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ORIGINAL ARTICLE

Nasal High-Flow Therapy for Primary Respiratory Support in Preterm Infants

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ABSTRACT

BACKGROUND

Treatment with nasal high-flow therapy has efficacy similar to that of nasal continuous positive airway pressure (CPAP) when used as postextubation support in neonates. The efficacy of high-flow therapy as the primary means of respiratory support for preterm infants with respiratory distress has not been proved.

METHODS

In this international, multicenter, randomized, noninferiority trial, we assigned 564 preterm infants (gestational age, ≥28 weeks 0 days) with early respiratory distress who had not received surfactant replacement to treatment with either nasal high-flow therapy or nasal CPAP. The primary outcome was treatment failure within 72 hours after randomization. Noninferiority was determined by calculating the absolute difference in the risk of the primary outcome; the chosen margin of noninferiority was 10 percentage points. Infants in whom high-flow therapy failed could receive rescue CPAP; infants in whom CPAP failed were intubated and mechanically ventilated.

RESULTS

Trial recruitment stopped early at the recommendation of the independent data and safety monitoring committee because of a significant difference in the primary outcome between treatment groups. Treatment failure occurred in 71 of 278 infants (25.5%) in the high-flow group and in 38 of 286 infants (13.3%) in the CPAP group (risk difference, 12.3 percentage points; 95% confidence interval [CI], 5.8 to 18.7; P<0.001). The rate of intubation within 72 hours did not differ significantly between the high-flow and CPAP groups (15.5% and 11.5%, respectively; risk difference, 3.9 percentage points; 95% CI, –1.7 to 9.6; P=0.17), nor did the rate of adverse events.

CONCLUSIONS

When used as primary support for preterm infants with respiratory distress, high-flow therapy resulted in a significantly higher rate of treatment failure than did CPAP. (Funded by the National Health and Medical Research Council and others; Australian New Zealand Clinical Trials Registry number, ACTRN12613000303741.)

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*A complete list of investigators in the High Flow Nasal Cannulae as Primary Support in the Treatment of Early Respiratory Distress (HIPSTER) Trial is provided in the Supplementary Appendix, available at NEJM.org.

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In 2014, there were more than 380,000 preterm births (i.e., births at a gestational age of <37 weeks) in the United States, accounting for approximately 10% of all births that year.[1] Preterm infants have a risk of the respiratory distress syndrome. The introduction of endotracheal ventilation has improved the survival rate among preterm infants but is associated with an increased risk of complications such as bronchopulmonary dysplasia.[2]

Clinicians aim to use noninvasive respiratory support to minimize the risk of such complications. The most widely used noninvasive approach, nasal continuous positive airway pressure (CPAP), has been shown to be an effective alternative to endotracheal ventilation as primary respiratory support for preterm infants.[3,4]

Treatment with heated, humidified, high-flow nasal cannulae (high-flow therapy) is an increasingly popular means of noninvasive respiratory support. Surveys have shown that approximately two thirds of neonatal intensive care units in the United States[5] and in Australia and New Zealand[6] used high-flow therapy. This approach has several reported advantages over CPAP, including reduced rates of nasal trauma[7-9] and reduced infant pain scores.[10] Surveys show that it is preferred by parents[11] and nursing staff.[12]

In a previous randomized trial comparing high-flow therapy with CPAP as respiratory support after extubation in infants born at a gestational age of less than 32 weeks, we found that high-flow therapy was noninferior to CPAP in preventing treatment failure.[8] This finding was consistent with the results of other randomized trials of neonatal respiratory support after extubation.[7,9] Previous studies comparing high-flow therapy with CPAP as primary support have not shown significant differences in treatment-failure or intubation rates. However, these studies were small, single-center trials,[13,14] reported interim data,[15] or constituted a substudy of a larger trial.[9]

The authors of a recent Cochrane Review suggested that additional, adequately powered randomized trials assessing high-flow therapy as primary respiratory support should be undertaken.[16] We performed an international, multicenter, randomized, controlled trial to test the hypothesis that high-flow therapy would be noninferior to CPAP as primary respiratory support for preterm infants (gestational age, ≥28 weeks 0 days) with early respiratory distress.

METHODS

STUDY DESIGN AND OVERSIGHT

Nine neonatal intensive care units in Australia and Norway participated in the study. The human research ethics committee at each participating center approved the study. All authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol, which was published previously[17] and is available with the full text of this article at NEJM.org. The study had no commercial support, and the respiratory device manufacturers had no input in study design, data accrual, data analysis, or manuscript preparation and no access to the study data.

PATIENTS

Infants were eligible for inclusion if they were born at a gestational age of 28 weeks 0 days to 36 weeks 6 days, were less than 24 hours old, and had not previously received endotracheal ventilation or surfactant treatment and if the attending clinician had decided to commence or continue noninvasive respiratory support. Infants were ineligible if there was an urgent need for intubation and ventilation (as determined by the attending clinician) or if they had already met the criteria for treatment failure, had a known major congenital abnormality or pneumothorax, or had received 4 hours or more of CPAP support.

RECRUITMENT AND CONSENT

The parents of all participating infants provided written informed consent. At all sites, antepartum consent was sought when possible. If antepartum consent was obtained, infants were randomly assigned to a study group as soon as they met the eligibility criteria. If antepartum consent was not sought, parents of eligible infants were approached at the earliest opportunity after birth. In addition, at the lead center (the Royal Women's Hospital, Melbourne, Australia), the human research ethics committee approved a retrospective consent process (see Section 2.2 in the Supplementary Appendix, available at NEJM.org).

RANDOMIZATION

A computer-generated randomization sequence with variable block sizes was used. Infants were stratified according to gestational age (<32 weeks vs. ≥32 weeks) and study center. Sequentially

numbered, sealed, opaque envelopes containing the treatment assignment were opened as soon as both eligibility and consent criteria had been met.

STUDY INTERVENTION

Eligible infants were randomly assigned to treatment with either high-flow therapy or CPAP. Infants weighing 1250 g or less received caffeine (intravenous loading dose, 20 mg per kilogram of body weight) on the first day of life. Other aspects of care were provided according to individual unit protocols.

Infants randomly assigned to the high-flow group received an initial gas flow of 6 to 8 liters per minute, from either the Optiflow Junior (Fisher and Paykel Healthcare) or Precision Flow (Vapotherm) device. The size of the nasal cannulae was determined according to the manufacturers' instructions in order to maintain a leak at the nares. The maximum permissible gas flow was 8 liters per minute, as recommended by the manufacturer. Infants assigned to high-flow therapy who met the criteria for treatment failure could receive CPAP as rescue therapy, initiated at 7 to 8 cm of water. Infants who continued to meet treatment-failure criteria were intubated and ventilated.

In the infants randomly assigned to CPAP, the starting pressure was 6 to 8 cm of water, achieved with a ventilator, an underwater "bubble" system, or a variable-flow device. Treatment was delivered through either short binasal prongs or a nasal mask, according to the protocol at each participating center, with sizing determined according to the manufacturer's recommendations. The maximum permissible pressure was 8 cm of water. Infants treated with CPAP who met the criteria for treatment failure were intubated and ventilated.

Changes in respiratory support were made in steps of 1 liter per minute (for high-flow therapy) or 1 cm of water (for CPAP). All infants were evaluated at least daily. Weaning from noninvasive respiratory support was considered if there was clinical improvement and the infants were receiving a fraction of inspired oxygen of 0.3 or lower, whereas discontinuation of noninvasive support was considered in infants who were receiving a fraction of inspired oxygen of 0.3 or lower, with gas flow of 4 liters per minute (in the high-flow group) or pressure of 5 cm of water (in the CPAP group); earlier cessation of support could be ordered at the discretion of the treating clinician. If further support was required after discontinuation of respiratory support, the randomly assigned treatment was reinitiated, except that infants in the high-flow group with previous treatment failure could receive CPAP at the treating clinician's discretion.

STUDY OUTCOMES

The primary outcome was treatment failure within 72 hours after randomization. Treatment was considered to have failed if an infant receiving maximal support (high-flow therapy at a gas flow of 8 liters per minute or CPAP at a pressure of 8 cm of water) met one or more of the following criteria: a fraction of inspired oxygen of 0.4 or higher, a pH of 7.2 or less plus a partial pressure of carbon dioxide greater than 60 mm Hg (8.0 kPa) in a sample of arterial or free-flowing capillary blood obtained at least 1 hour after commencement of the assigned treatment, or either two or more episodes of apnea requiring positive-pressure ventilation within a 24-hour period or six or more episodes requiring any intervention within a 6-hour period. Infants with an urgent need for intubation and mechanical ventilation (as determined by the treating clinician) were also considered to have treatment failure.

Prespecified secondary outcomes included the reason (or reasons) for treatment failure, the use of mechanical ventilation within 72 hours after randomization or at any time during admission, nasal trauma, other complications, including complications of prematurity, and other measures of the use of respiratory support and of neonatal health. An additional secondary outcome was the cost of care, calculated on the basis of data for infants at all participating Australian units (435 infants) (Section 4.1 in the Supplementary Appendix).[18] The complete list of prespecified secondary outcomes is provided in the study protocol and in Section 2.3 in the Supplementary Appendix.

Serious adverse events were defined as death before hospital discharge and pneumothorax or other air leak during the assigned treatment. Data were collected until death or discharge home.

STATISTICAL ANALYSIS

On the basis of data from the participating Australian centers, we estimated that treatment failure within 72 hours after randomization would

occur in 17% of 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. High-flow therapy would be considered noninferior to CPAP if the difference in the risk of treatment failure and the upper limit of the two-sided 95% confidence interval were less than 10% and the lower limit of the 95% confidence interval was below zero. For the study to have 90% power, a sample of 750 infants was required.[17,19]

We chose this margin of noninferiority after considering the following factors: high-flow therapy is already widely accepted in many neonatal intensive care units; infants in whom high-flow treatment failed could receive CPAP treatment, which we hypothesized would obviate the need for intubation and ventilation in some infants; and the primary study outcome was short-term efficacy, rather than death or disability (a lower margin of noninferiority would be required for death or disability). The neonatologists and parent representatives who were consulted during the design phase of the trial agreed to this noninferiority margin.

The primary and secondary outcomes were analyzed on an intention-to-treat basis. A prespecified subgroup analysis on the basis of gestational age (<32 weeks or ≥32 weeks) and a per-protocol analysis (not prespecified but recommended for noninferiority trials[19]) were performed for both the primary outcome and the intubation rate within 72 hours after randomization. For the primary outcome and dichotomous secondary outcomes, we calculated a risk difference (with a two-sided 95% confidence interval) in percentage points between treatment groups. We used chi-square tests to compare dichotomous outcomes and the appropriate parametric test (Student's t-test) or nonparametric test (difference in medians estimated by quantile regression) to compare continuous outcomes. All analyses were performed with the use of Stata/IC software, version 13.1 (StataCorp).

As specified in the trial protocol,[17] an independent data and safety monitoring committee, consisting of two neonatologists and a statistician, reviewed outcome data when the primary outcome was available for 250 infants and when it was available for 500 infants. The committee could recommend stopping the trial if there were safety concerns or if there was a highly significant difference (P<0.001) in the rate of the primary outcome between treatment groups.

RESULTS

DURATION AND CESSATION OF RECRUITMENT

Infants were recruited from May 27, 2013, to June 16, 2015. On June 12, 2015, after reviewing the primary outcome data for the first 515 recruited infants, the independent data and safety monitoring committee recommended that the trial be stopped, since there was a highly significant difference (P<0.001) in the rate of the primary outcome between treatment groups and continued recruitment was extremely unlikely to show the noninferiority of high-flow therapy to CPAP. The steering committee stopped recruitment on June 16, 2015.

STUDY PATIENTS

In total, 583 infants were randomly assigned to a treatment group (289 to the high-flow group and 294 to the CPAP group) (Fig. 1). Nineteen infants were excluded because they did not meet the eligibility criteria or their parents did not provide consent. The remaining 564 infants (278 in the high-flow group and 286 in the CPAP group) were followed until hospital discharge or death and were included in the analysis. Demographic and clinical characteristics of the mothers and infants were similar in the two groups (Table 1).

PRIMARY OUTCOME

Treatment failure within 72 hours after randomization occurred in 71 of the 278 infants (25.5%) in the high-flow group and in 38 of the 286 infants (13.3%) in the CPAP group (risk difference, 12.3 percentage points; 95% confidence interval, 5.8 to 18.7; P<0.001). Treatment failure was significantly more common in the high-flow group than in the CPAP group both among infants with a gestational age of less than 32 weeks and among those with a gestational age of 32 weeks or greater at randomization (Table 2).

INTUBATION DURING THE FIRST 72 HOURS AFTER RANDOMIZATION

There was no significant between-group difference in intubation rates within 72 hours after randomization, either in the overall study population or in the gestational-age subgroups (Table 2).

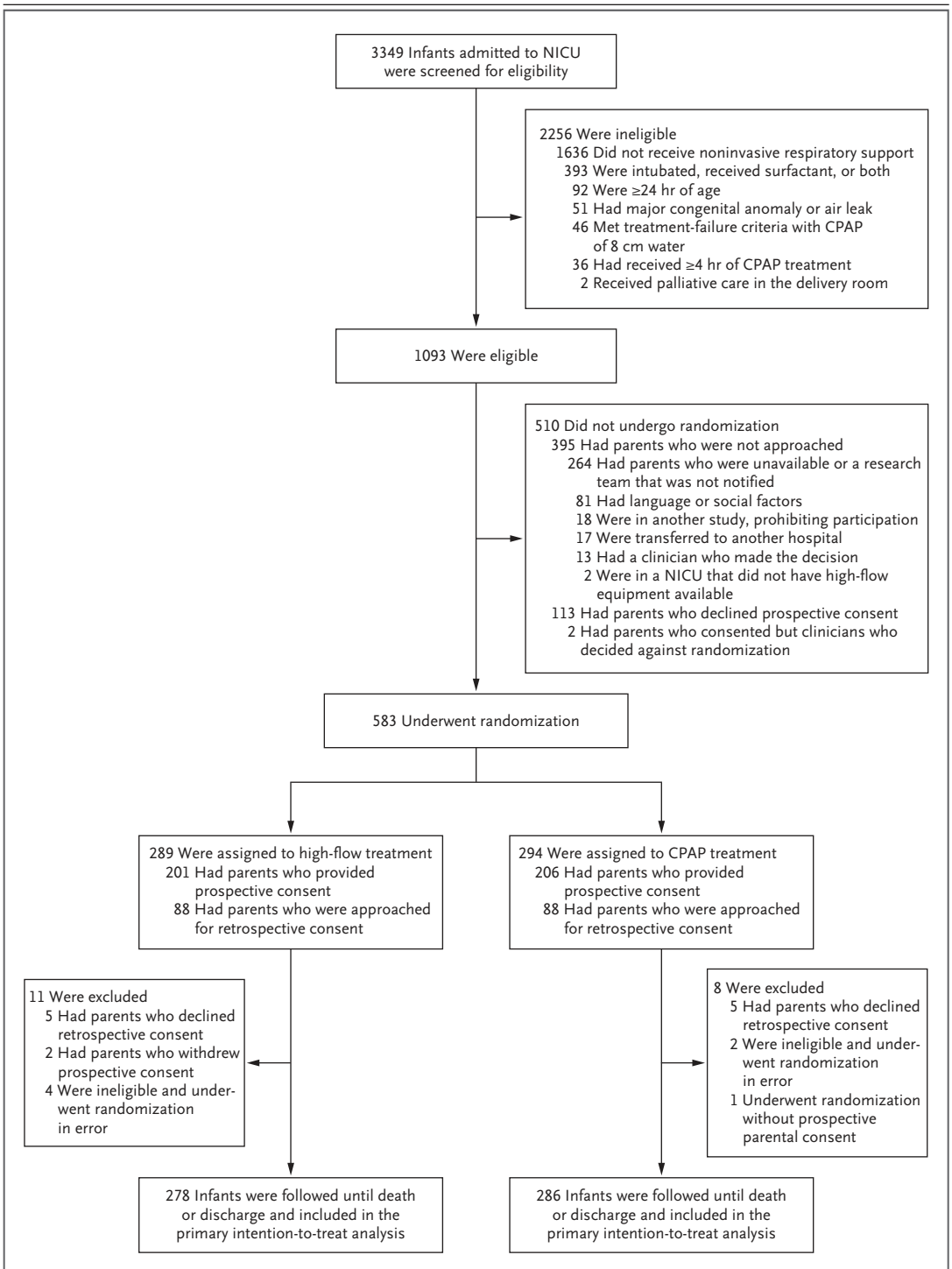

Figure 1. Numbers of Infants Who Were Screened, Assigned to a Study Group, and Included in the Primary Analysis.
Infants born at a gestational age of 28 weeks 0 days to 36 weeks 6 days were screened for eligibility. CPAP denotes continuous positive airway pressure, and NICU neonatal intensive care unit.

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

Characteristic	High-Flow Group (N=278)	CPAP Group (N=286)
Mothers		
White race — no. (%)†	217 (78.1)	225 (78.7)
Primigravida — no. (%)	117 (42.1)	119 (41.6)
Exposure to antenatal glucocorticoids — no. (%)‡	224 (80.9)	229 (80.4)
Cesarean section — no. (%)	204 (73.4)	200 (69.9)
Prolonged rupture of membranes ≥24 hr before delivery — no. (%)	33 (11.9)	37 (12.9)
Obstetrical diagnosis of chorioamnionitis — no. (%)§	22 (8.0)	13 (4.6)
Infants		
Gestational age		
No. of weeks	32.0±2.1	32.0±2.2
<32 wk — no. (%)	140 (50.4)	149 (52.1)
Birth weight — g	1737±580	1751±599
Male sex — no. (%)	157 (56.5)	156 (54.5)
Multiple birth — no. (%)	109 (39.2)	109 (38.1)
Median Apgar score at 5 min (IQR)¶	8 (8–9)	9 (8–9)
Median postnatal age at randomization (IQR) — hr	1.4 (0.6–2.9)	1.3 (0.7–2.8)
Treatment with CPAP before randomization		
No. of infants (%)	157 (56.5)	166 (58.0)
Median duration (IQR) — hr	1.6 (0.8–2.7)	1.5 (0.6–2.5)
Arterial or capillary blood pH before randomization‖	7.26±0.07	7.27±0.07
Partial pressure of arterial or capillary carbon dioxide before randomization — mm Hg‖	55.2±10.8	55.3±9.8
Median fraction of inspired oxygen at time of randomization (IQR)	0.21 (0.21–0.28)	0.21 (0.21–0.30)
Caffeine received in first 24 hr of life — no. (%)	109 (39.2)	125 (43.7)

* Plus–minus values are means ±SD. There were no significant differences between the groups. CPAP denotes continuous positive airway pressure, and IQR interquartile range.
† Race was reported by the investigators.
‡ Data on exposure to antenatal glucocorticoids were missing for 1 infant in each treatment group.
§ Obstetrical diagnosis of chorioamnionitis was not known for 2 infants in the high-flow group and 3 in the CPAP group.
¶ The Apgar score was not known for 2 infants in the high-flow group.
‖ Blood gases were not measured before randomization in 297 infants: 145 in the high-flow group and 152 in the CPAP group.

PER-PROTOCOL ANALYSIS

Results were similar in an analysis of the 543 infants (264 in the high-flow group and 279 in the CPAP group) who were treated as specified by the protocol (Table 2). A total of 21 infants were excluded from this analysis because either they did not receive the assigned treatment (14 infants) or the assigned treatment was changed during the primary-outcome period without the protocol-specified criteria for treatment failure or nasal trauma having been met (7 infants).

SECONDARY OUTCOMES AND ADVERSE EVENTS

The most common reason for treatment failure was a fraction of inspired oxygen of 0.4 or higher (Table 3). Treatment failure due to an urgent need for intubation occurred more frequently in the CPAP group than in the high-flow group (18.4% vs. 5.6%, P=0.03). The median duration of respiratory support was 1 day longer in the high-flow group than in the CPAP group (4 vs. 3 days, P=0.005), and infants in the high-flow group were significantly more likely to receive supple-

Table 2. Primary Outcome, Intubation within 72 Hours, and Outcomes in the Subgroup and Per-Protocol Analyses.

Outcome	High-Flow Group (N=278)	CPAP Group (N=286)	Risk Difference (95% CI)*	P Value
	no./total no. (%)		*percentage points*	
Primary intention-to-treat analysis				
Treatment failure within 72 hr	71/278 (25.5)	38/286 (13.3)	12.3 (5.8 to 18.7)	<0.001
Gestational age <32 wk	46/140 (32.9)	27/149 (18.1)	14.7 (4.8 to 24.7)	0.004
Gestational age ≥32 wk	25/138 (18.1)	11/137 (8.0)	10.1 (2.2 to 18.0)	0.01
Intubation within 72 hr	43/278 (15.5)	33/286 (11.5)	3.9 (–1.7 to 9.6)	0.17
Gestational age <32 wk	30/140 (21.4)	24/149 (16.1)	5.3 (–3.7 to 14.3)	0.25
Gestational age ≥32 wk	13/138 (9.4)	9/137 (6.6)	2.9 (–3.5 to 9.3)	0.38
Per-protocol analysis				
Treatment failure within 72 hr	64/264 (24.2)	36/279 (12.9)	11.3 (4.8 to 17.8)	<0.001
Intubation within 72 hr	39/264 (14.8)	33/279 (11.8)	2.9 (–2.8 to 8.7)	0.31

* Positive values favor the CPAP group, and negative values favor the high-flow group. Apparent discrepancies in some of the risk differences are due to rounding.

mental oxygen during their admission (78.1% vs. 69.6%, P=0.02). Respiratory diagnoses in the participating infants are reported in Section 3.3 in the Supplementary Appendix.

There was no significant difference between treatment groups in the rate of death before discharge (Table 4). Nasal trauma was significantly more common in the CPAP group than in the high-flow group (18.5% vs. 8.3%, P<0.001). The frequency of pneumothorax or other air leak from the lung was also significantly higher in the CPAP group during the assigned treatment (2.1% vs. 0.0%, P=0.02) but not overall (3.6% in the high-flow group and 2.8% in the CPAP group, P=0.59). Rates of other complications of prematurity did not differ significantly between the groups. The respiratory-support devices and nasal interfaces that were used initially in each treatment group are shown in Section 3.2 in the Supplementary Appendix.

The calculated total cost of the tertiary hospital stay (in U.S. dollars) per infant did not differ significantly between the CPAP and high-flow groups ($32,036 and $29,785, respectively; P=0.40). (Detailed information about the cost-effectiveness analysis is provided in Sections 4.2 and 4.3 in the Supplementary Appendix.)

DISCUSSION

In this multicenter, randomized trial, high-flow treatment resulted in a significantly higher rate of treatment failure than did CPAP when used as primary respiratory support for preterm infants born at 28 weeks 0 days of gestation or later and treated in neonatal intensive care units. Enrollment was stopped after a planned interim analysis (after 75% of the target sample had been recruited), on the recommendation of the data and safety monitoring committee, owing to the between-group difference in rates of treatment failure. The difference in the primary outcome was significant in both the primary intention-to-treat analysis and the per-protocol analysis.

Our results contrast with those of studies of high-flow therapy initiated after extubation, which have consistently shown that the efficacy of high-flow treatment is similar to that of CPAP.[7-9,16] Unlike the infants in the trials of postextubation high-flow therapy, no infants in our study received surfactant before randomization.[7-9] The higher rate of treatment failure among infants receiving high-flow therapy in our study may reflect its reduced effectiveness in infants with surfactant-deficient lungs. Although high-flow therapy does provide some distending pressure,[20-22] the higher, more consistent pressures produced during CPAP may account for the difference in treatment-failure rates that we report. We chose to include only infants with a gestational age of at least 28 weeks, on the basis of increased rates of treatment failure reported in infants with a lower gestational age who received high-flow therapy after extubation.[8]

Table 3. Reasons for Treatment Failure and Other Secondary Outcomes.*

Outcome	High-Flow Group (N=278)	CPAP Group (N=286)	Percentage-Point Difference in Risk (95% CI)†	Difference in Median (95% CI)	P Value
Reason for treatment failure — no./total no. (%)‡					
Apnea	9/71 (12.7)	2/38 (5.3)	7.4 (−3.1 to 17.9)	NA	0.22
Fraction of inspired oxygen ≥0.4	53/71 (74.6)	30/38 (78.9)	−4.3 (−20.7 to 12.1)	NA	0.62
Respiratory acidosis	9/71 (12.7)	6/38 (15.8)	−3.1 (−17.1 to 10.8)	NA	0.65
Urgent need for intubation	4/71 (5.6)	7/38 (18.4)	−12.8 (−26.2 to 0.7)	NA	0.03
Clinician's decision	4/71 (5.6)	2/38 (5.3)	0.4 (−8.5 to 9.3)	NA	0.94
Median time to treatment failure after randomization (IQR) — hr	7.8 (1.9 to 21.5)	9.0 (2.8 to 25.2)	NA	−1.2 (−10.1 to 6.3)	0.65
Surfactant treatment — no. (%)	40 (14.4)	30 (10.5)	3.9 (−1.5 to 9.3)	NA	0.16
Median no. of days of respiratory support during admission (IQR)	4 (2 to 7)	3 (2 to 6)	NA	1.0 (0.3 to 1.7)	0.005
Supplemental oxygen therapy					
Any received during admission — no. (%)	217 (78.1)	199 (69.6)	8.5 (1.3 to 15.7)	NA	0.02
Median age at cessation (IQR) — days§	2 (0 to 5)	2 (0 to 6)	NA	0.0 (−0.7 to 0.7)	1.00
Discharged home with oxygen therapy — no. (%)¶	1 (0.4)	2 (0.7)	−0.3 (−1.5 to 0.9)	NA	0.58
Median age at start of full-suck feeding (IQR) — days‖	32 (18 to 43)	32 (17 to 45)	NA	0.0 (−3.9 to 3.9)	1.00
Discharged home with gastric-tube feeding — no. (%)¶	21 (7.6)	17 (6.0)	1.6 (−2.5 to 5.8)	NA	0.45
Weight at discharge — g¶	2540±424	2551±492	NA	NA	0.77
Median no. of days in tertiary care center (IQR)¶	20 (10 to 35)	19 (10 to 34)	NA	1.0 (−2.3 to 4.3)	0.56
Median no. of days in any hospital (IQR)¶	37 (23 to 50)	38 (22 to 50)	NA	−1.0 (−5.4 to 3.4)	0.66

* NA denotes not applicable.
† Positive values favor the CPAP group, and negative values favor the high-flow group.
‡ Treatment may have failed for more than one reason. Clinician's decisions to change treatment were made in relation to the work of breathing, without fulfilling any prespecified treatment-failure criteria.
§ The 3 infants who were discharged home with oxygen therapy (1 in the high-flow group and 2 in the CPAP group) were excluded.
¶ The 2 infants who died before discharge (1 in each treatment group) were excluded.
‖ A total of 40 infants were excluded: the 38 infants who were discharged home with gastric-tube feeding (21 in the high-flow group and 17 in the CPAP group) and the 2 infants who died before discharge (1 in each treatment group).

Table 4. Adverse Events.

Event	High-Flow Group (N=278)	CPAP Group (N=286)	Risk Difference (95% CI)*	P Value
	no. of infants (%)		*percentage points*	
Death before discharge	1 (0.4)	1 (0.4)	0.0 (–1.0 to 1.0)	0.98
Oxygen supplementation, respiratory support, or both at postmenstrual age of 36 wk†	17 (12.1)	17 (11.4)	0.7 (–6.7 to 8.2)	0.85
Pneumothorax or other air leak syndrome				
During assigned treatment	0	6 (2.1)	–2.1 (–3.8 to –0.4)	0.02
Any time during admission	10 (3.6)	8 (2.8)	0.8 (–2.1 to 3.7)	0.59
Postnatal glucocorticoid treatment for lung disease	1 (0.4)	3 (1.0)	–0.7 (–2.1 to 0.7)	0.33
Nasal trauma	23 (8.3)	53 (18.5)	–10.3 (–15.8 to –4.7)	<0.001
Patent ductus arteriosus treated with medication or surgical ligation	11 (4.0)	6 (2.1)	1.9 (–1.0 to 4.7)	0.20
Confirmed sepsis‡	7 (2.5)	13 (4.5)	–2.0 (–5.1 to 1.0)	0.19
Necrotizing enterocolitis, Bell's stage II or III§	2 (0.7)	0	0.7 (–0.3 to 1.7)	0.15
Isolated intestinal perforation	0	1 (0.3)	–0.3 (–1.0 to 0.3)	0.32
Laser surgery for retinopathy of prematurity†	0	1 (0.7)	–0.7 (–2.0 to 0.6)	0.33
Intraventricular hemorrhage, grade 3 or 4†	4 (2.9)	1 (0.7)	2.2 (–0.9 to 5.2)	0.15
Cystic periventricular leukomalacia†	3 (2.1)	2 (1.3)	0.8 (–2.2 to 3.8)	0.60

* Positive values favor the CPAP group, and negative values favor the high-flow group.
† Data are reported for the 289 infants born at a gestational age of less than 32 weeks (140 infants in the high-flow group and 149 in the CPAP group).
‡ The criteria for confirmation of sepsis were a positive blood culture and treatment with intravenous antibiotics for 48 hours or longer.
§ Modified Bell's criteria stages range from I to III, with higher stages indicating greater disease severity.

In our study, intubation rates did not differ significantly between the groups, probably because the use of CPAP as rescue therapy for infants with treatment failure in the high-flow group meant that subsequent intubation was not required in 39% of those infants (28 of 71). We included rescue CPAP in our trial design because in our previous noninferiority study of high-flow treatment after extubation,[8] almost half of the infants in whom high-flow treatment failed did not require intubation after receiving rescue CPAP.

Although CPAP was associated with a lower rate of treatment failure than was high-flow therapy, intubation rates did not differ significantly between the two treatment groups; in addition, infants in the high-flow group had a significantly lower rate of nasal trauma. However, infants in the high-flow group were more likely to receive brief supplemental oxygen, and the median duration of respiratory support was 1 day longer in this group. The clinical importance of these findings is uncertain.

Blinding of the intervention was not possible; therefore, to minimize bias, we used prespecified, objective criteria to determine the primary outcome. We acknowledge that the use of CPAP as rescue therapy may have influenced the rates of secondary outcomes in the high-flow group. Furthermore, over half of the infants assigned to this group had received CPAP for a brief period (median, 1.6 hours) before randomization, which may also have influenced the outcomes.

Our study population was limited to preterm infants in neonatal intensive care units. Further studies are required to determine the safety and efficacy of high-flow therapy in nontertiary facilities and resource-limited settings, as well as in term infants.

We conclude that high-flow treatment results in a significantly higher rate of treatment failure than does CPAP, when used as primary support for preterm infants with respiratory distress.

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REFERENCES

1. Hamilton BE, Martin JA, Osterman MJK, Curtin SC. Births: preliminary data for 2014. Natl Vital Stat Rep 2015;64(6):1-19.
2. Chess PR, D'Angio CT, Pryhuber GS, Maniscalco WM. Pathogenesis of bronchopulmonary dysplasia. Semin Perinatol 2006;30:171-8.
3. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med 2010;362:1970-9.
4. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet J-M, Carlin JB. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 2008;358:700-8.
5. Hochwald O, Osiovich H. The use of high flow nasal cannulae in neonatal intensive care units: is clinical practice consistent with the evidence? J Neonat Perinat Med 2010;3:187-91.
6. Hough JL, Shearman AD, Jardine LA, Davies MW. Humidified high flow nasal cannulae: current practice in Australasian nurseries, a survey. J Paediatr Child Health 2012;48:106-13.
7. Collins CL, Holberton JR, Barfield C, Davis PG. A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants. J Pediatr 2013;162(5):949-54.e1.
8. Manley BJ, Owen LS, Doyle LW, et al. High-flow nasal cannulae in very preterm infants after extubation. N Engl J Med 2013;369:1425-33.
9. Yoder BA, Stoddard RA, Li M, King J, Dirnberger DR, Abbasi S. Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates. Pediatrics 2013;131(5):e1482-90.
10. Osman M, Elsharkawy A, Abdel-Hady H. Assessment of pain during application of nasal-continuous positive airway pressure and heated, humidified high-flow nasal cannulae in preterm infants. J Perinatol 2015;35:263-7.
11. Klingenberg C, Pettersen M, Hansen EA, et al. Patient comfort during treatment with heated humidified high flow nasal cannulae versus nasal continuous positive airway pressure: a randomised cross-over trial. Arch Dis Child Fetal Neonatal Ed 2014;99:F134-7.
12. Roberts CT, Manley BJ, Dawson JA, Davis PG. Nursing perceptions of high-flow nasal cannulae treatment for very preterm infants. J Paediatr Child Health 2014;50:806-10.
13. Nair G, Karna P. Comparison of the effects of Vapotherm and nasal CPAP in respiratory distress. Presented at the Pediatric Academic Societies Meeting, Baltimore, May 14–17, 2005. abstract (http://www.abstracts2view.com/pas/).
14. Iranpour R, Sadeghnia A, Hesaraki M. High-flow nasal cannula versus nasal continuous positive airway pressure in the management of respiratory distress syndrome. J Isfahan Med School 2011;29:761-71.
15. Ciuffini F, Pietrasanta C, Lavizzari A, et al. Comparison between two different modes of non-invasive ventilatory support in preterm newborn infants with respiratory distress syndrome mild to moderate: preliminary data. Pediatr Med Chir 2014;36:88.
16. Wilkinson D, Andersen C, O'Donnell CP, De Paoli AG, Manley BJ. High flow nasal cannula for respiratory support in preterm infants. Cochrane Database Syst Rev 2016;2:CD006405.
17. Roberts CT, Owen LS, Manley BJ, Donath SM, Davis PG. A multicentre, randomised controlled, non-inferiority trial, comparing high flow therapy with nasal continuous positive airway pressure as primary support for preterm infants with respiratory distress (the HIPSTER trial): study protocol. BMJ Open 2015;5(6):e008483.
18. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programmes. 3rd ed. Oxford, England: Oxford University Press, 2005.
19. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. JAMA 2012;308:2594-604.
20. Kubicka ZJ, Limauro J, Darnall RA. Heated, humidified high-flow nasal cannula therapy: yet another way to deliver continuous positive airway pressure? Pediatrics 2008;121:82-8.
21. Spence KL, Murphy D, Kilian C, McGonigle R, Kilani RA. High-flow nasal cannula as a device to provide continuous positive airway pressure in infants. J Perinatol 2007;27:772-5.
22. Wilkinson DJ, Andersen CC, Smith K, Holberton J. Pharyngeal pressure with high-flow nasal cannulae in premature infants. J Perinatol 2008;28:42-7.