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Two-Year Outcomes After Minimally Invasive Surfactant Therapy in Preterm Infants

Follow-Up of the OPTIMIST-A Randomized Clinical Trial

Peter A. Dargaville, MD; C. Omar F. Kamlin, DMedSci; Francesca Orsini, MSc; Xiaofang Wang, PhD; Antonio G. De Paoli, MD; H. Gozde Kanmaz Kutman, MD; Merih Cetinkaya, PhD; Lilijana Kornhauser-Cerar, PhD; Matthew Derrick, MBBS; Hilal Özkan, MD; Christian V. Hulzebos, PhD; Georg M. Schmölzer, PhD; Ajit Aiyappan, MD; Brigitte Lemyre, MD; Sheree Kuo, MD; Victor S. Rajadurai, MD; Joyce O'Shea, MD; Manoj Biniwale, MD; Rangasamy Ramanathan, MD; Alla Kushnir, MD; David Bader, MD; Mark R. Thomas, MD; Mallinath Chakraborty, PhD; Mariam J. Buksh, MD; Risha Bhatia, PhD; Carol L. Sullivan, MD; Eric S. Shinwell, MD; Amanda Dyson, MMed; David P. Barker, DM; Amir Kugelman, MD; Tim J. Donovan, MPH; Kevin C. W. Goss, PhD; Markus K. Tauscher, MD; Vadivelam Murthy, MD; Sanoj K. M. Ali, MD; Howard W. Clark, DPhil; Roger F. Soll, MD; Samantha Johnson, PhD; Jeanie L. Y. Cheong, MD; John B. Carlin, PhD; Peter G. Davis, MD; for the OPTIMIST-A Trial Investigators

IMPORTANCE The long-term effects of surfactant administration via a thin catheter (minimally invasive surfactant therapy [MIST]) in preterm infants with respiratory distress syndrome remain to be definitively clarified.

OBJECTIVE To examine the effect of MIST on death or neurodevelopmental disability (NDD) at 2 years' corrected age.

DESIGN, SETTING, AND PARTICIPANTS Follow-up study of a randomized clinical trial with blinding of clinicians and outcome assessors conducted in 33 tertiary-level neonatal intensive care units in 11 countries. The trial included 486 infants with a gestational age of 25 to 28 weeks supported with continuous positive airway pressure (CPAP). Collection of follow-up data at 2 years' corrected age was completed on December 9, 2022.

INTERVENTIONS Infants assigned to MIST (n = 242) received exogenous surfactant (200 mg/kg poractant alfa) via a thin catheter; those assigned to the control group (n = 244) received sham treatment.

MAIN OUTCOMES AND MEASURES The key secondary outcome of death or moderate to severe NDD was assessed at 2 years' corrected age. Other secondary outcomes included components of this composite outcome, as well as hospitalizations for respiratory illness and parent-reported wheezing or breathing difficulty in the first 2 years.

RESULTS Among the 486 infants randomized, 453 had follow-up data available (median gestation, 27.3 weeks; 228 females [50.3%]); data on the key secondary outcome were available in 434 infants. Death or NDD occurred in 78 infants (36.3%) in the MIST group and 79 (36.1%) in the control group (risk difference, 0% [95% CI, −7.6% to 7.7%]; relative risk [RR], 1.0 [95% CI, 0.81-1.24]); components of this outcome did not differ significantly between groups. Secondary respiratory outcomes favored the MIST group. Hospitalization with respiratory illness occurred in 49 infants (25.1%) in the MIST group vs 78 (38.2%) in the control group (RR, 0.66 [95% CI, 0.54-0.81]) and parent-reported wheezing or breathing difficulty in 73 (40.6%) vs 104 (53.6%), respectively (RR, 0.76 [95% CI, 0.63-0.90]).

CONCLUSIONS AND RELEVANCE In this follow-up study of a randomized clinical trial of preterm infants with respiratory distress syndrome supported with CPAP, MIST compared with sham treatment did not reduce the incidence of death or NDD by 2 years of age. However, infants who received MIST had lower rates of adverse respiratory outcomes during their first 2 years of life.

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Visual Abstract

Supplemental content

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

Group Information: The OPTIMIST-A Trial Investigators appear in Supplement 4.

Corresponding Author: Peter A. Dargaville, MD, Department of Paediatrics, Royal Hobart Hospital, 48 Liverpool St, Hobart, TAS 7000, Australia (peter.dargaville@ths.tas.gov.au).

Bronchopulmonary dysplasia (BPD), the chronic disease of the preterm lung, has lasting effects on respiratory health in infancy and childhood[1] and may be associated with a greater risk of neurodevelopmental disability (NDD) throughout childhood and adolescence.[2] It has been posited that interventions to reduce BPD frequency could produce lasting benefit on neurodevelopment and/or respiratory health.

Delivery of surfactant via a thin catheter, an emerging technique for spontaneously breathing preterm infants with respiratory distress syndrome (RDS), is known to improve survival without BPD in preterm infants. A meta-analysis of data from 14 randomized clinical trials (RCTs) found surfactant delivery via thin catheter, compared with administration via endotracheal tube, to be associated with a lower frequency of the composite outcome of death or BPD (relative risk [RR], 0.59 [95% CI, 0.48-0.73]) and of BPD in survivors (RR, 0.57 [95% CI, 0.45-0.74]).[3] However, only 1 of these 14 studies specifically targeted infants less than 29 weeks' gestation, the group most at risk of BPD and other morbidities.[4] Only this study reported outcomes beyond the first hospitalization, finding a benefit of surfactant delivery via thin catheter in relation to neurodevelopment[5] but not respiratory function at 5 to 9 years.[6] Another RCT comparing surfactant delivery via a thin catheter with ongoing respiratory support with continuous positive airway pressure (CPAP) did not detect a difference in incidence of BPD,[7] nor was there a discernible effect on the rate of NDD at 2 years of age.[8]

The OPTIMIST-A Trial (One of Collaborative Paired Trials Investigating Minimally Invasive Surfactant Therapy) compared surfactant delivery via thin catheter (minimally invasive surfactant therapy [MIST]) with sham treatment, and in relation to outcomes during first hospitalization, found no clear difference in the primary outcome of death or BPD, but a reduction in BPD in survivors to 36 weeks' postmenstrual age (RR, 0.83 [95% CI, 0.70-0.98]).[9] The current study reports outcomes at 2 years' corrected age in infants enrolled in the OPTIMIST-A Trial, examining the hypothesis that application of MIST would reduce the incidence of the composite outcome of death or moderate to severe NDD or its components.

Key Points

Question For preterm infants with respiratory distress syndrome supported with continuous positive airway pressure (CPAP), does administration of surfactant via a thin catheter improve survival without moderate to severe neurodevelopmental disability (NDD) at 2 years of age compared with sham treatment?

Findings In this follow-up of a randomized clinical trial of 486 infants at 25 to 28 weeks' gestation, the composite outcome of death or NDD at 2 years of age occurred in 36.3% receiving minimally invasive surfactant therapy compared with 36.1% receiving sham treatment.

Meaning In preterm infants supported with CPAP, minimally invasive surfactant therapy did not lead to a reduction in the composite outcome of death or neurodevelopmental disability at 2 years of age.

Methods

Study Design and Oversight

The trial was an investigator-initiated, international, multicenter, blinded RCT conducted in 33 tertiary-level neonatal intensive care units in Australia, Canada, Israel, New Zealand, Qatar, Singapore, Slovenia, the Netherlands, Turkey, the United Kingdom, and the United States. The human research ethics committees of all participating centers approved the trial protocol, which included description of the methods for ascertainment of outcomes at 2 years' corrected age[10] (Supplement 1). An independent data and safety monitoring committee reviewed interim analyses of in-hospital outcomes for safety and efficacy. Prospective written parental consent was obtained for participation in all aspects of the trial, including the 2-year follow-up study (OPTIMIST-A2).

A separate statistical analysis plan (Supplement 2) was developed for the OPTIMIST-A2 study prior to any review or analysis of follow-up data, in which the follow-up outcomes and methods of analysis originally outlined in the trial protocol were expanded on. The composite outcome of death or NDD was selected as the key secondary outcome of this follow-up study based on preferences for outcomes reported by parents of preterm infants.[11]

Participants

Infants were included in the trial if within the gestation range between 25 weeks 0 days and 28 weeks 6 days, born at a study center, admitted to the neonatal intensive care unit, and supported with CPAP (5-8 cm H_2O) or noninvasive positive pressure ventilation for respiratory insufficiency without prior intubation (**Table 1** and **Figure**). Infants were eligible if needing fraction of inspired oxygen of 0.30 or greater in the first 6 hours from birth. Exclusion criteria were imminent need for intubation, respiratory disease other than RDS, or a serious congenital anomaly. All infants originally enrolled in the study were eligible to be included in the OPTIMIST-A2 study, including those who died during the first hospitalization. Follow-up data were gathered in all infants alive at 2 years' corrected age unless they had been withdrawn or if parents declined to participate or could not be contacted.

Intervention

The design of the intervention and the procedures for randomization and blinding have been previously described[9] and are detailed in Supplement 1. The MIST intervention was administered using the Hobart method,[12] whereby a dose of 200 mg/kg surfactant (poractant alfa, Chiesi Farmaceutici) was administered intratracheally. Infants in the control group received a sham treatment consisting only of transient repositioning without airway instrumentation. Treating clinicians, outcome assessors, and parents were blinded to intervention group status. Noninvasive respiratory support continued in both groups after the intervention unless intubation criteria were met, including fraction of inspired oxygen of 0.45 or greater. Other aspects of management during hospitalization were at the discretion of treating clinicians.

Table 1. Baseline Characteristics for Infants Contributing Data to the Follow-Up Study

	No. (%)[a]	
	Minimally invasive surfactant therapy (n = 224)	Control treatment (n = 229)
Demographic characteristics		
Gestation, median (IQR), wk	27.3 (26.3-28.1)	27.3 (26.4-28.0)
Birth weight, median (IQR), g	932 (780-1065)	905 (777-1070)
Birth weight <10th centile	32 (14.3)	31 (13.5)
Sex		
Female	108 (48.2)	120 (52.4)
Male	116 (51.8)	109 (47.6)
Plurality, birth order		
Singleton	140 (62.5)	158 (69.0)
First of multiples	40 (17.8)	30 (13.1)
Second or subsequent multiple	44 (19.6)	41 (17.9)
Peripartum details		
Exposure to antenatal glucocorticoids		
≥2 Doses prior to delivery	144 (64.3)	162 (70.7)
1 Dose prior to delivery	60 (26.8)	48 (21.0)
None	20 (8.9)	19 (8.3)
Delivery mode		
Vaginal delivery	40 (17.9)	49 (21.4)
Cesarean delivery with labor	91 (40.6)	75 (32.8)
Cesarean delivery, no labor	93 (41.5)	105 (45.9)
Apgar score[b]		
At 5 min, median (IQR)	8 (7-9)	8 (7-9)
<7 at 5 min	28 (12.5)	30 (13.1)
Clinical state at randomization		
Age, median (IQR), h	2.7 (1.6-4.0)	2.6 (1.7-3.6)
CPAP level at randomization, median (IQR), cm H_2O	7 (6-8)	7 (6-8)
F_{IO_2} at randomization, median (IQR)	0.35 (0.30-0.40)	0.35 (0.30-0.40)
F_{IO_2} ≤0.35	141 (62.9)	141 (61.6)
Data gathered after first hospital discharge		
Oxygen therapy at home, No./total (%)	24/195 (12.3)	46/205 (22.4)
Immunized against, No./total (%)		
RSV	119/175 (68.0)	128/185 (69.2)
Influenza	91/173 (52.6)	104/184 (56.5)
Family history of asthma (in parents or siblings), No./total (%)	50/177 (28.2)	53/188 (28.2)
Corrected age at 2 y assessment, median (IQR), y	2.05 (2.00-2.15)	2.04 (2.00-2.18)

Abbreviations: CPAP, continuous positive airway pressure; F_{IO_2}, fraction of inspired oxygen; RSV, respiratory syncytial virus.

[a] Complete data available for all prerandomization and perirandomization variables; postdischarge data shown for survivors with follow-up data available.

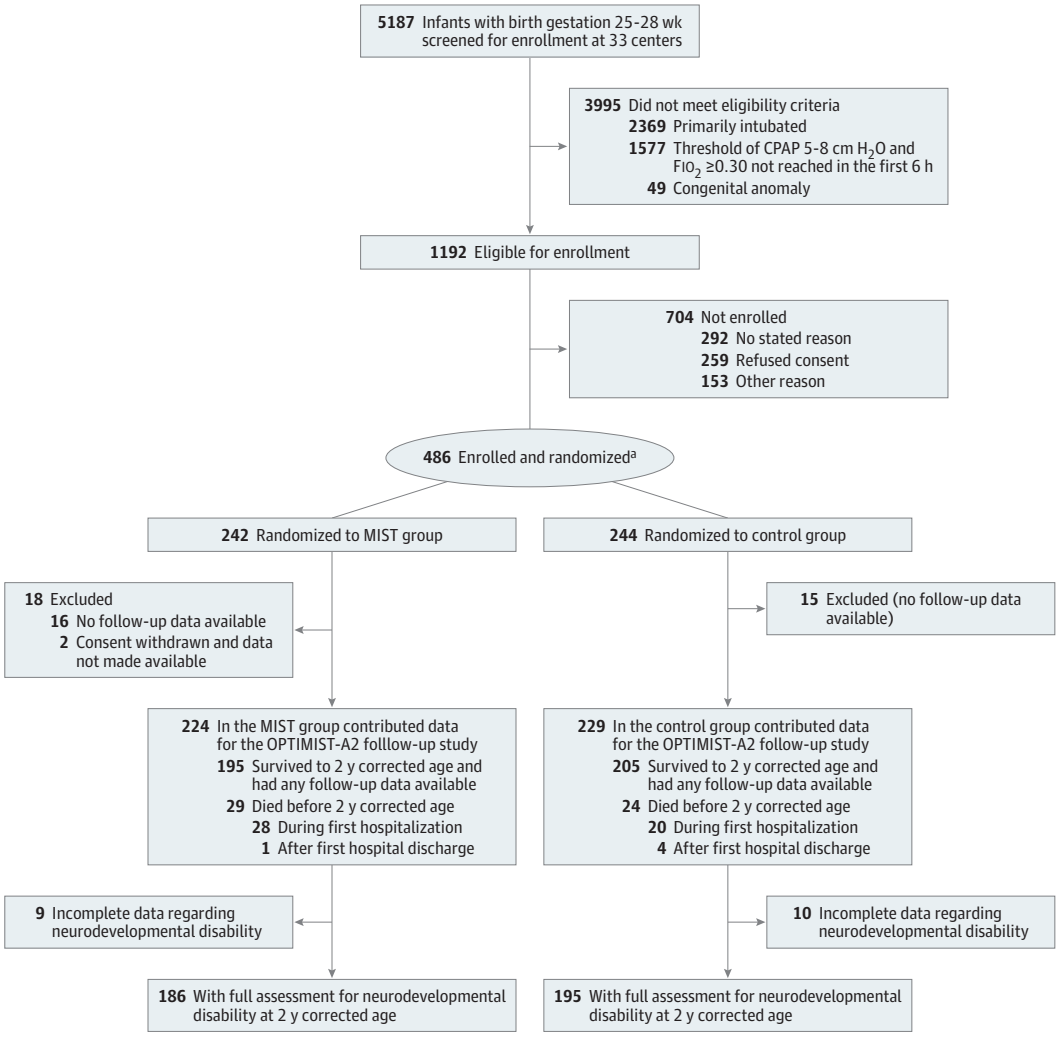
[b] Indicates success of transition at birth. The score range is 0 to 10. A score of 0 to 2 is given for each of the following: heart rate, respiratory effort, reflex irritability, muscle tone, and skin color. An Apgar score of 7 or greater at 5 minutes after birth generally indicates a satisfactory transition for a preterm infant.

Data Collection

Outcome data collection for the OPTIMIST-A2 study commenced in February 2014, performed in all cases by individuals blinded to trial allocation (site trial or follow-up personnel, parents). At the outset, data collection was by face-to-face follow-up assessment at 2 years' corrected age, including history taking to gather posthospital data on immunizations, family history of asthma, subsequent hospitalizations, and respiratory health, along with a clinical examination and a Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III[13]) standardized assessment.

With the involvement of more international sites, an online questionnaire was developed in 2016 as an alternative means of follow-up, to be completed by parents and submitted electronically. This questionnaire allowed collection of the same posthospital data, along with a detailed description of neurodevelopmental outcomes at 2 years' corrected age, incorporating the Parent Report of Children's Abilities-Revised

Figure. Screening, Enrollment, Randomization, and Follow-Up



CPAP indicates continuous positive airway pressure; FIO_2, fraction of inspired oxygen; and MIST, minimally invasive surfactant therapy.

[a] An additional 2 infants were enrolled but randomization failed in 1 case and in another was performed when the infant was ineligible (FIO_2 = 0.24). Treatment allocation was not revealed in either case.

(PARCA-R[14,15]), a standardized assessment of children's cognitive and language development that has been validated against the BSID-III[16] and has been used previously in RCTs in preterm infants.[17-19] For the OPTIMIST-A2 study, the questionnaire including the PARCA-R was uploaded to an online survey platform and was translated into 8 languages. An electronic link was sent by study personnel to the parents, with periodic reminders if a response was not forthcoming. Where no data could be collected by either of these methods, an abbreviated questionnaire was administered where possible, consisting of 6 questions related to NDD and respiratory hospitalizations.

Outcomes

The key secondary outcome in this follow-up study was the composite of death or moderate to severe NDD by 2 years' corrected age, defined as any of (1) moderate to severe cognitive or language impairment; (2) cerebral palsy equivalent to Gross Motor Function Classification System level of 2 or greater[20]; (3) visual impairment; and (4) hearing impairment (see eTable 1 in Supplement 3 for details of the method for ascertainment of neurodevelopmental outcomes in the different domains and modalities of follow-up). Other outcomes included the components of the key secondary outcome; subcomponents of the NDD outcome; requirement for at least 1, and 3 or more, hospitalizations in the first 2 years (any cause and for respiratory illness); measures of respiratory morbidity in the first 2 years (parent-reported wheezing or breathing difficulty, frequency of use of bronchodilator therapy, parental report of a physician diagnosis of asthma); and frequency of tube feeding beyond 1 year corrected age. See the statistical analysis plan for further details (Supplement 2).

Sample Size Calculation

The sample size was limited to that recruited for the inception cohort (486 infants correctly randomized). The original projected sample size for the trial was 606 infants, based on detection of a 13% absolute risk reduction in the primary outcome of death or BPD with 90% power.

Statistical Analysis

For the key secondary outcome and its components, RRs comparing active treatment with control, with 95% CIs, were estimated according to randomization group using a generalized linear model (GLM), adjusting for gestational age strata and incorporating a cluster-robust standard error calculation to account for clustering by study site. The GLM used the modified Poisson approach of Zou[21] with a log link function. An extended GLM additionally adjusted for covariates likely to influence death or NDD: birth weight less than the 10th centile, sex, mode of delivery, plurality, antenatal glucocorticoid exposure, and 5-minute Apgar score. For other binary outcomes, RR was estimated using GLMs, adjusting for gestation strata only. Treatment effects were also estimated as risk difference (RD), using a GLM approach with gaussian error distribution (to avert convergence difficulties with low-prevalence outcomes) and linear link function.[22] Because of the potential for type I error due to multiple comparisons, findings for the analyses of the follow-up outcomes were interpreted with caution.

A preplanned exploratory subgroup analysis was performed for all binary outcomes by gestational age strata. Further, a preplanned sensitivity analysis was conducted on the key secondary outcome and its second component of moderate to severe NDD using only information collected in the parent questionnaire, this being the predominant mode of follow-up. For this sensitivity analysis, data were included if the questionnaire was completed between 24 and 27 months' corrected age, inclusive. Data in relation to those participants who did not complete the parent questionnaire, or completed the PARCA-R questionnaire outside the time frame of 24 to 27 months, were handled using multiple imputation, using chained equations.[23,24] Within the chained equations algorithm, ordinal variables were imputed using ordinal regression and binary variables using logistic regression, and baseline variables were included as auxiliary variables in the imputation model. Imputation was carried out separately by treatment group to ensure that any treatment effects were maintained, using 50 imputed data sets. Two-tailed *P* values less than .05 were labeled significant. All analyses were conducted with Stata Statistical Software release 17 (StataCorp LLC).

Results

Study Conduct

Infants were enrolled between December 16, 2011, and March 26, 2020, and ceased thereafter short of the recruitment target in the wake of the COVID-19 pandemic, with 486 infants randomized from 5187 infants screened in 33 participating centers (Figure). Collection of follow-up data at 2 years' corrected age was completed on December 9, 2022.

Study Infants

Of the 486 infants randomized, 453 contributed data at 2 years' corrected age to the OPTIMIST-A2 study (MIST: n = 224 [29 deaths <2 years' corrected age including 28 during first hospitalization; 195 survivors with follow-up data]; control: n = 229 [24 deaths including 20 during first hospitalization; 205 survivors with follow-up data]) (Figure). Among 431 infants continuing in the study and surviving to 2 years' corrected age, 400 (93%) had follow-up data available, and 381 (88%) had sufficient data for a full assessment of NDD (Figure), including 186 and 195 infants in the MIST and control groups, respectively.

For the 453 infants for whom data were included in the OPTIMIST-A2 study, the median gestational age was 27.3 weeks (IQR, 26.4-28.1 weeks); 228 (50.3%) were female. Baseline characteristics of the OPTIMIST-A2 study infants were similar between the groups overall (Table 1), although within the 25 to 26 week gestation stratum, the frequency of male sex, incomplete or no steroid exposure, and multiple birth were each 13% to 15% higher in the MIST group (eTable 2 in Supplement 3).

Key Secondary Outcome and Components

Death or NDD assessed at 2 years' corrected age occurred in 78 infants (36.3%) in the MIST group and 79 (36.1%) in the control group (RR, 1.00 [95% CI, 0.81 to 1.24]; *P* = .99; RD, 0.0% [95% CI, −7.6% to 7.7%]) (**Table 2**). Death before 2 years occurred in 29 infants (12.9%) in the MIST group and 24 infants (10.5%) in the control group (RR, 1.23 [95% CI, 0.69 to 2.19]; *P* = .48; RD, 2.4% [95% CI, −3.6% to 8.4%]). NDD in survivors at 2 years occurred in 49 of 186 infants (26.3%) in the MIST group and 55 of 195 infants (28.2%) in the control group (RR, 0.94 [95% CI, 0.71 to 1.25]; *P* = .69; RD, −1.6% [95% CI, −9.4% to 6.2%]). These findings were not changed in an analysis using the extended GLM with additional covariates (eTable 3 in Supplement 3), nor in the sensitivity analysis solely using data collected with the parent questionnaire including PARCA-R between 24 and 27 months' corrected age (eTable 4 in Supplement 3).

Other Secondary Outcomes

Subcomponents of the NDD outcome were broadly similar between infants in the MIST and control groups (**Table 3**). There were benefits for the MIST group compared with the control group in relation to all secondary respiratory outcomes (**Table 4**; eTable 5 in Supplement 3). In particular, there was a relative reduction of 34% (MIST: 25.1%, control: 38.2%; RR, 0.66 [95% CI, 0.54-0.81]) in the frequency of 1 or more hospitalizations for respiratory illness in the MIST group compared with the control group. The first respiratory hospitalization was related to respiratory syncytial virus infection/bronchiolitis in more than 70% of instances in both groups, and the median age at admission was 4.2 and 4.7 months' corrected age in the MIST and control groups, respectively (eTable 5 in Supplement 3). The frequency of

Table 2. Key Secondary Outcome Analysis

Outcome	No./total (%)		Risk difference, % (95% CI)[a]	Relative risk (95% CI)[a]	*P* value[b]
	Minimally invasive surfactant therapy (n = 224)	Control treatment (n = 229)			
Death or neurodevelopmental disability[c,d,e]	78/215 (36.3)	79/219 (36.1)	0.0 (−7.6 to 7.7)	1.00 (0.81 to 1.24)	.99
Death prior to 2 y corrected age	29/224 (12.9)	24/229 (10.5)	2.4 (−3.6 to 8.4)	1.23 (0.69 to 2.19)	.48
Neurodevelopmental disability[c,d,e]	49/186 (26.3)	55/195 (28.2)	−1.6 (−9.4 to 6.2)	0.94 (0.71 to 1.25)	.69

[a] Adjusted for gestational age group.

[b] *P* value for relative risk derived from generalized linear model.

[c] Neurodevelopmental disability, defined as any of (1) moderate to severe cognitive or language impairment; (2) cerebral palsy equivalent to Gross Motor Function Classification System ≥2[20]; (3) visual impairment; and (4) hearing impairment. See eTable 1 in Supplement 3 for further details of the approach to outcome ascertainment with the different modalities of data capture.

[d] Key secondary outcome not determinable from available follow-up data in 9 of 224 infants in the minimally invasive surfactant therapy group and 10 of 229 infants in the control group.

[e] Neurodevelopmental disability assessment at 2 years was by online questionnaire including Parent Report of Children's Abilities–Revised in 315 infants (minimally invasive surfactant therapy: 152, control: 163, including 64 and 69 cases, respectively, in which the questionnaire was administered using a translated version). Other modes of follow-up were face-to-face assessment including Bayley Scales of Infant and Toddler Development, Third Edition in 38 infants (minimally invasive surfactant therapy: 19, control: 19), abbreviated questionnaire in 25 (minimally invasive surfactant therapy: 14, control: 11), and a combination of modalities in 3 (minimally invasive surfactant therapy: 1, control: 2).

Table 3. Indices of Neurodevelopment Assessed at 2 Years

Outcome	No./total (%)		Risk difference, % (95% CI)[a]	Relative risk (95% CI)[a]	*P* value[b]
	Minimally invasive surfactant therapy	Control treatment			
Cognitive or language impairment	42/183 (23.0)	47/195 (24.1)	−0.9 (−7.5 to 5.6)	0.96 (0.73 to 1.27)	.77
Cognitive impairment	26/171 (15.2)	34/183 (18.6)	−3.3 (−10.7 to 4.1)	0.82 (0.54 to 1.27)	.38
BSID-III cognitive composite standard score, median (IQR)[c]	95 (80 to 95) [n = 18]	95 (85 to 105) [n = 19]			
PARCA-R nonverbal cognitive scale standard score, median (IQR)[d]	91 (78 to 107) [n = 153]	92 (75 to 106) [n = 164]			
Language impairment	29/170 (17.1)	25/180 (13.9)	3.5 (−2.6 to 9.6)	1.25 (0.85 to 1.85)	.25
BSID-III language composite standard score, median (IQR)[c]	81 (74 to 106) [n = 18]	93 (83 to 103) [n = 18]			
PARCA-R language scale standard score, median (IQR)[d]	89 (77 to 99) [n = 152]	88 (79 to 97) [n = 162]			
Cerebral palsy	9/195 (4.6)	15/204 (7.4)	−2.7 (−6.3 to 0.9)	0.63 (0.36 to 1.11)	.11
Visual impairment	0/193	5/204 (2.5)	−2.5 (−4.4 to −0.6)	Not estimable	
Hearing impairment	4/194 (2.1)	4/205 (2.0)	0.1 (−2.3 to 2.6)	1.06 (0.31 to 3.61)	.93

Abbreviations: BSID-III, Bayley Scales of Infant and Toddler Development Third Edition; PARCA-R, Parent Report of Children's Abilities–Revised.

[a] Adjusted for gestational age group.

[b] *P* value for relative risk derived from generalized linear model.

[c] BSID-III composite scores: population mean (SD), 100 (15); range, 47-153, with higher scores indicating better performance. A score <80 was indicative of moderate to severe disability.

[d] PARCA-R standard scores: population mean (SD), 100 (15); range, 10-147, with higher scores indicating better performance. A score <70 was indicative of moderate to severe disability.

wheezing or breathing difficulty reported by parents showed a 24% relative reduction in the MIST group compared with the control group (40.6% vs 53.6%; RR, 0.76 [95% CI, 0.63-0.90]), with a similar reduction in the frequency of bronchodilator use (Table 4). Reported use of inhaled relievers (β_2 agonists) was 23.9% in the MIST group and 38.7% in the control group. Reported use of inhaled preventers (corticosteroids) was 5.6% in the MIST group and 15.5% in the control group (eTable 5 in Supplement 3). Asthma diagnosed by a physician was reported in 4.4% and 11.9% of MIST and control group infants, respectively.

The incidence of tube feeding beyond 1 year corrected age was very low, with no observed difference between groups.

Subgroups

In the exploratory analysis by gestational age groups, for the outcome of death prior to 2 years, there was evidence of an interaction between treatment group and gestational age group (lower proportion of the outcome in the control group at lower gestation and lower proportion of the outcome in the MIST group at higher gestation, *P* for interaction = .04) (eTable 6 in Supplement 3). Among other secondary outcomes, the treatment effect favoring the MIST group was more prominent in the 27 to 28 weeks' gestation stratum for 1 or more hospitalizations with respiratory and any illness, and for parent-reported wheezing or breathing difficulty (eTable 7 in Supplement 3).

Table 4. Hospitalizations and Respiratory Health in the First 2 Years

Outcome	No./total (%)		Risk difference, % (95% CI)[a]	Relative risk (95% CI)[a]	*P* value[b]
	Minimally invasive surfactant therapy	Control treatment			
Hospitalizations with any illness					
≥1	77/194 (39.7)	104/204 (51.0)	−11.2 (−18.2 to −4.3)	0.78 (0.66 to 0.92)	.003
≥3	22/194 (11.3)	39/204 (19.1)	−7.8 (−13.7 to −1.8)	0.59 (0.40 to 0.87)	.008
Hospitalizations with respiratory illness					
≥1	49/195 (25.1)	78/204 (38.2)	−13.1 (−19.5 to −6.7)	0.66 (0.54 to 0.81)	<.001
≥3	14/195 (7.2)	23/204 (11.3)	−4.1 (−8.6 to 0.4)	0.63 (0.41 to 0.98)	.04
Parent-reported wheeze or breathing difficulty	73/180 (40.6)	104/194 (53.6)	−13.1 (−20.1 to −6.1)	0.76 (0.63 to 0.90)	.002
Use of any bronchodilator therapy	57/180 (31.7)	83/194 (42.8)	−11.2 (−20.0 to −2.4)	0.74 (0.57 to 0.96)	.03
Parent report of a physician diagnosis of asthma	8/180 (4.4)	23/194 (11.9)	−7.6 (−13.7 to −1.5)	0.37 (0.19 to 0.73)	.004

[a] Adjusted for gestational age group.

[b] *P* value for relative risk derived from generalized linear model.

No adverse events were reported in relation to outcomes beyond the first hospitalization.

Discussion

In this follow-up study of a multicenter RCT in preterm infants supported with CPAP and exhibiting features of RDS, administration of surfactant via a thin catheter at a low oxygenation threshold, compared with sham treatment, did not significantly reduce the incidence of the composite outcome of death or NDD at 2 years' corrected age, nor its components. The neurodevelopmental outcomes of the groups based on analysis of the subcomponents of the NDD outcome were broadly similar. However, the MIST group had better outcomes than the control group in all secondary measures related to respiratory health in the first 2 years of life.

To our knowledge, the OPTIMIST-A2 study cohort is the largest to date to have follow-up assessment after an RCT of surfactant delivery via thin catheter, with any form of comparator. The importance of the follow-up component is emphasized when considering the RCT design, which in the first days of life resulted in there being a substantial difference between the MIST and control groups in the number of procedures involving laryngoscopy, which is known to be a major cause of hypoxemic and bradycardic episodes[25,26] that could have lasting neurodevelopmental consequences. Infants in the MIST group each had on average 1.37 such procedures (100% having laryngoscopy for thin catheter placement and 37% being intubated in the first 72 hours[9]). For the control group, the average number of procedures involving laryngoscopy was 0.72 (72% being intubated <72 hours). Reassuringly, the disparity in the rate of airway instrumentation between the groups was not followed by any discernible difference in the risk of NDD assessed at 2 years' corrected age.

On the other hand, the lower incidence of BPD at 36 weeks' postmenstrual age that was noted in the MIST group[9] did not confer a reduction in NDD at 2 years' corrected age. Although a diagnosis of BPD is a known risk factor for NDD in childhood and adolescence,[27] the mechanisms by which these conditions are linked are complex, likely involving diverse intermediaries at play during the first hospitalization and beyond.[1,28] A previous RCT in infants less than 27 weeks' gestation found surfactant administration via a thin catheter, compared with administration via endotracheal tube with delayed extubation, to be associated with a reduced incidence of severe intraventricular hemorrhage but not BPD during first hospitalization[4] and a lower rate of moderate to severe motor impairment at 2 years' corrected age (22% vs 42%).[5] Another RCT with a similar comparator group to the OPTIMIST-A trial (continuation of CPAP) found no difference in the incidence of BPD during first hospitalization,[7] nor was there a discernible effect on rate of NDD using the BSID-II assessment.[8] The smaller inception cohorts in each of these trials (N = 211 and N = 220, respectively) limit the impact of these follow-up data.

In exploratory subgroup analysis for the outcome of death prior to 2 years' corrected age, there was some evidence of an interaction suggesting a higher mortality risk in the 25 to 26 weeks' gestation stratum associated with allocation to the MIST group (eTable 6 in Supplement 3), in parallel with findings this study team reported previously for death prior to 36 weeks' postmenstrual age.[9] This finding may have been due in part to a chance imbalance in risk profile in this subgroup, but behooves caution in application of MIST at 25 to 26 weeks' gestation. Subgroup analysis also suggested that the benefits of MIST in relation to longer-term respiratory outcomes (eTable 7 in Supplement 3) may be more prominent at later than 26 weeks' gestation. The influence of gestation on the effect of MIST on respiratory outcomes after first hospitalization warrants further study.

Notwithstanding some differences in definitions of NDD and modalities of data capture, the neurodevelopmental outcomes in this follow-up cohort were comparable with those reported previously in preterm infants of similar gestational age. The finding of an overall rate of cognitive or language impairment of 23.5% was similar to that reported for preterm infants less than 29 weeks' gestation enrolled in an RCT of docosahexaenoic acid supplementation, in which the overall rate of general cognitive impairment assessed at 5 years was approximately 29%.[29] Another RCT examining

oxygen saturation targets in preterm infants born before 28 weeks' gestation reported the overall language or cognitive score on BSID-III assessment to be <85 in around 27% of infants surviving to 2 years' corrected age.[30]

As with other investigations of respiratory health in preterm infants after first hospital discharge, this study observed a high rate of hospitalization for respiratory illness in the first 2 years (32% overall), compared with 31% overall between 6 and 22 months' corrected age in a large RCT involving extremely preterm infants,[31] and approximately 31% in registry data including infants at 22 to 26 weeks' gestation.[32] The frequency of parent-reported wheezing and breathing difficulty (46% overall) also matched that of other studies.

The effects of MIST on respiratory health in infancy appeared to be greater than on the outcome of BPD at 36 weeks' postmenstrual age. This finding bespeaks the difficulty of accurately quantifying the degree of lung injury in early life after preterm birth, with the current metrics of BPD being overly reductionist for this purpose.[1,33,34] It is speculated that many infants in this study cohort without a diagnosis of BPD had a lasting lung injury that manifested in early life with respiratory symptoms and rendered them vulnerable to respiratory infection. Rates of respiratory symptoms and hospitalizations observed in other studies in the first 2 years in preterm infants without a BPD diagnosis would support this contention.[33] Further, the application of MIST on the first day of life appears to have attenuated lung injury. This is likely related to the lessening of exposure to positive pressure ventilation in the critical first days of life,[35] with the rate of intubation at less than 72 hours being nearly halved in the MIST group compared with the control group (37% vs 72%).[9]

Limitations

This study has several limitations. First, this was a follow-up study of a clinical trial that was not specifically designed to detect differences in 2-year outcomes and analysis of the follow-up data involved multiple additional comparisons beyond those previously reported. Second, the sample size was limited by the early closure of recruitment due to the COVID-19 pandemic. Third, several methods of data capture were used, with the dominant method being an online questionnaire rather than a face-to-face assessment. However, the PARCA-R assessment involved a parent report (blinded to group assignment) of their child's language and nonverbal cognitive ability, the totality of which may be difficult to elicit completely in a single face-to-face BSID-III assessment.

Conclusion

In this follow-up of an RCT of preterm infants with respiratory distress syndrome supported with CPAP, MIST compared with sham treatment did not reduce the incidence of death or NDD by 2 years of age. However, infants who received MIST had lower rates of adverse respiratory outcomes during their first 2 years of life.

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Author Affiliations: Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia (Dargaville); Department of Paediatrics, Royal Hobart Hospital, Hobart, Tasmania, Australia (Dargaville, De Paoli); Neonatal Services, Royal Women's Hospital, Melbourne, Victoria, Australia (Kamlin, Cheong, Davis); Department of Obstetrics and Gynaecology, University of Melbourne, Melbourne, Victoria, Australia (Kamlin, Cheong, Davis); Clinical Epidemiology and Biostatistics Unit, Murdoch Children's Research Institute, Melbourne, Victoria, Australia (Orsini, Wang, Carlin); Department of Neonatology, Zekai Tahir Burak Maternity Teaching Hospital, Ankara, Turkey (Kanmaz Kutman); Division of Neonatology, Department of Pediatrics, Istanbul Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Turkey (Cetinkaya); Division of Gynaecology and Obstetrics, Department of Perinatology, University Medical Centre, Ljubljana, Slovenia (Kornhauser-Cerar); Division of Neonatology, Northshore University Health System, Evanston, Illinois (Derrick); Division of Neonatology, Department of Pediatrics, Uludağ University Faculty of Medicine, Bursa, Turkey (Özkan); Division of Neonatology, Beatrix Children's Hospital, University Medical Center Groningen, Groningen, the Netherlands (Hulzebos); Division of Neonatology, Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada (Schmölzer); Neonatal Services, Mercy Hospital for Women, Heidelberg, Victoria, Australia (Aiyappan); Department of Obstetrics, Gynecology, and Newborn Care, The Ottawa Hospital, Ottawa, Ontario, Canada (Lemyre); Department of Pediatrics, Kapi'olani Medical Center for Women and Children, Honolulu, Hawai'i (Kuo); Department of Neonatology, KK Women's and Children's Hospital, Duke-NUS Medical School, Singapore (Rajadurai); Neonatal Unit, Royal Hospital for Children, Glasgow, United Kingdom (O'Shea); Division of Neonatology, Department of Pediatrics, Los Angeles County + USC Medical Center and Good Samaritan Hospital, Keck School of Medicine of USC, Los Angeles, California (Biniwale, Ramanathan); Department of Pediatrics, Children's Regional Hospital, Cooper University Health Care, Camden, New Jersey (Kushnir); Rappaport Faculty of Medicine, Department of Neonatology, Bnai Zion Medical Center, Technion, Haifa, Israel (Bader); Department of Neonatal Medicine, Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom (Thomas); Regional Neonatal Intensive Care Unit, University Hospital of Wales, Cardiff, United Kingdom (Chakraborty); Newborn Service, Starship Child Health, Auckland Hospital, Auckland, New Zealand (Buksh); Monash Newborn, Monash Children's Hospital, Clayton, Victoria, Australia (Bhatia); Department of Neonatology, Singleton Hospital, Swansea, United Kingdom (Sullivan); Faculty of Medicine, Department of Neonatology, Ziv Medical Center, Bar-Ilan University, Tsfat, Israel (Shinwell); Department of Neonatology, Centenary Hospital for Women and Children, Canberra Hospital, Woden, New South Wales, Australia (Dyson); Neonatal Intensive Care Unit, Dunedin Hospital, Dunedin, New Zealand (Barker); Rappaport Faculty of Medicine, Department of Neonatology, Rambam Medical Center, Technion, Haifa, Israel (Kugelman); Division of Neonatology, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia (Donovan); Neonatal Intensive Care Unit, Princess Anne Hospital, Southampton, United Kingdom (Goss); Division of Neonatology, Peyton Manning Children's Hospital, Ascension St Vincent, Indianapolis, Indiana (Tauscher); Neonatal Intensive Care Centre, The Royal London Hospital-Barts Health NHS Foundation Trust, London, United Kingdom (Murthy); Division of Neonatology, Sidra Medicine, Doha, Qatar (Ali); Faculty of Population Health Sciences, Neonatology, EGA Institute for Women's Health, University College London, London, United Kingdom (Clark); Division of Neonatal-Perinatal Medicine, Larner College of Medicine, The University of Vermont, Burlington (Soll); Infant Mortality and Morbidity Studies Research Group, Department of Population Health Sciences, University of Leicester, Leicester, United Kingdom (Johnson); Clinical Sciences, Murdoch Children's Research Institute, Melbourne, Victoria, Australia (Cheong); Department of Paediatrics, University of Melbourne, Melbourne, Victoria, Australia (Carlin).

Author Contributions: Dr Dargaville and Ms Orsini had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The trial coordinating center and data management and statistics center were led by Drs Dargaville and Carlin, respectively.

Concept and design: Dargaville, Kamlin, Orsini, Soll, Carlin, Davis.
Acquisition, analysis, or interpretation of data: Dargaville, Kamlin, Orsini, Wang, De Paoli, Kanmaz Kutman, Cetinkaya, Kornhauser-Cerar, Derrick, Özkan, Hulzebos, Schmölzer, Aiyappan, Lemyre, Kuo, Rajadurai, O'Shea, Biniwale, Ramanathan, Kushnir, Bader, Thomas, Chakraborty, Buksh, Bhatia, Sullivan, Shinwell, Dyson, Barker, Kugelman, Donovan, Goss, Tauscher, Murthy, Ali, Clark, Johnson, Cheong, Carlin, Davis.
Drafting of the manuscript: Dargaville, Orsini, Wang, Kanmaz Kutman, Cetinkaya, Carlin.
Critical review of the manuscript for important intellectual content: Dargaville, Kamlin, Orsini, De Paoli, Kanmaz Kutman, Cetinkaya, Kornhauser-Cerar, Derrick, Özkan, Hulzebos, Schmölzer, Aiyappan, Lemyre, Kuo, Rajadurai, O'Shea, Biniwale, Ramanathan, Kushnir, Bader, Thomas, Chakraborty, Buksh, Bhatia, Sullivan, Shinwell, Dyson, Barker, Kugelman, Donovan, Goss, Tauscher, Murthy, Ali, Clark, Soll, Johnson, Cheong, Carlin, Davis.
Statistical analysis: Orsini, Wang, Carlin.
Obtained funding: Dargaville, Kamlin.
Administrative, technical, or material support: Dargaville, De Paoli, Kanmaz Kutman, Derrick, Hulzebos, Buksh, Donovan, Johnson, Davis.
Supervision: Dargaville, Orsini, Rajadurai, Biniwale, Ramanathan, Kushnir, Chakraborty, Clark, Carlin.
Other–site investigator: Özkan, Schmölzer, Aiyappan, Kuo, Thomas, Sullivan, Dyson, Barker, Kugelman, Goss, Tauscher, Murthy.
Other: Bader.

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Group Information: The OPTIMIST-A Trial Investigators appear in Supplement 4.

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