secondary outcome was survival without major complications. These complications included BPD, severe intraventricular hemorrhage,¹⁶ cystic periventricular leukomalacia, and surgery for necrotizing enterocolitis, focal intestinal perforation, or retinopathy of prematurity.

Further prespecified secondary outcomes were the incidence of (1) pneumothorax, (2) severe intraventricular hemorrhage,¹⁶ (3) cystic periventricular leukomalacia, (4) laser therapy for retinopathy of prematurity,¹⁷ (5) surgery required for necrotizing enterocolitis or focal intestinal perforation, (6) persistent ductus arteriosus requiring surgery, (7) treatment failure (need for intubation and ventilation within the first 72 hours of life), (8) duration of mechanical ventilation, (9) CPAP, (10) oxygen supplementation, (11) length of stay, and (12) daily weight gain until 36 weeks' GA.

Additional safety analyses included the incidence of bradycardia (heart rate <100/min), oxygen desaturation of less than 80%, coughing, choking, laryngeal spasms during application, and surfactant application failure. Investigators were advised to report any bradycardia and desaturation, including the nadir and the duration. Data on serious adverse events were collected until death or 36 weeks' GA.

Statistical Analysis

The primary data set for analysis comprised the recorded data of all randomized patients from the intention-to-treat popu-

lation included in the study. Data were analyzed according to the randomized assignments, and analysis was conducted from September 6, 2012, to June 20, 2013.

Baseline characteristics and secondary outcomes were compared between randomized treatment groups using, for nominal variables, frequencies and Fisher exact test and, for continuous variables, means (SDs) (or medians and interquartile ranges for skew distributions) and the Wilcoxon rank sum test. Analysis of secondary outcomes was exploratory and not adjusted for multiple comparisons.

The efficacy of the intervention therapy was compared with the control therapy using the dichotomous primary outcome variable *survival without BPD*. Superiority was tested with allowance for GA strata using the Cochran-Mantel-Haenszel test with adjusted odds ratios for stratified 2×2 tables with a 2-tailed error probability of 5% ($\alpha = .05$). Test results were adjusted using the data-estimated design effect to allow for clustering due to multiple births.¹⁸ To allow for possible differences between study centers, a multivariate logistic regression model for survival without BPD, including the explanatory factors of randomized treatment group, center, and GA stratum, was fitted as a sensitivity analysis.

The main secondary outcome variable, survival without major complications, which was the first secondary outcome listed in the study protocol, was analyzed identically to the primary outcome variable. However, as with the other secondary end points, no adjustment was made for clustering.

The incidence of the primary outcome measure survival without BPD was 30% for infants at 23 and 24 weeks' GA, and 60% for infants at 25 and 26 weeks' GA in historical control data of participating centers. The data from an earlier feasibility study¹⁸ predicted survival rates without BPD in the intervention group of 55% for infants with 23 weeks to 24 weeks 6 days' GA, and of 80% for infants with 25 weeks to 26 weeks 6 days' GA.

A ratio of 9:11 was assumed for the numbers of patients in the 2 GA strata, and the primary end point (survival without BPD) for the pooled results was anticipated to occur in 47% of the control group and 69% of the intervention group (odds ratio, 2.51). With an allocation ratio of 1:1, these assumptions led to a calculated sample size of $2 \times 87 = 174$ to be able to reject the null hypothesis of equal event rates with a 2-tailed, type I error probability of 5% and a power of 80% (continuity-corrected statistics determined using χ^2 testing).

In a protocol amendment (October 17, 2011), the sample size was multiplied by a design effect of 1.15 because of the increased multiple-birth rate observed at that time and the possible correlation of outcomes within multiple births. The final target sample size was 210 patients, assuming a maximum of 25% multiple births in 15% of the mothers.

Statistical analysis was performed using SAS, version 9.3 (SAS Institute Inc). The required sample size was computed using Addplan software, version 5 (AddPlan GmbH).

Results

A total 211 of 558 eligible infants (37.8%) were recruited. Of these, 200 infants (35.8%) were excluded because parental con-

Figure 1. CONSORT Diagram

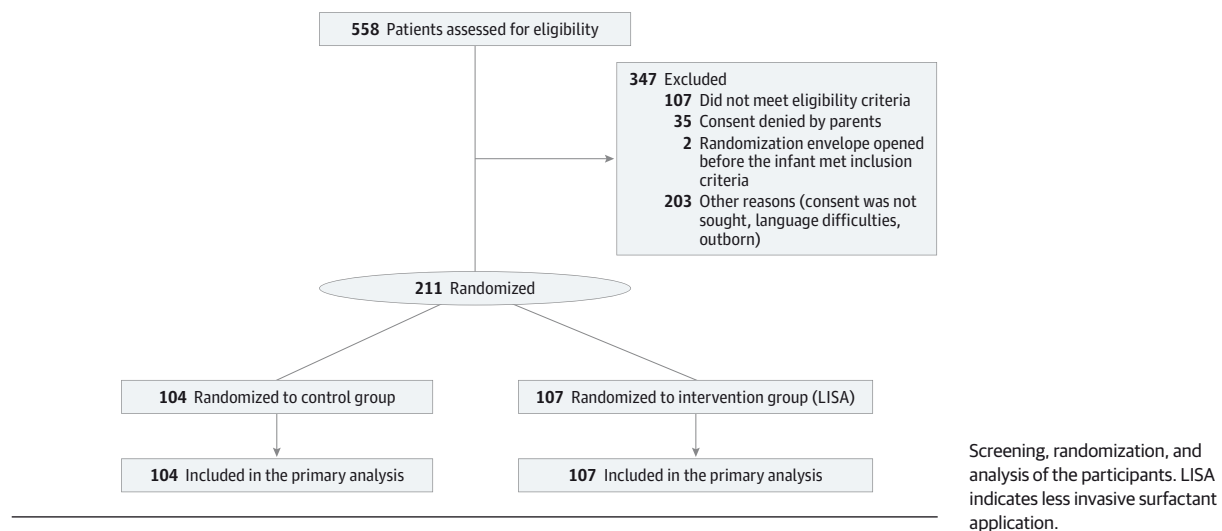


Table 1. Baseline Clinical Characteristics

Characteristic	Group	
	Intervention (n = 107)	Control (n = 104)
Gestational age, mean (SD), wk	25.3 (1.1)	25.2 (0.91)
Birth weight, mean (SD), g	711 (195)	674 (165)
Apgar score, median (IQR)		
5 min	8 (7-9)	8 (7-8)
10 min	8 (8-9)	8 (8-9)
Cord arterial pH, mean (SD)	7.34 (0.09)	7.35 (0.08)
Male sex, No. (%)	63 (58.9)	52 (50.0)
Multiple births, No. (%)	32 (30.0)	35 (33.7)
Antenatal corticosteroids, No. (%)		
Full course	88 (82.2)	79 (76.0)
Incomplete course	17 (15.9)	23 (22.1)
Cesarean section, No. (%)	94 (87.8)	96 (92.3)

Abbreviation: IQR, interquartile range.

sent was not obtained within the short time available for patient enrollment (prenatally to 120 minutes after birth) owing to organizational reasons. Two infants (0.9%) were excluded because the randomization envelope was opened before all inclusion criteria were fulfilled. A total of 104 infants were assigned to the control group and 107 were assigned to the intervention group (Figure 1). All infants had complete follow-ups performed; the last follow-up was June 21, 2012. Recruitment rates differed markedly between the various study centers, ranging from 9% to 70% of eligible infants.

Baseline clinical characteristics were similar in both groups (Table 1). There was no significant difference for the primary outcome between the 2 study groups. In the intervention group, 67.3% of all infants survived without BPD compared with 58.7% of the control group. Reduction in absolute risk for the primary outcome was 8.6% (95% CI, −5.0% to 21.9%; $P = .20$) (Table 2). These results were confirmed by multivariate logistic regression analysis of BPD and/or death on treat-

ment group, center, and GA: absolute risk reduction was 8.9% (95% CI, −5.0% to 20.5%; $P = .21$). In this model, GA stratum had a significant effect ($P = .001$), but center did not ($P = .38$).

Intubation and mechanical ventilation data during the first 72 hours of life are shown in Figure 2. Since infants in the control group were intubated for surfactant treatment, a lower rate of mechanical ventilation was expected for the intervention group as a whole. However, the observed absolute risk reduction of 24.3% (95% CI, 16.2%-33.8%) (Table 2) was attributable mainly to differences in the more mature infants of 25 and 26 weeks' GA. Treatment failure occurred in 49 infants (47.1%) of the intervention group, whereas 60 infants (57.7%) of the control group were extubated during the first 72 hours. The duration of mechanical ventilation was shorter in the intervention group. No significant differences in the duration of respiratory support (CPAP and mechanical ventilation), use of supplemental oxygen, or incidence of pulmonary hemorrhage were observed (Table 2). The occurrence of pneumothorax was significantly lower in the intervention group vs the control group (4.8% vs 12.6%; $P = .04$); the intervention group also had significantly less severe intraventricular hemorrhage (10.3% vs 22.1%; $P = .02$). Cystic periventricular leukomalacia and retinopathy of prematurity requiring laser therapy seemed to occur less frequently in the intervention group, but these results were not statistically significant. The incidence of deaths and intestinal complications requiring surgery were similar in both groups. There was a significant effect in favor of the intervention group regarding the prespecified composite secondary outcome of survival without major complications. This outcome occurred in 54 of 107 cases (50.5%) in the intervention group and in 37 of 104 cases (35.6%) in the control group, resulting in an absolute risk reduction of 14.9% (95% CI, 1.4%-28.2%) (Table 2) and a number needed to treat of 6.7 (95% CI, 3.5-71.4).

The length of stay was not significantly shorter in the intervention group (103 vs 105 days; $P = .11$). Neither the number of surfactant applications nor the cumulative surfactant dose differed significantly between the groups.

Table 2. Primary Outcome and Predefined Secondary Outcomes

Characteristic	Group, No. (%)		Absolute Risk Reduction (95% CI)	P Value ^a
	Intervention (n = 107)	Control (n = 104)		
Survival without BPD ^b	72 (67.3)	61 (58.7)	8.6 (−5.0 to 21.9)	.20
Death	10 (9.3)	12 (11.5)	2.2 (−11.5 to 15.6)	.59
Surviving infants with BPD	25 (23.4)	31 (29.8)	7.9 (−6.6 to 22.1)	.19
Survival without major complications ^c	54 (50.5)	37 (35.6)	14.9 (1.4 to 28.2)	.02 ^a
Mechanical ventilation ^d				
All infants	80 (74.8)	103 (99.0) ^e	24.3 (16.2 to 33.8)	<.001
Gestation, wk				
23	14/15 (93.3)	9/9 (100.0)	6.7 (−26.6 to 33.5)	>.99
24	24/26 (92.3)	30/31 (96.8)	4.5 (−9.9 to 22.3)	.59
25	24/31 (77.4)	41/41 (100.0)	22.6 (9.4 to 41.1)	.002
26	18/35 (51.4)	23/23 (100.0)	48.6 (30.3 to 66.0)	<.001
Pulmonary outcome ^d				
Duration of mechanical ventilation, median (IQR), d				
All infants	5 (0 to 17)	7 (2.5 to 19.5)		.031, .029 ^f
Intubated infants	8 (4 to 20)	7 (3 to 20)		.27, .30 ^f
Any respiratory support (MV or CPAP), median (IQR), d	47 (30 to 60)	48.5 (35 to 64)		.60, .22 ^f
Supplemental oxygen (all infants), median (IQR), d	22 (5 to 53)	35 (9 to 56)		.36
Pulmonary hemorrhage	4 (4.8)	6 (5.8)		.53
Pneumothorax	5/105 (4.8)	13/103 (12.6)		.04
Clinical BPD	14/97 (14.4)	23/92 (25.0)		
Serious adverse events				
Grade 3 or 4 intraventricular hemorrhage	11 (10.3)	23 (22.1)		.02
Cystic periventricular leukomalacia	4 (3.7)	11 (10.6)		.06 ^g
Surgical treatment of NEC or FIP	19 (17.8)	17 (16.3)		.74
Laser therapy of ROP	2 (1.9)	7 (6.7)		.10 ^g
Patent ductus arteriosus ligated	2 (1.9)	5 (4.8)		.25 ^g
Other outcomes, median (IQR)				
Length of stay, d	103 (84 to 119)	105 (91 to 132)		.11 ^h
Daily weight gain, g /kg/d	22.4 (16 to 27)	25.0 (19 to 30)		.07 ^h

Abbreviations: BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; IQR, interquartile range; FIP, focal intestinal perforation; MV, mechanical ventilation; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

^a Cluster-adjusted Cochrane-Mantel-Haenszel test stratified by gestational age (mean design effect, 1.15) was used to determine *P* values.

^b Primary outcome.

^c Composite secondary outcome: survival without BPD, severe intraventricular hemorrhage, cystic periventricular leukomalacia, laser therapy for ROP, or surgical treatment of FIP or NEC.

^d The method of Farrington and Manning¹⁹ was used to determine absolute risk reduction with 95% CI. The *P* values were determined using Cochrane-Mantel-Haenszel test stratified by gestational age except if within strata; Fisher exact test was then used.

^e One infant in the control group was not intubated and was given surfactant since the fraction of inspired oxygen dropped to below 0.3 immediately after randomization.

^f Results of worst-case analysis of duration outcomes: the duration was set to maximum observed value for all infants who died.

^g Fisher exact test was used owing to low frequencies.

^h Wilcoxon rank sum test was used.

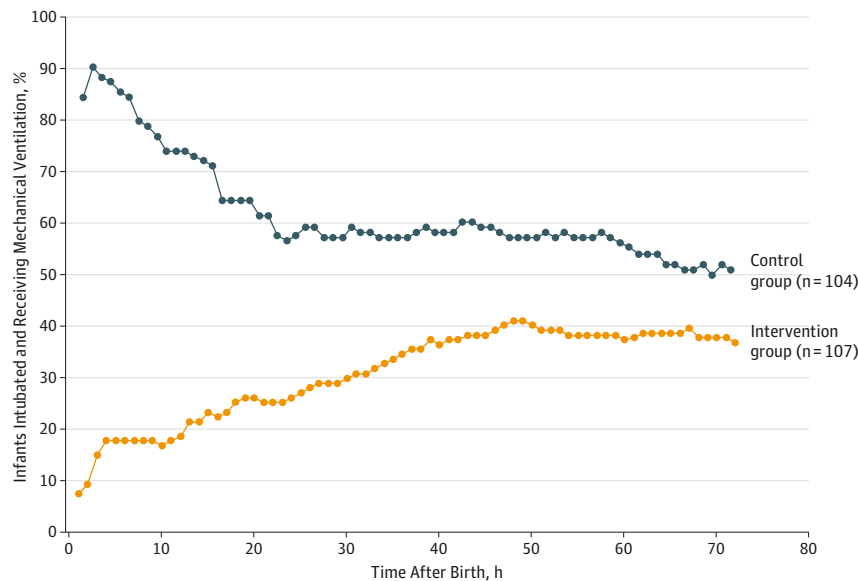
The rate of successful applications and adverse events during applications were evaluated as short-term safety variables. LISA was performed successfully in all intervention group infants. Correct application was achieved for 78 of infants (72.9%) at the first attempt, 24 (22.4)% at the second attempt, and 5 (4.7%) at the third. Bradycardia was detected in 12 infants (11.2%) of the intervention group, and desaturation was identified in 60 infants (56.1%) of this group. In all cases, desaturation could be successfully treated with mask ventilation. No significant differences in any concomitant treatment were observed (Table 3).

Discussion

This study evaluated whether LISA is feasible in infants at 23 weeks to 26 weeks 6 days' GA, and whether this treatment increases survival without BPD at 36 weeks' GA compared with

conventional surfactant administration protocols. An increased rate of survival without BPD was not demonstrated, possibly because the primary outcome of the control group was better than expected. Survival without BPD in both groups was higher than that reported in earlier comparable randomized trials,^{2,3} which raises the possibility that the NINSAPP trial enrolled healthier infants. However, the inclusion rate of NINSAPP (37.8%) was similar to that of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial³ and Continuous Positive Airway Pressure or Intubation at Birth² trial (28% and 37%, respectively), and none of the trials enrolled infants younger than 24 weeks' GA who have the highest risk for BPD and death. Furthermore, some centers participating in the NINSAPP trial enrolled up to 70% of eligible infants and logistic regression analysis including GA, center, and allocation group revealed no influence of the center. This finding indicates that the effect persists even if, perhaps based on certain resuscitation strategies, most infants are stabilized with CPAP and

Figure 2. Infants Who Were Intubated and Receiving Mechanical Ventilation



Percentage of intervention and control infants who were intubated and received mechanical ventilation in hours 1 to 96 after birth.

Table 3. Surfactant and Other Drug Treatment

	Group, No. (%)		
Characteristic	Intervention (n = 107)	Control (n = 104)	P Value ^a
Surfactant			
No. of surfactant applications per infant, median, (IQR) [range]	1 (1-2) [1-9]	1 (1-2) [0-7]	.67 ^b
Cumulative surfactant doses per infant, median (IQR), mg	200 (145-300)	191 (145-260)	.54 ^b
During application			
Bradycardia	12 (11.2)	3 (2.9)	.029
SpO ₂ <80%	60 (56.1)	27 (26.0)	<.001
≥2 Attempts needed for successful application	29 (27.1)	28 (27.0)	.98
Medical closure of duct			
			.89 ^c
Only indomethacin meglumine	42 (39.3)	42 (40.3)	
Only ibuprofen	36 (33.6)	31 (29.8)	
Indomethacin and ibuprofen	1 (0.9)	2 (1.9)	
Respiratory stimulants			
Caffeine	105 (98.1)	99 (95.2)	.28
Theophylline	8 (7.5)	12 (11.5)	.11
Doxapram hydrochloride	31 (29.0)	24 (23.1)	.07
Other drugs			
Analgesics	46 (43.0)	46 (44.2)	.11
Sedatives	32 (30.0)	40 (38.5)	.08
Systemic corticosteroids	39 (36.4)	44 (42.3)	.08

Abbreviations: IQR, interquartile range; SpO₂, oxygen saturation as measured by pulse oximetry.

^a Fisher exact test was used, except where otherwise specified.

^b Wilcoxon rank sum test was used.

^c Four categories were compared: indomethacin, ibuprofen, both, and neither.

LISA. An alternative explanation for the unexpectedly favorable outcome of the NINSAPP control group is the short duration of mechanical ventilation. Recent meta-analyses^{20,21} revealed a superiority of interventions that avoided mechanical ventilation compared with those that used positive pressure ventilation.

Although we failed to show a benefit with regard to the primary outcome, we observed significant differences in important secondary outcomes. Rates of pneumothorax and

severe intraventricular hemorrhage were lower in the intervention group, in line with LISA studies^{9,10} that reported lower rates of severe intraventricular hemorrhage. Furthermore, for the intervention group, an increased rate of survival without major complications was observed. Combined outcomes are problematic since each morbidity may be influenced by several factors. We had prespecified this secondary outcome since it is the most predictive factor for a life without disability^{22,23} Survival without major complications was part of the analyti-

cal statistical plan, but this was analyzed only in an exploratory manner and was not adjusted for multiple comparison. This lack of adjustment is a limitation of the study.

With regard to the short-term safety of the LISA method, we evaluated the rates of successful applications and adverse events during applications. More than one attempt at surfactant administration was needed in 27% of the infants in both groups. LISA resulted in higher rates of transient hypoxemia and bradycardia. Desaturation and bradycardia have been seen in other trials^{8,11,12} using LISA. Although desaturation and bradycardia have no obvious effect on short-term outcome but could theoretically have an influence on long-term development, follow-up of infants who experience these complications is mandatory.

Our study has some limitations. First, it was not blinded, so it is possible that the clinical course of individual infants was influenced by the treating physicians knowing the group allocation. Although extubation criteria were defined, delay of extubation in some cases of the intervention group cannot be ruled out, resulting in longer times of mechanical ventilation than necessary.

Second, in the study protocol a pragmatic decision was made concerning surfactant dosing. Infants received at least 100 mg/kg elevated to the content of the vial. This resulted in different doses depending on the birth weight of the infants. Because a dose of 200 mg/kg is considered to be superior to

100 mg/kg, infants with a higher birth weight may be at a disadvantage.²⁴ However, the dose did not influence the results of the present study since it was identical in both groups.

Third, the intervention group received early caffeine treatment, whereas the control group received caffeine first at extubation. Because caffeine is known to have an effect on BPD,²⁵ an influence of the timing of caffeine administration on the primary outcome cannot be excluded. Furthermore, drug therapy was not standardized between study centers. However, this lack of standardization seems to be of minor importance since randomization was stratified by centers, and no significant differences between control and intervention groups were observed with regard to medication.

Conclusions

The NINSAPP trial is unique with regard to the immaturity of enrolled infants and a rate of survival without BPD that is, to date, higher than any other published for a randomized multicenter trial. LISA was not superior concerning the primary end point of the study, but it was associated with benefits in important secondary outcomes that are closely related to life-long disabilities. LISA is a promising new therapy for extremely preterm infants with respiratory distress syndrome, but it certainly deserves further investigation.

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Author Affiliations: Department of Neonatology, Children's Hospital University of Cologne, Cologne, Germany (Kribs, Mehler, Roth); Department of Neonatology and Pediatric Intensive Care, University Witten-Herdecke, Vest Children's Hospital, North Rhine-Westphalia, Germany (Roll); Department of Neonatology, Children's Hospital, University of Lübeck, Lübeck, Germany (Göpel, Herting); Department of Neonatology, Children's Hospital Aschaffenburg, Aschaffenburg, Germany (Wieg); Department of Neonatology, Children's Hospital Leverkusen, Leverkusen, Germany (Groneck); Department of Neonatology, Asklepios Klinik Barmbek, Hamburg, Germany (Laux); Department of Neonatology, Children's Hospital, Ruhr-University Bochum, Bochum, Germany (Teig); Department of General Pediatrics, University Hospital Düsseldorf, Düsseldorf, Germany (Hoehn); Department of Neonatology, Children's Hospital Siegen, Siegen, Germany (Böhm); Department of Neonatology, University of Bonn, Bonn, Germany (Welzing); Department of Neonatology, Olgahospital Stuttgart, Stuttgart, Germany (Vochem); Department of Neonatology and Pediatric Intensive Care Medicine, Children's Hospital, Cologne, Germany (Hoppenz); Department of Neonatology, Charité University Medical Center, Berlin, Germany (Bührer); Institute of Medical Statistics, Informatics, and Epidemiology, University of Cologne, Cologne, Germany (Stützer, Franklin); Center for Clinical Studies, Cologne, Germany (Stöhr).

Author Contributions: Drs Kribs and Göpel contributed equally to the work. Dr Kribs had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kribs, Roll, Göpel, Wieg, Groneck, Teig, Stützer, Herting, Roth.
Acquisition, analysis, or interpretation of data: Kribs, Roll, Göpel, Wieg, Groneck, Laux, Teig, Hoehn, Böhm, Welzing, Vochem, Hoppenz, Bührer, Mehler, Franklin, Stöhr, Herting, Roth.
Drafting of the manuscript: Kribs, Wieg, Groneck, Laux, Teig, Mehler, Franklin.
Critical revision of the manuscript for important intellectual content: Kribs, Roll, Göpel, Wieg, Teig, Hoehn, Böhm, Welzing, Vochem, Hoppenz, Bührer, Stützer, Stöhr, Herting, Roth.
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Study supervision: Kribs, Teig, Hoehn, Welzing, Bührer, Stöhr, Herting, Roth.

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Group Information: The following hospitals and investigators participated in the Nonintubated Surfactant Application (NINSAPP) trial, listed according to the numbers of infants enrolled: **Department of Neonatology, Children's Hospital University of Cologne:** Angela Kribs, MD, Katrin Mehler, MD, Bernhard Roth, MD, Andre Oberthür, MD, Ruth Klein, MD, Frank Eifinger, MD, Anne Vierzig, MD, and Christoph Hünseler, MD. **University of Cologne, Institute of Medical Statistics, Informatics and Epidemiology:** Hartmut Stützer, PhD, and Jeremy Franklin, PhD. **Center for Clinical Studies, Cologne:** Andreas Stöhr, PhD; Ulrike Zettelmeyer, MA, Stefanie Koch, Susanne Staub, and Hao Pham, MD. **Department of Neonatology and Pediatric Intensive Care, University Witten-Herdecke, Vest Children's Hospital:** Claudia Roll, MD, Wolfgang Pielemeier, MD, Sirma Supcun, MD, Patrizia Kutz, MD, Barbara Steich, MD, Nikola Lueg, MD, Uta Schuermann, MD, and Friedemann Hornschuh, MD. **University of Lübeck, Children's Hospital:** Wolfgang Göpel, MD, Egbert Herting, MD, Meike Bendiks, MD, Guido Stichenoth, MD, Alexander Herz, MD, and Christoph Härtel, MD. **Children's Hospital Aschaffenburg:** Christian Wieg, MD, Oliver Stangl, MD, Christina Boesche, MD, and Katja Moser, MD. **Children's Hospital Leverkusen:** Peter Groneck, MD, Peter Jahn, MD, Armin Stach, MD, Beatrix Middendorf, MD, Julia Bode, MD, Isabel

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