

ORIGINAL ARTICLE

A Trial Comparing Noninvasive Ventilation Strategies in Preterm Infants

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ABSTRACT

BACKGROUND

To reduce the risk of bronchopulmonary dysplasia in extremely-low-birth-weight infants, clinicians attempt to minimize the use of endotracheal intubation by the early introduction of less invasive forms of positive airway pressure.

METHODS

We randomly assigned 1009 infants with a birth weight of less than 1000 g and a gestational age of less than 30 weeks to one of two forms of noninvasive respiratory support — nasal intermittent positive-pressure ventilation (IPPV) or nasal continuous positive airway pressure (CPAP) — at the time of the first use of noninvasive respiratory support during the first 28 days of life. The primary outcome was death before 36 weeks of postmenstrual age or survival with bronchopulmonary dysplasia.

RESULTS

Of the 497 infants assigned to nasal IPPV for whom adequate data were available, 191 died or survived with bronchopulmonary dysplasia (38.4%), as compared with 180 of 490 infants assigned to nasal CPAP (36.7%) (adjusted odds ratio, 1.09; 95% confidence interval, 0.83 to 1.43; $P=0.56$). The frequencies of air leaks and necrotizing enterocolitis, the duration of respiratory support, and the time to full feedings did not differ significantly between treatment groups.

CONCLUSIONS

Among extremely-low-birth-weight infants, the rate of survival to 36 weeks of postmenstrual age without bronchopulmonary dysplasia did not differ significantly after noninvasive respiratory support with nasal IPPV as compared with nasal CPAP. (Funded by the Canadian Institutes of Health Research; NIPPV ClinicalTrials.gov number, NCT00433212; Controlled-Trials.com number, ISRCTN15233270.)

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IN EXTREMELY-LOW-BIRTH-WEIGHT INFANTS, bronchopulmonary dysplasia remains a leading cause of early death,¹ a strong predictor of later neurologic impairment,² and a major reason for resource use³ and rehospitalization during the first year of life.⁴ Improvements in survival rates among such infants have led to rates of bronchopulmonary dysplasia of up to 60% at the lowest gestational ages.^{1,5,6} Tracheal intubation and mechanical ventilation are associated with ventilator-induced lung injury and airway inflammation, leading to bronchopulmonary dysplasia.^{7,8} Prolonged duration of intubation and mechanical ventilation in extremely-low-birth-weight infants is associated with an increased risk of death or survival with neurologic impairment.^{9,10} Caffeine reduces the risk of bronchopulmonary dysplasia, probably by reducing the duration of intubation.¹¹

Because of these risks, clinicians strive to avoid intubation and respiratory support in extremely-low-birth-weight infants. Nasal continuous positive airway pressure (CPAP) is an alternative to intubation and intermittent positive-pressure ventilation (IPPV).¹² A meta-analysis of trials of early nasal CPAP versus intubation and ventilation¹³⁻¹⁵ showed that nasal CPAP reduces the risk of bronchopulmonary dysplasia.⁷ Nonetheless, use of CPAP in the delivery room may fail in extremely-low-birth-weight infants, with 34 to 83% of such infants requiring subsequent intubation.¹³⁻¹⁵ Furthermore, postextubation support with nasal CPAP in these infants is associated with a 40% failure rate at 1 week.¹⁶

In addition, nasal IPPV is more complicated and costly than nasal CPAP and has been associated with nasal trauma^{17,18} and necrotizing enterocolitis.¹⁹ Nasal IPPV superimposes an intermittent peak pressure on CPAP, delivering both into the pharynx. When the ventilator cycling is synchronized to the infant's own spontaneous inspiration, nasal IPPV increases tidal volume²⁰ and reduces thoracoabdominal asynchrony.²¹ Only small randomized trials have compared nasal CPAP with nasal IPPV. Four meta-analyses²²⁻²⁵ differed on which of 10 trials were included and reached inconsistent conclusions regarding the question of whether nasal IPPV reduces the risk of bronchopulmonary dysplasia. Despite the conflicting evidence, nasal IPPV is commonly used in extremely-low-birth-weight infants in several countries.²⁶⁻²⁸ To recommend

nasal IPPV over the current standard of care, nasal CPAP, a larger superiority trial was needed.

We conducted this multinational, randomized trial to test the hypothesis that nasal IPPV would improve the rate of survival without bronchopulmonary dysplasia at 36 weeks of postmenstrual age, as compared with nasal CPAP, as a method of noninvasive respiratory support in extremely-low-birth-weight infants.

METHODS

ELIGIBILITY CRITERIA

We enrolled infants at 34 tertiary care neonatal intensive care units in 10 countries. Infants were eligible if they had a birth weight of less than 1000 g and a gestational age of less than 30 weeks and if they were candidates for noninvasive respiratory support, either as initial support between birth and 7 days of life (as deemed appropriate by clinicians) or after the first extubation and withdrawal of mechanical support during the first 28 days of life. Infants were excluded if they were expected to die, had congenital abnormalities (including any airway abnormality [e.g., the Pierre Robin sequence and cleft lip and palate]), required surgery, or had a neuromuscular disorder.

STUDY OVERSIGHT

The trial was approved by the research ethics boards at McMaster University and the participating centers. Written informed consent was obtained from parents or guardians of eligible infants before randomization. The first and last authors take responsibility for the accuracy and completeness of the reported data and for the fidelity of the report to the study protocol, available with the full text of this article at NEJM.org.

RANDOMIZATION

Enrollment and treatment assignments were performed with the use of a secure study website after verification of eligibility and consent status. Treatment assignments (in a 1:1 ratio) were based on a prespecified randomized sequence (with a random block size of 2 or 4), with stratification according to center and two infant characteristics: birth weight (<750 g or 750 to 999 g) and status with respect to prior intubation (reflecting the duration and timing of intubation). The non-intubated stratum comprised infants deemed eligible within the first 7 days of life whose cumu-

lative duration of intubation was 24 hours or less, and the prior-intubation stratum consisted of babies exposed to more than 24 hours of intubation and ventilatory support who were extubated and given noninvasive support within the first 28 days of life. For all infants in the prior-intubation stratum, randomization was performed at the time of the first decision to use noninvasive support.

TREATMENT STRATEGIES

Our broad definition of nasal IPPV encompassed any technique that combines nasal CPAP with an intermittent increase in applied pressure.²⁹ We compared nasal IPPV with nasal CPAP as a means to avoid intubation or as a means of ventilatory support after extubation. Mirroring current usage, no devices were specified; centers could use any standard equipment that would be consistent with the assigned treatment. Synchronization was permitted but not mandated, because no Food and Drug Administration (FDA)-approved devices are currently available. Infants assigned to nasal CPAP were not permitted by protocol to receive nasal IPPV; however, those assigned to nasal IPPV and whose condition was stable for 7 days after extubation could be switched to nasal CPAP. Weaning from the study treatment to respiratory support with low-flow oxygen cannulae (≤ 2 liters per minute) or to breathing of ambient air was at the discretion of the local clinicians and could occur at any time after randomization. Infants whose condition could not be maintained with the assigned method of noninvasive respiratory support were reintubated, and the originally assigned intervention was resumed after extubation. Adherence to treatment was monitored and reported.

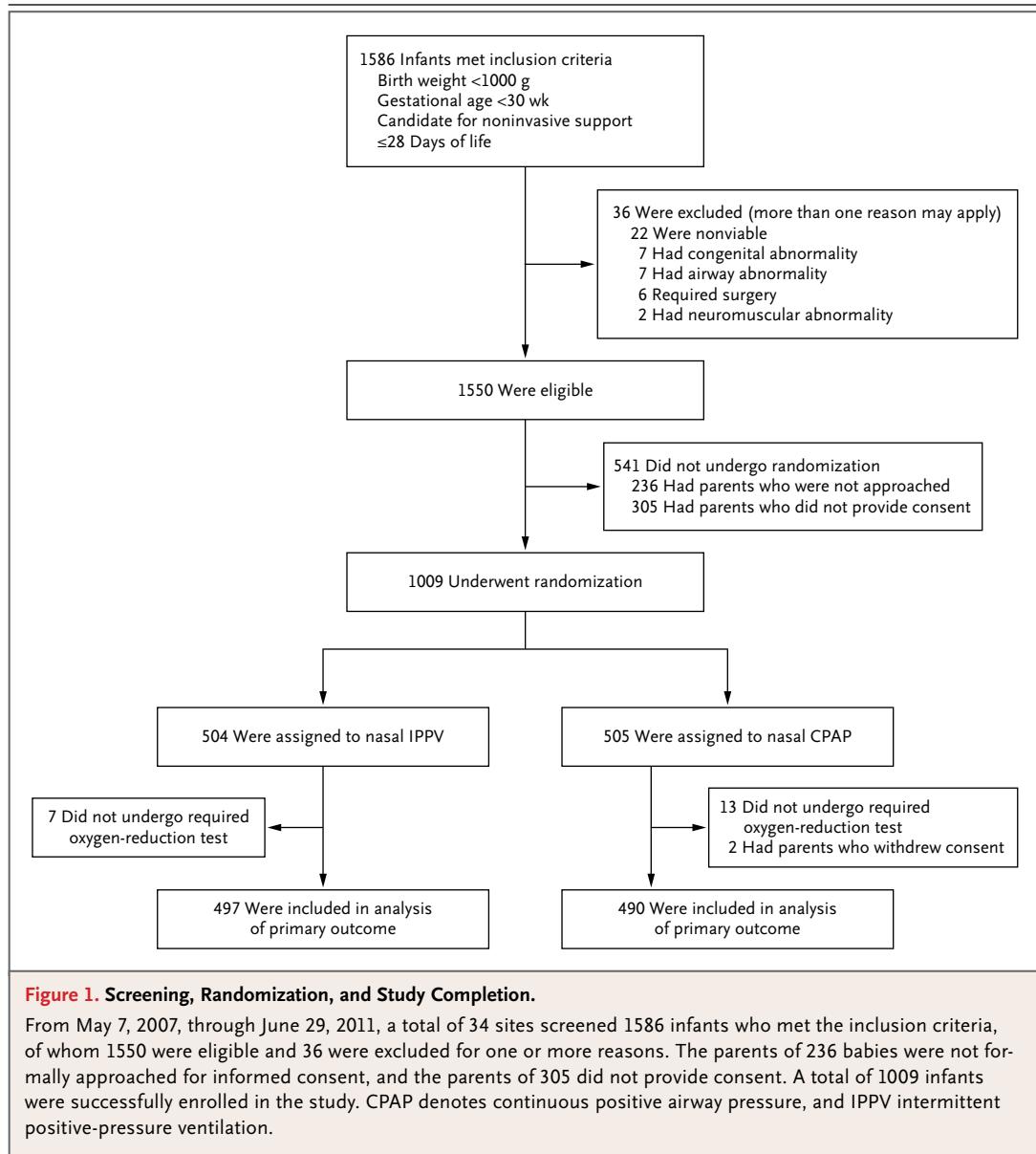
Suggested initial and maximum settings for respiratory support were provided to the study sites (Table S1 in the Supplementary Appendix, available at NEJM.org), although clinicians could individualize care. Guidelines stressed assessment to initiate weaning if the mean airway pressure was less than 8 cm of water and the fraction of inspired oxygen (FIO_2) was less than 0.40, allowing arterial or capillary carbon dioxide values of 40 to 70 torr with a pH greater than 7.22. Reintubation was recommended if there was more than one episode of apnea requiring bag-mask ventilation or if there were more than six episodes of apnea requiring stimulation in a 6-hour period. The use of high-flow nasal cannulae (> 2 liters per minute) was not permitted.

PRIMARY OUTCOME

The primary outcome was a composite of death before 36 weeks of postmenstrual age or survival with bronchopulmonary dysplasia at 36 weeks of postmenstrual age. Bronchopulmonary dysplasia was defined, according to National Institutes of Health (NIH) criteria,³⁰ by the receipt of any form of positive-airway-pressure support or a requirement for supplemental oxygen at 36 weeks. A requirement for supplemental oxygen at 36 weeks was defined as an FIO_2 of 0.30 or more or, if the FIO_2 was 0.22 to 0.29, confirmation of a supplemental oxygen requirement by means of the oxygen-reduction test.³¹ This standardized method reduces FIO_2 in 2% decrements to ambient air, with stable oxygen saturation, heart rate, and respiration in ambient air ruling out the need for supplemental oxygen and ruling out bronchopulmonary dysplasia.³¹ It was performed by respiratory therapists who were unaware of the treatment assignments. Babies who did not undergo a required oxygen-reduction test were not included in the primary analysis but were included in a supportive analysis in which bronchopulmonary dysplasia was defined by any supplemental oxygen use at 36 weeks of postmenstrual age (the older NIH definition).³⁰

SECONDARY OUTCOMES

Prespecified secondary outcomes were death before 36 weeks of postmenstrual age, death before the first discharge home, bronchopulmonary dysplasia in survivors at 36 weeks of postmenstrual age, a need for reintubation, the rate of air leak, postmenstrual age at last provision of mechanical ventilation, postmenstrual age at last provision of any respiratory support (including nasal CPAP or nasal IPPV), postmenstrual age at last provision of supplemental oxygen, brain injury (intraparenchymal echodense lesion, cystic periventricular leukomalacia, porencephalic cyst, or ventriculomegaly as the worst possible finding on ultrasonography of the head performed at ≤ 36 weeks of postmenstrual age), retinopathy of prematurity requiring laser therapy or surgery, nasal trauma (defined as trauma to the columella nasi, necrosis, or epistaxis), nosocomial sepsis (defined as a positive blood culture, a positive cerebrospinal fluid culture, or a diagnosis of pneumonia), the time to full feeding, weight gain at 36 weeks, and intestinal perforation or necrotizing enterocolitis according to Bell staging.³²



SUBGROUP ANALYSES

We conducted three preplanned subgroup analyses, according to birth-weight stratum, prior-intubation status, and within the nasal-IPPV group, the form of the intervention used (synchronized or nonsynchronized).

STATISTICAL ANALYSIS

The sample-size calculation was based on an anticipated rate of death or bronchopulmonary dysplasia of 46%, a value derived from a trial³³ that was conducted at many of the centers participating in the current study. We estimated that with

a sample of 1000 infants, the study would have 80% power to detect a relative risk reduction of 20% in the primary outcome with nasal IPPV as compared with nasal CPAP, at a two-tailed type I error rate of 0.05. This was more conservative than the relative risk reduction of 27% (relative risk, 0.73; 95% confidence interval [CI], 0.49 to 1.07) reported in Cochrane meta-analyses of previous trials comparing nasal IPPV with nasal CPAP.^{24,25}

Comparison of the primary outcome rate between treatment groups was based on a prespecified logistic-regression model adjusted for center,

birth-weight category, and prior-intubation status (i.e., the randomization stratification factors). Comparisons of secondary outcomes were performed similarly. All statistical analyses were performed with the use of SAS statistical software, version 9.2 (SAS Institute). Two-sided P values of less than 0.05 were considered to indicate statistical significance. Prespecified subgroup analyses for birth-weight stratum, prior-intubation status, and the effects of synchronized or nonsynchronized forms of nasal IPPV were performed with the use of logistic regression by incorporating an additional treatment-by-subgroup interaction term.

An external safety and efficacy monitoring committee conducted regular reviews of patient safety (on a treatment A vs. treatment B basis) using data summaries compiled by an independent statistician, ensuring that the study statistician (the last author) was unaware of the results. Formal interim analyses of efficacy were carried out by the safety and efficacy monitoring committee when 25%, 50%, and 75% of the outcome data were available. A Haybittle–Peto stopping guideline was set at $P < 0.001$ for each interim analysis. The study team was not informed of interim results. The final analysis was conducted at the end of the study only after all efficacy data were complete and finalized.

RESULTS

STUDY INFANTS

From May 7, 2007, through June 29, 2011, a total of 34 sites screened 1586 infants, of which 1550 were eligible and 1009 were enrolled (Fig. 1). Important baseline characteristics were well balanced between the groups, except that the proportion of male infants was higher in the nasal-IPPV group than in the nasal-CPAP group (Table 1).

PRIMARY OUTCOME

The primary outcome of death or bronchopulmonary dysplasia was ascertained in 98.6% of the infants in the nasal-IPPV group and in 97.0% of those in the nasal-CPAP group (Fig. 1). Twenty infants (7 in the nasal-IPPV group and 13 in the nasal-CPAP group) did not undergo a required oxygen-reduction test (typically owing to early transfer) and were thus not included in the primary analysis. The observed rate of death or bronchopulmonary dysplasia was 38.4% (191 of

Table 1. Baseline Characteristics.*

Characteristic	Nasal IPPV (N = 504)	Nasal CPAP (N = 503) [†]
Mother		
Age — yr	30.3±6.3	30.5±6.1
Race or ethnic group — no. (%) [‡]		
White	284 (56.3)	289 (57.5)
Black	110 (21.8)	107 (21.3)
Asian	65 (12.9)	65 (12.9)
Other	38 (7.5)	30 (6.0)
Unknown	7 (1.4)	12 (2.4)
Single-parent family — no. (%) [§]	75 (15.2)	66 (13.6)
Educational level — no. (%)		
<High-school graduate	49 (9.7)	45 (8.9)
High-school graduate	101 (20.0)	102 (20.3)
Some college or university	196 (38.9)	186 (37.0)
Unknown	158 (31.3)	170 (33.8)
Antenatal glucocorticoids received — no. (%)	465 (92.3)	458 (91.1)
Infant		
Birth weight		
Mean — g	802±131	805±127
<750 g — no. (%)	162 (32.1)	163 (32.4)
750–999 g — no. (%)	342 (67.9)	340 (67.6)
Gestational age — wk	26.1±1.5	26.2±1.5
Male sex — no. (%) [¶]	265 (52.6)	232 (46.1)
Caffeine treatment — no. (%)	418 (82.9)	417 (82.9)
Multiple birth — no. (%)	114 (22.6)	121 (24.1)
Birth in the center hospital — no. (%)	459 (91.1)	452 (89.9)
SNAP II	34.1±10.4	33.7±9.9
Intubation status		
Not intubated — no. (%)	247 (49.0)	255 (50.7)
Age at randomization — hr		
Median	18	19
Interquartile range	11–23	11–24
Intubated — no. (%)	257 (51.0)	248 (49.3)
Age at randomization — days		
Median	3.4	3.7
Interquartile range	1.7–6.8	1.7–7.1

* Plus–minus values are means ±SD. Unless otherwise indicated, there were no significant differences between the treatment groups for any characteristic. CPAP denotes continuous positive airway pressure, and IPPV intermittent positive-pressure ventilation.

[†] Data are not included for two babies in this group whose parents withdrew consent.

[‡] Race or ethnic group was self-reported.

[§] Owing to missing data, the denominators for this variable were 493 for nasal IPPV and 487 for nasal CPAP.

[¶] $P = 0.04$.

^{||} The Score for Neonatal Acute Physiology II (SNAP II) scale ranges from 0 to 103, with higher scores indicating greater severity of illness and a higher risk of death.

Table 2. Primary Outcome.*

Outcome	Nasal IPPV <i>no./total no. (%)</i>	Nasal CPAP <i>no./total no. (%)</i>	Odds Ratio	Odds Ratio Adjusted for Strata (95% CI)	P Value	Odds Ratio Adjusted for Strata and Baseline Covariates (95% CI)†
Primary outcome: death at <36 wk of postmenstrual age or BPD	191/497 (38.4)	180/490 (36.7)	1.07	1.09 (0.83–1.43)‡	0.56	1.05 (0.80–1.39)
Components of primary outcome						
Death at <36 wk of postmenstrual age	34/504 (6.7)	41/503 (8.2)	0.82	0.81 (0.51–1.31)§	0.39	0.77 (0.48–1.24)
Survival with BPD	157/463 (33.9)	139/449 (31.0)	1.14	1.17 (0.86–1.57)‡	0.32	1.14 (0.84–1.54)
Death at <36 wk of postmenstrual age or BPD according to older NIH criteria in 20 infants	197/504 (39.1)	193/503 (38.4)	1.03	1.03 (0.79–1.35)‡	0.82	1.00 (0.76–1.31)
Subgroup analyses						
Prior intubation						
No	72/241 (29.9)	72/252 (28.6)	1.07	1.08 (0.72–1.62)¶	0.70	1.05 (0.70–1.57)
Yes	119/256 (46.5)	108/238 (45.4)	1.05	1.04 (0.73–1.50)¶	0.81 Interaction 0.85	1.02 (0.70–1.46)
Birth weight						
<750 g	93/161 (57.8)	79/158 (50.0)	1.37	1.35 (0.87–2.10)¶	0.18	1.30 (0.83–2.04)
750–999 g	98/336 (29.2)	101/332 (30.4)	0.94	0.92 (0.66–1.29)¶	0.64 Interaction 0.15	0.90 (0.64–1.26)

* BPD denotes bronchopulmonary dysplasia, CI confidence interval, and NIH National Institutes of Health.

† Baseline covariates were sex, antenatal receipt or nonreceipt of glucocorticoids, and use or nonuse of caffeine treatment.

‡ Odds ratios were adjusted for center, birth-weight stratum, and prior-intubation status.

§ Odds ratios were adjusted for birth-weight stratum and prior-intubation status but not for center because event rates were too low for satisfactory adjustment.

¶ Odds ratios were adjusted for birth-weight stratum.

|| Odds ratios were adjusted for prior-intubation status.

497 infants) with nasal IPPV, as compared with 36.7% (180 of 490) with nasal CPAP; the odds ratio, adjusted for stratification according to birth weight, prior-intubation status, and center, was 1.09 (95% CI, 0.83 to 1.43) (Table 2). Additional adjustment for sex, receipt or nonreceipt of antenatal glucocorticoids, and use or nonuse of caffeine resulted in a similar odds ratio for bronchopulmonary dysplasia or death (1.05; 95% CI, 0.80 to 1.39). Between-center differences in treatment effect were consistent with chance variation ($P=0.89$ for homogeneity). The results of an analysis defining bronchopulmonary dysplasia on the basis of either the required oxygen-reduc-

tion test (in 371 infants) or respiratory support or any use of oxygen at 36 weeks of postmenstrual age³¹ (which included the 20 infants with missing primary-outcome data) were similar to those of the primary analysis (strata-adjusted odds ratio, 1.03; 95% CI, 0.79 to 1.35).

SECONDARY OUTCOMES

There were no significant differences between groups in the individual components of the primary outcome: death before 36 weeks of postmenstrual age or bronchopulmonary dysplasia in survivors at 36 weeks (Table 2). The groups also did not differ significantly in the frequencies of

Table 3. Secondary Outcomes.*

Outcome	Nasal IPPV	Nasal CPAP	Odds Ratio	Adjusted Odds Ratio (95% CI)	P Value
	<i>no./total no. (%)</i>				
Air leaks	13/498 (2.6)	18/499 (3.6)	0.72	0.71 (0.34–1.46)†	0.35
Pulmonary hemorrhage	16/498 (3.2)	13/499 (2.6)	1.24	1.24 (0.59–2.62)†	0.56
PDA	169/498 (33.9)	193/499 (38.7)	0.81	0.79 (0.60–1.03)‡	0.08
PDA ligation	44/498 (8.8)	45/499 (9.0)	0.98	0.97 (0.62–1.51)†	0.89
Nosocomial sepsis	195/498 (39.2)	192/499 (38.5)	1.03	1.02 (0.77–1.35)‡	0.89
Meningitis	27/498 (5.4)	29/499 (5.8)	0.93	0.93 (0.54–1.60)†	0.79
Culture-confirmed meningitis	9/498 (1.8)	11/499 (2.2)	0.82	0.82 (0.34–2.00)†	0.66
Pneumonia	69/498 (13.9)	75/499 (15.0)	0.91	0.90 (0.63–1.29)†	0.57
Any ROP	257/464 (55.4)	264/451 (58.5)	0.88	0.86 (0.65–1.15)‡	0.32
Severe ROP	35/464 (7.5)	33/451 (7.3)	1.03	1.03 (0.62–1.71)†	0.90
Brain injury	57/475 (12.0)	56/486 (11.5)	1.05	1.04 (0.70–1.54)†	0.83
Nasal trauma	2/498 (0.4)	0/499	—	—	—
Confirmed NEC	69/504 (13.7)	66/502 (13.1)	1.05	1.04 (0.73–1.50)†	0.82
Death before discharge from NICU	37/504 (7.3)	45/503 (8.9)	0.81	0.80 (0.51–1.27)†	0.34
Reintubated after randomization	300/504 (59.5)	311/503 (61.8)	0.91	0.91 (0.70–1.20)‡	0.52

* Nosocomial sepsis was defined by a positive blood culture, a positive cerebrospinal fluid culture, or a diagnosis of pneumonia; severe retinopathy of prematurity (ROP) as ROP requiring laser therapy or surgery; brain injury as an intraparenchymal echodense lesion, cystic periventricular leukomalacia, porencephalic cyst, or ventriculomegaly as the worst possible finding on ultrasonography of the head performed at up to 36 weeks of postmenstrual age; and nasal trauma as trauma to the columella nasi, necrosis, or epistaxis. NEC denotes necrotizing enterocolitis, NICU neonatal intensive care unit, and PDA patent ductus arteriosus.

† Odds ratios were adjusted for birth-weight stratum and prior-intubation status only, owing to low event rates.

‡ Odds ratios were adjusted for center, birth-weight stratum, and prior-intubation status.

other prespecified secondary outcomes (Table 3), including potential adverse effects of treatment (e.g., nasal trauma and necrotizing enterocolitis), or in the time to full feeding, weight gain at 36 weeks of postmenstrual age, and the postmenstrual age at last use of mechanical ventilation or supplemental oxygen (Table S2 in the Supplementary Appendix).

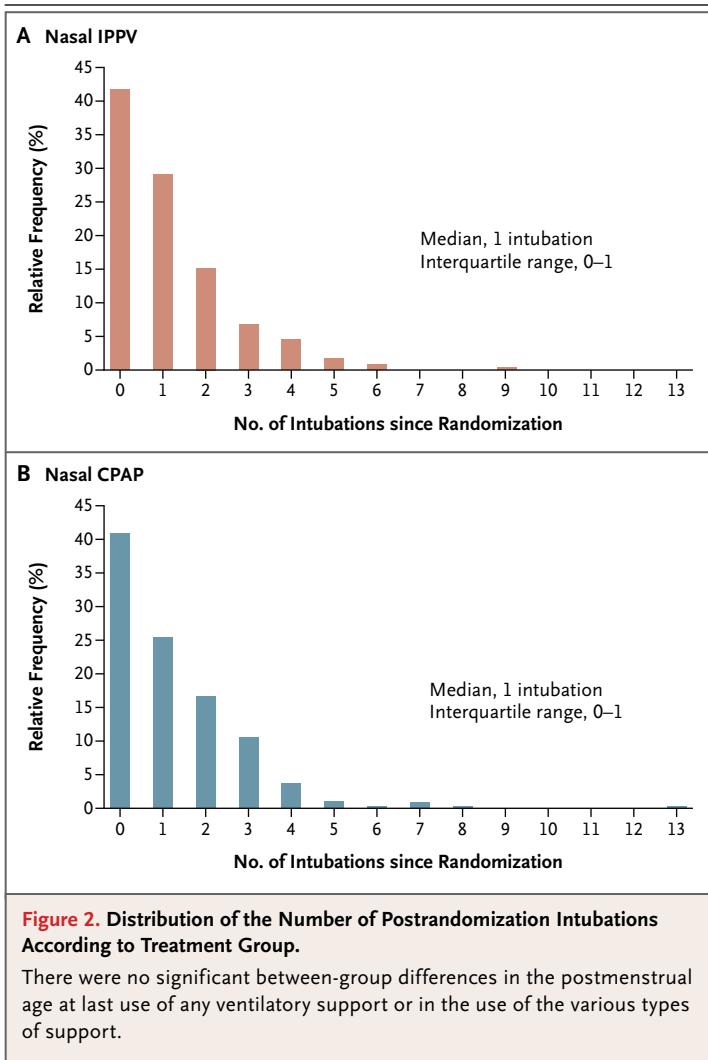
RESPIRATORY OUTCOMES

The rate of adherence to the assigned treatment was high. Of infants assigned to nasal IPPV, 98.5% received this intervention (median duration, 14 days, followed by a median of 6 days of nasal CPAP, up to 36 weeks of postmenstrual age). A similar proportion of the nasal-CPAP group received nasal CPAP (median duration, 22 days), although protocol violations (typically administrative errors) resulted in the use of nasal IPPV in 9.5% of infants assigned to nasal CPAP. These violations were quickly corrected to limit

exposure. The proportion of surviving infants in whom noninvasive support failed and who therefore required postrandomization intubation was 58.3% in the nasal-IPPV group and 59.1% in the nasal-CPAP group. Figure 2 shows the distribution of the number of postrandomization reintubations. The median number of reintubations was the same for each treatment. The high number of reintubations in some infants in both groups reflects difficulty in discontinuing respiratory support, despite the equally high use of caffeine in both groups (in 98.8% of the infants in the nasal-IPPV group and 99.4% of those in the nasal-CPAP group) on at least one occasion after randomization.

SUBGROUP ANALYSES

In preplanned subgroup analyses, there were no significant interactions between treatment and center, birth weight, or prior-intubation status. Because synchronized versus nonsynchronized



support is relevant only to the nasal-IPPV group, this nonrandomized comparison was not strictly a subgroup analysis. However, the rates of bronchopulmonary dysplasia or death for synchronized nasal IPPV (35.6% [36 of 101 infants]) versus nonsynchronized nasal IPPV (38.7% [108 of 279 infants]) did not differ significantly ($P=0.63$). There were no significant between-group differences in the type of device used (Table S3 in the Supplementary Appendix).

DISCUSSION

In this large, international, pragmatic trial, we compared two current strategies for noninvasive respiratory support that are intended to avoid tracheal intubation in extremely-low-birth-weight

preterm infants. We included early use aimed at avoiding tracheal intubation (within the first week of life) and also respiratory support after extubation. We found no significant difference between nasal IPPV and nasal CPAP in the risk of death or survival with bronchopulmonary dysplasia overall, nor were there significant differences according to birth-weight stratum or prior-intubation status. Although the overall rates of death or survival with bronchopulmonary dysplasia were similar in the two groups, on the basis of the 95% confidence interval around the adjusted odds ratio, our results are compatible with an efficacy that ranges from a 21% reduction to a 35% increase in the risk of this outcome with the use of nasal IPPV versus nasal CPAP. These findings call into question the current widespread use of nasal IPPV.^{27,28}

Prior trial results supporting the promise of nasal IPPV, as summarized in four meta-analyses,²²⁻²⁵ were inconsistent with respect to whether it reduces the risk of bronchopulmonary dysplasia. The most likely mechanism for reducing bronchopulmonary dysplasia would be a reduction in the need for intubation. Two of these meta-analyses included both intubation and bronchopulmonary dysplasia as outcomes and showed a reduction in the frequency of intubation but not of bronchopulmonary dysplasia.^{23,24} Our trial showed no significant benefit of nasal IPPV with respect to either of these outcomes. The results of these earlier studies may differ from our own for several reasons. Most were single-center studies, and most enrolled larger infants (with a birth weight of up to 1500 g), who therefore had a lower baseline risk of bronchopulmonary dysplasia than the infants in our study. Smaller infants are more vulnerable to reintubation with a collapsing chest wall and poor diaphragmatic strength.³⁴ We speculate that although limiting mechanical injury is important, additional therapeutic strategies are needed for infants with extremely immature lungs.

We also found no significant difference in rates of other neonatal complications between the two treatment groups. These findings contrast with those of some other studies, which showed an increased risk of bowel perforation or necrotizing enterocolitis³² or of nasal trauma^{17,18} with nasal IPPV or an increased risk of pneumothorax with CPAP.¹³

Our interventions did not permit blinding,

leaving a potential for bias, despite guidelines for weaning, extubation, and reintubation. However, a strength of the study was the objective assessment of bronchopulmonary dysplasia, with the use of a standardized, blinded oxygen-reduction test to eliminate clinical uncertainty regarding the oxygen requirement. Although results of oxygen-reduction testing were not available for 20 infants, a secondary analysis that included these infants by using an older NIH criterion for bronchopulmonary dysplasia yielded similar results.

This pragmatic trial did not specify the ventilator device or synchronization. Whether synchronized nasal IPPV improves respiratory mechanics remains controversial.^{20,21,35,36} In addition, randomized trials of synchronization during IPPV in intubated infants have failed to show significant reductions in rates of bronchopulmonary dysplasia, severe intraventricular hemorrhage, death, or pneumothorax.³⁷ Observational data have not shown significantly better outcomes with synchronized nasal IPPV versus nonsynchronized IPPV.³⁸

Flow synchronization may be superior to other synchronization methods during nasal IPPV,³⁵ but this has not been assessed in large trials, and these devices are not FDA-approved.³⁵ A widely available bilevel device (Infant Flow SiPAP,

CareFusion)³⁹ was used by several centers in the current study. A criticism of these devices is that they limit the peak pressure above resting positive end-expiratory pressure, often resulting in lower peak inspiratory pressure. One trial tested the Infant Flow SiPAP device against CPAP and showed no difference in rates of reintubation or bronchopulmonary dysplasia, but the trial was underpowered.³⁹ Our study was not designed or powered to compare synchronized with nonsynchronized nasal IPPV; however, in a secondary analysis, we found no significant differences in outcomes between these approaches or among various devices. Future devices incorporating new triggering modes will need to be assessed in large randomized trials.

In summary, among high-risk preterm infants eligible for noninvasive modes of respiratory support during the first month of life, nasal IPPV was not superior to nasal CPAP with respect to survival without bronchopulmonary dysplasia at 36 weeks of postmenstrual age. No other clinically important outcomes differed significantly between groups.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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