ORIGINAL ARTICLE

Nasal High-Flow Therapy for Newborn Infants in Special Care Nurseries

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ABSTRACT

BACKGROUND

Nasal high-flow therapy is an alternative to nasal continuous positive airway pressure (CPAP) as a means of respiratory support for newborn infants. The efficacy of high-flow therapy in nontertiary special care nurseries is unknown.

METHODS

We performed a multicenter, randomized, noninferiority trial involving newborn infants (<24 hours of age; gestational age, ≥31 weeks) in special care nurseries in Australia. Newborn infants with respiratory distress and a birth weight of at least 1200 g were assigned to treatment with either high-flow therapy or CPAP. The primary outcome was treatment failure within 72 hours after randomization. Infants in whom high-flow therapy failed could receive CPAP. Noninferiority was determined by calculating the absolute difference in the risk of the primary outcome, with a noninferiority margin of 10 percentage points.

RESULTS

A total of 754 infants (mean gestational age, 36.9 weeks, and mean birth weight, 2909 g) were included in the primary intention-to-treat analysis. Treatment failure occurred in 78 of 381 infants (20.5%) in the high-flow group and in 38 of 373 infants (10.2%) in the CPAP group (risk difference, 10.3 percentage points; 95% confidence interval [CI], 5.2 to 15.4). In a secondary per-protocol analysis, treatment failure occurred in 49 of 339 infants (14.5%) in the high-flow group and in 27 of 338 infants (8.0%) in the CPAP group (risk difference, 6.5 percentage points; 95% CI, 1.7 to 11.2). The incidences of mechanical ventilation, transfer to a tertiary neonatal intensive care unit, and adverse events did not differ significantly between the groups.

CONCLUSIONS

Nasal high-flow therapy was not shown to be noninferior to CPAP and resulted in a significantly higher incidence of treatment failure than CPAP when used in nontertiary special care nurseries as early respiratory support for newborn infants with respiratory distress. (Funded by the Australian National Health and Medical Research Council and Monash University; HUNTER Australian and New Zealand Clinical Trials Registry number, ACTRN12614001203640.)

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Clinicians aim to avoid the use of mechanical ventilation through an endotracheal tube in newborn infants with respiratory distress by providing noninvasive respiratory support. In Australia, infants for whom ongoing mechanical ventilation is indicated are typically transferred to a tertiary-level neonatal intensive care unit (NICU). Owing to potentially large distances between regional or rural nontertiary special care nurseries and metropolitan NICUs, a transfer may result in family disruptions, with associated psychosocial and financial costs.[1,2]

The use of nasal continuous positive airway pressure (CPAP) in large Australian special care nurseries is beneficial and cost-effective, and it is associated with a lower incidence of treatment failure or transfer to a NICU than supplemental oxygen alone.[3] Infants with respiratory distress now routinely receive CPAP in large special care nurseries in Australia. However, CPAP may be associated with an increased incidence of pneumothorax,[4] and experienced medical and nursing specialists are required in order to provide CPAP safely and effectively; this precludes its use in smaller special care nurseries in Australia[5] and around the world. Nasal high-flow therapy is an increasingly popular alternative to CPAP for neonatal respiratory support.[6-8] High-flow therapy delivers heated, humidified gas at flows of greater than 1 liter per minute through small binasal prongs. It has a simple interface that is easier to use and appears to be more comfortable than CPAP, and it is preferred by parents and nurses.[9,10]

We previously found that when used in tertiary-level NICUs as primary respiratory support for preterm infants born at a gestational age of 28 weeks 0 days to 36 weeks 6 days, high-flow therapy resulted in a significantly higher incidence of treatment failure than did CPAP.[11] However, special care nurseries have far more mature infants with fewer coexisting conditions than do NICUs; they also differ from NICUs with respect to medical and nursing experience and the ratio of providers to patients. For these reasons, high-flow therapy may be well suited to special care nurseries. Since most late-preterm and term infants with respiratory distress receive treatment in special care nurseries, data to guide respiratory support in this setting are relevant to many thousands of infants in developed countries each year.[12] We performed the multicenter, randomized, noninferiority High-Flow Use in Non-Tertiary Centres for Early Respiratory Distress (HUNTER) trial in Australian special care nurseries to test the hypothesis that high-flow therapy is noninferior to CPAP as primary respiratory support for newborn infants with early respiratory distress.

Methods

Trial Design and Oversight

Eligible nontertiary centers were similar to level 2 special care nurseries as defined by the Committee on Fetus and Newborn of the American Academy of Pediatrics.[13] The driving time from the centers to the closest tertiary NICU was up to 90 minutes. The centers routinely cared for infants born at or after 32 weeks of gestation, and occasionally they cared for infants born at 31 weeks of gestation. At least 2000 births per year occurred in each center, and all centers had extensive experience treating infants with CPAP.

Multisite ethical approval was obtained from the Royal Children's Hospital, Melbourne, Australia, and site-specific approval was obtained from each center. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (published previously[14] and available with the full text of this article at NEJM.org). The trial had no commercial support, and the manufacturers of the respiratory devices had no input in the trial design, data accrual, data analysis, or manuscript preparation and no access to the trial data.

Patients

Infants were eligible for inclusion if they were born at a gestational age of 31 weeks 0 days or later, had a birth weight of at least 1200 g, were less than 24 hours of age, and if the treating clinician determined that noninvasive respiratory support was indicated, the infant had received supplemental oxygen for more than 1 hour, or both. Since CPAP treatment was the standard of care for respiratory distress, up to 2 hours of CPAP treatment was permitted while consent was sought. Infants were ineligible if, before randomization, they had received CPAP for more than 2 hours, had undergone endotracheal intubation, had a known major congenital abnormality, or if the treating clinician had decided that endotracheal intubation or transfer to a NICU was indicated.

CONSENT AND RANDOMIZATION

The parent or parents of all participating infants provided written informed consent before randomization. A computer-generated randomization sequence with variable block sizes was used. Infants were stratified according to gestational age (<34 weeks vs. ≥34 weeks) and trial center. Enrolled infants who were part of multiple births underwent randomization individually. Sequentially numbered, sealed, opaque envelopes containing the treatment assignment were opened once eligibility criteria were met and consent was obtained.

TRIAL INTERVENTION

Eligible infants were randomly assigned to treatment with either high-flow therapy or CPAP generated with the use of an underwater "bubble" system. Other aspects of care were provided according to local protocols, including blood gas analysis, chest radiography, intravenous fluids, and enteral feeding.

Infants assigned to the high-flow group received an initial gas flow of 6 liters per minute from the Optiflow Junior device (Fisher and Paykel Healthcare). The maximum permissible gas flow was 8 liters per minute, consistent with the maximum gas flow used in previous studies.[11,15,16] Infants assigned to high-flow therapy who met the criteria for treatment failure could receive CPAP as rescue therapy, initiated at a pressure of 8 cm of water.

In infants who were assigned to CPAP, the starting pressure was 6 cm of water delivered through short binasal prongs or a nasal mask. The maximum permissible CPAP pressure was 8 cm of water. The trial protocol recommended that infants from either group who met the criteria for treatment failure while receiving CPAP be discussed with members of the local neonatal retrieval service and receive endotracheal intubation as appropriate. The decision to transfer the infant to a NICU remained with the treating clinician, irrespective of whether the criteria for treatment failure were met. High-flow therapy was not permitted for infants in the CPAP group. Guidance on weaning and discontinuation of respiratory support was included in the trial protocol.[14]

TRIAL OUTCOMES

The primary outcome was treatment failure within 72 hours after randomization. Infants receiving maximal support (gas flow of 8 liters per minute [in the high-flow group] or pressure of 8 cm of water [in the CPAP group]) were considered to have treatment failure if they met one or more of the following criteria: a fraction of inspired oxygen of 0.4 or higher for more than 1 hour to maintain target oxygen saturation levels of 91 to 95%; a pH of less than 7.2 plus a partial pressure of carbon dioxide greater than 60 mm Hg in two samples of arterial or capillary blood obtained at least 1 hour after commencement of the assigned treatment and obtained 1 hour apart; or two or more episodes of apnea for which positive-pressure ventilation was indicated within a 24-hour period or six or more episodes for which any intervention was indicated within a 6-hour period. Infants who had an urgent need for endotracheal intubation and mechanical ventilation or required transfer to a NICU (as determined by the treating clinician) were also considered to have treatment failure. Infants in whom respiratory management was escalated at the discretion of the clinician and who had not clearly met the criteria for treatment failure were classified as having another reason for treatment failure.

Prespecified secondary outcomes included the reason or reasons for treatment failure; endotracheal intubation; transfer to a NICU; the duration of respiratory support, supplemental oxygen, and hospitalization; and the cost of care. The complete list of prespecified secondary outcomes is provided in the trial protocol[14] and in Section 2 in the Supplementary Appendix, available at NEJM.org. The methods for the cost-of-care analysis are also provided Section 3 in the Supplementary Appendix.

STATISTICAL ANALYSIS

On the basis of recent admission data from participating centers, we estimated that treatment failure within 72 hours after randomization would occur in 17% of the infants assigned to receive CPAP. We prespecified a noninferiority margin for high-flow treatment of 10 percentage points above the failure rate for CPAP treatment. Data from previous trials comparing high-flow therapy with CPAP in the nontertiary setting on which to base our sample-size calculation were lacking. We chose this margin of noninferiority on clinical grounds, taking into consideration that infants in whom high-flow treatment failed could receive CPAP treatment, which we hypoth-

esized might obviate the need for endotracheal intubation. The pediatricians, neonatologists, and parent representatives consulted during the trial-design phase agreed that a treatment failure rate that was 10 percentage points higher with high-flow therapy than with CPAP would be the maximum acceptable rate. High-flow therapy would thus be considered noninferior to CPAP if the upper limit of the two-sided 95% confidence interval for the risk difference was less than 10 percentage points. For the trial to have 90% power, a sample of 750 infants was required (one-sided alpha level of 0.025).

In accordance with the prespecified statistical analysis plan (available with the protocol at NEJM.org), we performed both a primary intention-to-treat analysis and a secondary per-protocol analysis, as recommended for noninferiority trials.[17] The intention-to-treat analysis included all eligible infants for whom consent had been provided. Exclusion criteria for the per-protocol analysis were determined prospectively (see Section 4 in the Supplementary Appendix). Both analyses were performed without adjustment and with adjustment for gestational age, trial center, birth weight, exposure to antenatal glucocorticoids (<7 days before birth), and sex; analyses with adjustment were designated as secondary analyses.

Secondary outcomes were analyzed on an intention-to-treat basis. A prespecified subgroup analysis according to gestational age (<34 weeks or ≥34 weeks) was performed for the primary outcome and selected secondary outcomes; heterogeneity was assessed by including an interaction term in the models. Since we did not prespecify a plan to adjust for multiple secondary outcomes, we do not report P values for these outcomes.

For the primary outcome and dichotomous secondary outcomes, we calculated a risk difference (with a two-sided 95% confidence interval) in percentage points between the treatment groups. Since the widths of the confidence intervals were not adjusted for multiple comparisons, the intervals should not be used to infer definitive treatment effects for secondary outcomes. We used chi-square tests to compare dichotomous outcomes, the appropriate parametric test (Student's t-test) or nonparametric test (difference in medians estimated by quantile regression) to compare continuous outcomes, and generalized linear models for analyses with adjustment. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute), or Stata software, version 14.0 (StataCorp).

Figure 1 (facing page). Numbers of Infants Who Were Screened, Assigned to a Trial Group, and Included in the Primary and Secondary Analyses.

Infants who were born at a gestational age of 31 weeks 0 days or later, had a birth weight of at least 1200 g, and had a clinical diagnosis of respiratory distress were screened for eligibility. (Additional information regarding infants who did not meet the treatment-failure criteria before respiratory support was escalated is provided in Section 4 in the Supplementary Appendix). CPAP denotes continuous positive airway pressure.

An independent data and safety monitoring committee undertook a planned review of the primary outcome at the midpoint of the trial. Safety analyses for predefined serious adverse events, blinded to the intervention, were undertaken after recruitment of 150 infants (20%), 375 infants (50%), and 562 infants (75%).

RESULTS

RECRUITMENT

Infants were recruited from April 13, 2015, through November 28, 2017, at nine Australian nontertiary centers. The data and safety monitoring committee performed interim efficacy and safety reviews as planned and recommended that the trial continue unaltered.

TRIAL PATIENTS

In total, 768 infants were randomly assigned to a treatment group (385 to the high-flow group and 383 to the CPAP group). Fourteen infants were excluded because they did not meet the eligibility criteria or their parents did not provide consent or withdrew consent. A total of 754 infants (mean gestational age, 36.9 weeks, and mean birth weight, 2909 g) were included in the primary intention-to-treat analysis (381 in the high-flow group and 373 in the CPAP group) and were followed until hospital discharge or death (Fig. 1). The demographic and clinical characteristics of the mothers and infants included in the intention-to-treat analysis were similar in the two groups (Table 1). After exclusion of 77 infants (42 in the high-flow group and 35 in the CPAP group), 677 infants were included in the

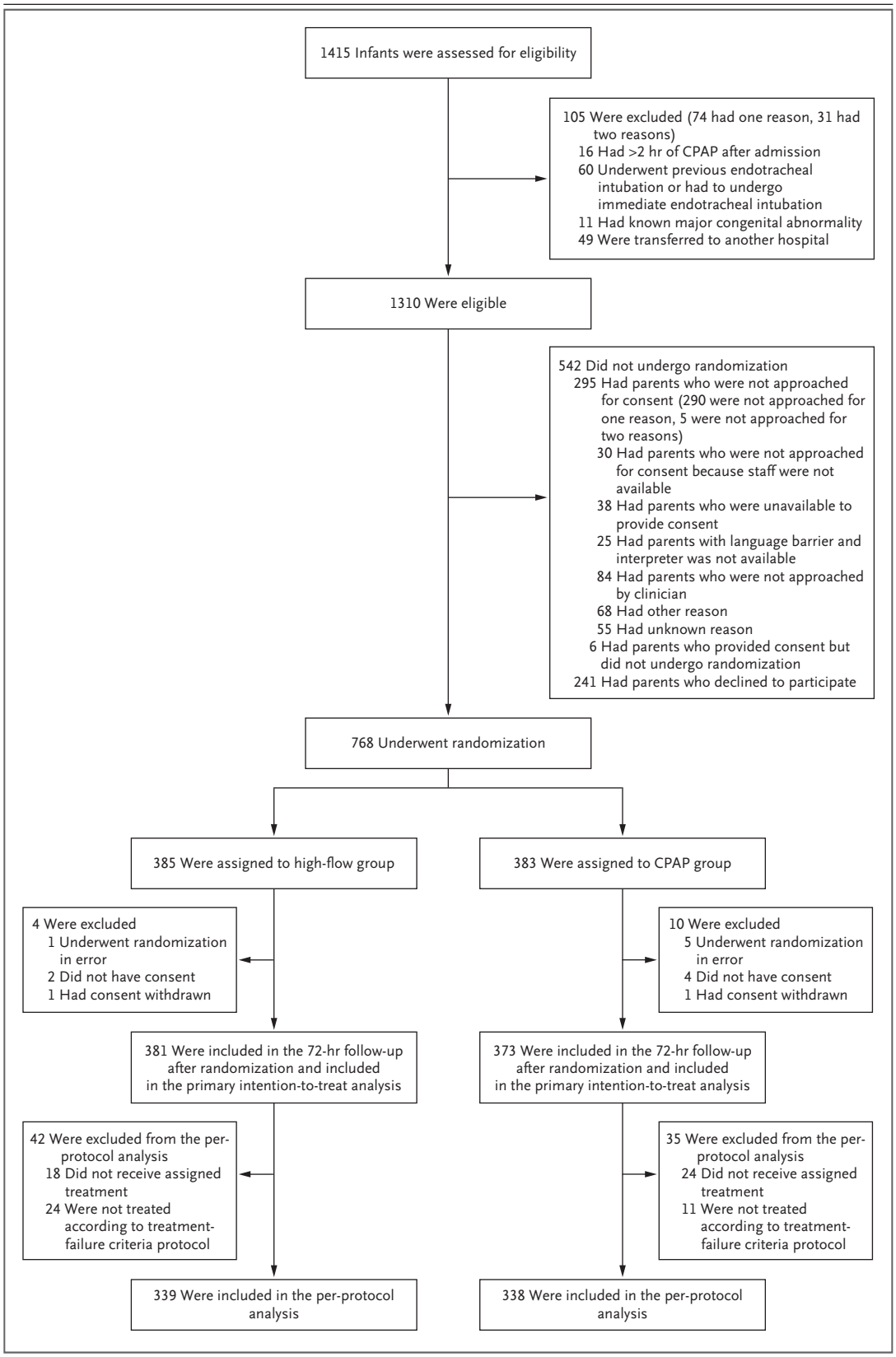

Table 1. Baseline Characteristics of the Mothers and Infants.*

Characteristic	High-Flow Group (N=381)	CPAP Group (N=373)
Mothers		
Age — yr	29.8±5.6	30.1±5.7
Multigravida — no. (%)	209 (54.9)	169 (45.3)
Use of antenatal glucocorticoids <7 days before birth — no. (%)	107 (28.1)	91 (24.4)
Labor — no. (%)	263 (69.0)	265 (71.0)
Cesarean section — no. (%)	204 (53.5)	177 (47.5)
Ruptured membranes ≥24 hr before delivery — no. (%)†	36 (9.4)	33 (8.8)
Chorioamnionitis — no. (%)	14 (3.7)	9 (2.4)
Meconium-stained amniotic fluid — no. (%)	77 (20.2)	74 (19.8)
Infants		
Gestational age		
No. of weeks	36.9±2.8	36.9±3.0
<34 wk — no. (%)	72 (18.9)	68 (18.2)
Birth weight — g	2936±786	2885±790
Male sex — no. (%)	246 (64.6)	237 (63.5)
Multiple birth — no. (%)	26 (6.8)	37 (9.9)
Median Apgar score at 5 min (IQR)‡	8.0 (7.0–9.0)	8.0 (7.0–9.0)
Treatment with CPAP before randomization§		
No. of infants (%)	60 (15.7)	70 (18.8)
Median duration (IQR) — min	55.0 (30–90)	46.0 (28–70)
Blood gas analysis before randomization — no. (%)	216 (56.7)	209 (56.0)
pH¶	7.20±0.09	7.20±0.09
Partial pressure of carbon dioxide — mm Hg‖	64.5±14.1	63.8±14.4
Fraction of inspired oxygen before randomization**	26.9±9.6	27.5±11.6

* Plus–minus values are means ±SD. There were no significant differences between the two groups, except in the multigravida category (P<0.05). CPAP denotes continuous positive airway pressure, and IQR interquartile range.
† Data on ruptured membranes were missing for one infant in the CPAP group.
‡ The 5-minute Apgar score was not known for one infant in the high-flow group and three infants in the CPAP group.
§ It was not known whether CPAP was used before randomization in one infant in the CPAP group.
¶ Data on pH were missing for one infant in the CPAP group.
‖ Data on the partial pressure of carbon dioxide were missing for one infant in the high-flow group.
** Data on the fraction of inspired oxygen were missing for two infants in the high-flow group and two infants in the CPAP group.

per-protocol analysis (Fig. 1). The demographic characteristics of the per-protocol population are shown in Table S1 in the Supplementary Appendix.

PRIMARY OUTCOME

In the intention-to-treat analysis, treatment failure within 72 hours after randomization occurred in 78 of the 381 infants (20.5%) randomly assigned to high-flow therapy and in 38 of the 373 infants (10.2%) randomly assigned to CPAP (risk difference, 10.3 percentage points; 95% confidence interval [CI], 5.2 to 15.4). High-flow therapy was therefore not shown to be noninferior and, since zero was excluded from the 95% confidence interval, CPAP was statistically superior (Table 2); a Kaplan–Meier survival curve of these data is shown in Figure S1 in the Supplementary Appendix. Results of adjusted analyses yielded similar results (Table 2). In the per-protocol analysis, treatment failure within 72 hours after randomization occurred in 49 of the 339 infants (14.5%) in the high-flow group and in 27 of the 338 infants (8.0%) in the CPAP group (risk difference, 6.5 percentage points; 95% CI, 1.7 to 11.2), also indicating that high-flow therapy was

Table 2. Primary Outcome in the Intention-to-Treat and Per-Protocol Analyses.*

Outcome	All Patients	High-Flow Group (N=381)	CPAP Group (N=373)	Risk Difference (95% CI)†	
				Univariate Analysis	Adjusted Analysis‡
	no.	*no./total no. (%)*			
Intention-to-treat analysis					
Treatment failure within 72 hr after randomization	754	78/381 (20.5)	38/373 (10.2)	10.3 (5.2 to 15.4)§	9.2 (3.9 to 14.5)
Gestational age <34 wk	140	20/72 (27.8)	12/68 (17.6)	10.1 (–3.6 to 23.9)	8.7 (–5.8 to 23.1)
Gestational age ≥34 wk	614	58/309 (18.8)	26/305 (8.5)	10.3 (4.9 to 15.6)§	8.3 (2.7 to 14.0)
Per-protocol analysis					
Treatment failure within 72 hr after randomization	677	49/339 (14.5)	27/338 (8.0)	6.5 (1.7 to 11.2)	5.5 (0.5 to 10.4)
Gestational age <34 wk	129	14/65 (21.5)	10/64 (15.6)	5.9 (–7.5 to 19.3)	6.0 (–8.0 to 19.9)
Gestational age ≥34 wk	548	35/274 (12.8)	17/274 (6.2)	6.6 (1.7 to 11.5)	5.5 (0.2 to 10.7)

* P=0.99 for the interaction in the intention-to-treat analysis and P=0.93 for the interaction in the per-protocol analysis (both unadjusted). On the basis of a noninferiority margin of 10 percentage points, high-flow therapy was not noninferior to CPAP in all analyses. CI denotes confidence interval.

† Apart from the primary analysis (univariate intention-to-treat analysis for all infants), other differences in risk are secondary outcomes that were not adjusted for multiple outcomes, and inferences drawn from these intervals may not be reproducible.

‡ The analysis was adjusted for stratification variables (gestational-age group and trial center) and prespecified confounders (birth weight, exposure to antenatal glucocorticoids, and sex). Data from hospitals with a low incidence of treatment failure were aggregated before controlling for trial center in all per-protocol analyses and for the intention-to-treat analysis involving infants younger than 34 weeks of gestational age; different levels of aggregation were used in each analysis (see Section 6 and Table S3 in the Supplementary Appendix).

§ P<0.001.

not noninferior to CPAP. A Kaplan–Meier survival curve of the data for the per-protocol population is shown in Figure S2 in the Supplementary Appendix.

A prespecified analysis according to gestational age showed similar findings in the two subgroups (Table 2) (P=0.99 for the interactions in both the unadjusted and adjusted models). Post hoc sensitivity analyses excluding infants who received CPAP before randomization yielded similar results (Table S4 in the Supplementary Appendix). A small percentage of infants who underwent randomization in the intention-to-treat population (3.7%) were twin pairs who underwent randomization individually; results of a post hoc sensitivity analysis excluding these infants are shown in Table S5 in the Supplementary Appendix.

SECONDARY OUTCOMES AND ADVERSE EVENTS

All secondary outcomes and adverse events are presented for the intention-to-treat population. The secondary outcome for the per-protocol population (transfer to a tertiary-level NICU) is included in Table S2 in the Supplementary Appendix.

Secondary outcomes and adverse events are listed in Table 3. The reasons for treatment failure are listed in Table S6 in the Supplementary Appendix. The most common reason for treatment failure in the two trial groups was a fraction of inspired oxygen of at least 0.40 for more than 1 hour. Treatment failure due to apnea occurred more frequently in the high-flow group than in the CPAP group. The most common other reason for treatment failure in the high-flow group was escalation of therapy in infants in whom the criteria for treatment failure had not been met (in 17 of 23 infants). In the CPAP group, the most common other reason for treatment failure was pneumothorax (in 8 of 11 infants).

Of the 78 infants in the high-flow group in whom treatment failure occurred, 62 infants received backup CPAP during the primary outcome period, and 32 were not intubated or transferred to a NICU within 72 hours after randomization. The incidences of mechanical ventilation and transfer to a NICU did not differ significantly between the groups. The median duration of respiratory support and the median

Table 3. Secondary Outcomes and Adverse Events.*

Outcome	High-Flow Group (N=381)	CPAP Group (N=373)	Difference (95% CI)†
			percentage points
Mechanical ventilation through an endotracheal tube — no. (%)			
<72 hr after randomization	21 (5.5)	22 (5.9)	–0.4 (–3.7 to 2.9)
At any time after randomization	25 (6.6)	22 (5.9)	0.7 (–2.8 to 4.1)
Transfer to tertiary NICU — no. (%)‡			
<72 hr after randomization	39 (10.2)	32 (8.6)	1.7 (–2.5 to 5.8)
At any time after randomization	49 (12.9)	41 (11.0)	1.9 (–2.8 to 6.5)
Surfactant treatment <72 hr after randomization — no. (%)	21 (5.5)	22 (5.9)	–0.4 (–3.7 to 2.9)
Median no. of hr of respiratory support after randomization (IQR)	20 (10 to 48)	15 (7 to 35)	5.0 (1.5 to 8.5)
Median no. of hr of supplemental oxygen (IQR)	5 (0 to 18)	1 (0 to 14)	4.0 (2.1 to 5.9)
Final respiratory diagnosis — no. (%)§			
Transient tachypnea of the newborn	169 (44.4)	160 (42.9)	NC
Respiratory distress syndrome	161 (42.3)	162 (43.4)	NC
Pneumothorax	4 (1.1)	11 (2.9)	NC
Other	47 (12.3)	40 (10.7)	NC
Full breast-feeding at hospital discharge — no. (%)	163 (42.8)	155 (41.6)	1.2 (–5.8 to 8.3)
Median no. of days of intravenous fluids after randomization (IQR)	3 (2 to 5)	3 (2 to 5)	0.0 (–0.3 to 0.3)
Median age at start of full-suck feeding (IQR)¶	4 (2 to 13)	4 (2 to 14)	0 (–1.2 to 1.2)
Weight gain from birth to final hospital discharge — g/kg/day	–2.4±9.2	–1.9±9.1	–0.5 (–1.8 to 0.8)
Median no. of days in hospital (IQR)			
Total no. of days in any hospital	7 (3 to 18)	7 (4 to 17)	0 (–2.2 to 2.2)
Tertiary NICU‖	6.9 (5.0 to 11.5)	5.8 (3.3 to 11.8)	1.1 (–2.1 to 4.3)
Death before hospital discharge — no. (%)**,††	2 (0.5)	0	0.5 (–0.2 to 1.3)
Supplemental oxygen or respiratory support			
At 28 days of life; born ≥32 wk gestational age‡‡	2 (0.5)	0	0.5 (–0.2 to 1.3)
At 36 wk postmenstrual age; born <32 wk gestational age§§	0	0	NC
Pneumothorax diagnosed after randomization			
Any	23 (6.0)	28 (7.5)	–1.5 (–5.1 to 2.1)
Drained with needle thoracocentesis or intercostal catheter**	9 (2.4)	18 (4.8)	–2.5 (–5.1 to 0.2)
Nasal trauma after randomization	2 (0.5)	6 (1.6)	–1.1 (–2.6 to 0.4)

* Plus–minus values are means ±SD. NC denotes not calculated, and NICU neonatal intensive care unit.
† Differences were calculated as the difference in percentages for dichotomous data or as the difference in medians or means for continuous data. These differences have not been adjusted for multiple comparisons, and inferences drawn from these intervals may not be reproducible.
‡ This category includes decisions made by a clinician after treatment failure to transfer an infant to a NICU.
§ This outcome was not included in the original statistical analysis plan, but it was added as a post hoc comparison. The final respiratory diagnosis was based on the discharge summary provided by the clinician who was caring for the infant. Cases in which there were major inconsistencies between the clinical course and the recorded diagnosis were reviewed by the investigators and clinicians who were unaware of the treatment group, and a diagnosis was reached by consensus.
¶ The age at the start of full-suck feeding was missing for 10 infants in the high-flow group and 4 infants in the CPAP group.
‖ Data shown are for 49 infants in the high-flow therapy group and 41 infants in the CPAP group who were admitted to a NICU at any time before final discharge.
** These events were specified as serious adverse events in the trial.
†† Both deaths occurred after 1 month of age in association with genetic conditions; these deaths were determined by the investigators to be unrelated to the trial intervention.
‡‡ Data shown are for 731 infants (368 in the high-flow group and 363 in the CPAP group); 7 infants were never assessed (4 in the high-flow group and 3 in the CPAP group).
§§ Data shown are for 16 infants (9 in the high-flow group and 7 in the CPAP group); all infants were assessed.

number of hours after birth at which supplemental oxygen was discontinued were higher in the high-flow group than in the CPAP group. The incidence of adverse events did not differ significantly between the groups (Table 3).

There were no significant differences in the calculated mean costs of nontertiary special care nursery hospital stays, tertiary NICU stays, or interhospital transfers between the two groups. More information is provided in Section 3 in the Supplementary Appendix.

DISCUSSION

In this multicenter, randomized trial comparing two types of primary respiratory support for newborn infants in nine Australian nontertiary special care nurseries, high-flow treatment was not shown to be noninferior to CPAP for preventing treatment failure within the first 72 hours after randomization in the primary intention-to-treat analysis or in the secondary per-protocol analysis. Both analyses suggested that CPAP was superior to high-flow therapy.

High-flow therapy was successful in approximately 80% of the infants and, with CPAP available as backup treatment when primary high-flow therapy failed, there was no increase in the need for mechanical ventilation or NICU transfer or in adverse events. It is plausible that the use of backup CPAP was responsible for avoiding intubation or NICU transfer in up to 32 of 78 infants (41%) in the high-flow group with treatment failure. Our previous noninferiority studies of high-flow therapy in preterm infants also showed that the use of backup CPAP prevented intubation in almost half the infants in whom high-flow treatment failure occurred.[11,15] Infants in the high-flow group received respiratory support for a median of 5 hours longer and supplemental oxygen for a median of 4 hours longer than the infants in the CPAP group, but the clinical importance of these differences is uncertain. Interpretation of these results may vary according to the circumstances of individual treatment centers. Important considerations include the number of staff, staff expertise, and the distances to treatment centers offering mechanical ventilation. Although high-flow therapy was not noninferior, the facts that CPAP served as effective backup therapy and that many infants were successfully treated with high-flow therapy mean that these results may not preclude a role for high-flow therapy in treating some newborn infants.

We included infants born at 31 weeks of gestational age or later, with a birth weight of at least 1200 g; this population was representative of the usual population cared for in Australian nontertiary special care nurseries. The results of this trial are consistent with those of previous randomized trials comparing high-flow therapy with CPAP as early respiratory support for preterm infants in NICUs who have not received exogenous surfactant treatment.[18,19]

A previous noninferiority trial[11] involving preterm infants born at 28 to 36 weeks of gestation and cared for in tertiary-level NICUs was discontinued early when CPAP was shown at the interim analysis to be superior to high-flow therapy at preventing treatment failure. That trial also showed that the use of high-flow therapy in conjunction with rescue CPAP did not result in important adverse outcomes. It is possible that inconsistent generation of distending pressures with high-flow therapy may account for the difference in the incidence of treatment failure.[20-23] Other studies comparing high-flow therapy with CPAP as primary respiratory support for preterm infants have shown little difference between the treatments,[24,25] but this may be explained by the use of exogenous surfactant before determination of the primary outcome. Administration of exogenous surfactant is unlikely to be generalizable to special care nurseries, where it is challenging for clinicians to maintain the skills required for delivery of surfactant.

Blinding of the intervention in our trial was not possible. To minimize bias, we used prespecified, objective criteria to determine the primary outcome. The use of backup CPAP may have influenced the incidences of secondary outcomes in the high-flow group. We took a pragmatic approach of including infants who had received up to 2 hours of CPAP before randomization. Post hoc sensitivity analyses excluding these infants did not show a material difference in the results.

In conclusion, in this trial with a margin of noninferiority of 10 percentage points, we found that high-flow therapy was not noninferior to CPAP. High-flow therapy resulted in a significantly higher incidence of treatment failure than CPAP when used as early respiratory support for

newborn infants with respiratory distress in nontertiary special care nurseries.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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