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Published on: 14 Feb 2008 - The New England Journal of Medicine (Massachusetts Medical Society)

Topics: Bronchopulmonary dysplasia, Intubation, Bubble CPAP, Continuous positive airway pressure and Positive airway pressure

ORIGINAL ARTICLE

Nasal CPAP or Intubation at Birth for Very Preterm Infants

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ABSTRACT

BACKGROUND

Bronchopulmonary dysplasia is associated with ventilation and oxygen treatment. This randomized trial investigated whether nasal continuous positive airway pressure (CPAP), rather than intubation and ventilation, shortly after birth would reduce the rate of death or bronchopulmonary dysplasia in very preterm infants.

METHODS

We randomly assigned 610 infants who were born at 25-to-28-weeks' gestation to CPAP or intubation and ventilation at 5 minutes after birth. We assessed outcomes at 28 days of age, at 36 weeks' gestational age, and before discharge.

RESULTS

At 36 weeks' gestational age, 33.9% of 307 infants who were assigned to receive CPAP had died or had bronchopulmonary dysplasia, as compared with 38.9% of 303 infants who were assigned to receive intubation (odds ratio favoring CPAP, 0.80; 95% confidence interval [CI], 0.58 to 1.12; P=0.19). At 28 days, there was a lower risk of death or need for oxygen therapy in the CPAP group than in the intubation group (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006). There was little difference in overall mortality. In the CPAP group, 46% of infants were intubated during the first 5 days, and the use of surfactant was halved. The incidence of pneumothorax was 9% in the CPAP group, as compared with 3% in the intubation group (P<0.001). There were no other serious adverse events. The CPAP group had fewer days of ventilation.

CONCLUSIONS

In infants born at 25-to-28-weeks' gestation, early nasal CPAP did not significantly reduce the rate of death or bronchopulmonary dysplasia, as compared with intubation. Even though the CPAP group had more incidences of pneumothorax, fewer infants received oxygen at 28 days, and they had fewer days of ventilation. (Australian New Zealand Clinical Trials Registry number, 12606000258550.)

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N Engl J Med 2008;358:700-8.

For two decades, the standard treatment for very preterm infants was with assisted ventilation and surfactant.[1,2] However, since ventilation may damage the lungs,[3,4] it has been hypothesized that the avoidance of ventilation might lead to less bronchopulmonary dysplasia.

Bronchopulmonary dysplasia[5,6] is a major cause of mortality and morbidity in very preterm infants.[7] Despite the increased use of antenatal corticosteroids,[8] surfactant,[9] and improved ventilation techniques, the incidence has not decreased.[10,11] Observational studies of variations in clinical practice have suggested that treating very preterm infants with nasal continuous positive airway pressure (CPAP) during resuscitation is possible and may reduce the intubation rate and incidence of bronchopulmonary dysplasia without increasing morbidity.[2,12-23]

Some studies have suggested that CPAP may be started at birth for most infants of more than 25 weeks' gestation.[24] However, observational studies alone do not provide strong enough evidence to justify changing clinical practice. Studies of the early use of CPAP[25-29] have cited the need for a randomized, controlled trial comparing CPAP with intubation and ventilation. One randomized trial involving 104 infants showed the feasibility of the early use of CPAP but was not designed to evaluate safety and efficacy.[30]

In the randomized, controlled Continuous Positive Airway Pressure or Intubation at Birth (COIN) trial, we based our comparison of CPAP with intubation and ventilation on the hypothesis that the use of CPAP shortly after birth would reduce the rates of death and bronchopulmonary dysplasia (defined as the need for oxygen treatment at 36 weeks' gestational age).

METHODS

STUDY DESIGN

We organized an international, multicenter trial in perinatal centers, which was approved by the local institutional review board or ethics committee at each center. The study was funded by the Australian National Health and Medical Research Council. The trial coordinator monitored data collection, entry, and checking. An independent data and safety monitoring committee reviewed the data after the enrollment of each group of 100 infants.

The eligibility criteria for infants were a gestational age at delivery between 25 weeks 0 days and 28 weeks 6 days, no known condition that might adversely affect breathing after birth apart from prematurity, birth in a hospital participating in the trial, and an ability to breathe at 5 minutes after birth but needing respiratory support because of increased respiratory effort, grunting respiration, or cyanosis. Infants were ineligible if they had been intubated before randomization or if they required no respiratory support or oxygen. Written informed consent from parents was obtained before delivery.

RANDOMIZATION

Infants were assigned to receive either nasal CPAP or intubation and ventilation in a 1:1 ratio with variable block sizes. Randomization was stratified according to center and gestational age (25 or 26 weeks and 27 or 28 weeks) and was performed by an independent statistician, who prepared sequentially numbered, sealed, opaque envelopes.

STUDY INTERVENTION

After birth, the infants received mask ventilation if required. At 5 minutes after birth, the clinician leading the resuscitation team decided whether ongoing respiratory support was needed. If the infant fulfilled the entry criteria, the randomization envelope was opened and the allocated treatment was started immediately.

Nasal CPAP was started at a pressure of 8 cm of water with short single or binasal prongs. After infants were admitted to the nursery, short binasal prongs were used. The CPAP pressure could then be altered as required.

Infants who were assigned to receive CPAP were intubated and underwent ventilation only if they had any of the following symptoms: apnea unresponsive to stimulation and methlyxanthine treatment (>6 episodes requiring stimulation in 6 hours or requiring >1 episode of positive-pressure ventilation), an arterial pH of less than 7.25 with a partial pressure of arterial carbon dioxide ($PaCO_2$) of more than 60 mm Hg (8.0 kPa), metabolic acidosis not responsive to treatment, or treatment with more than a 60% concentration of oxygen. Infants receiving CPAP could be treated with surfactant only after intubation. Criteria for extubation were not specified. Surfactant treatment, ventilation settings, and extubation and reintubation criteria were not mandated and followed local protocols.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was death or bronchopulmonary dysplasia (defined as the need for oxygen treatment at 36 weeks' gestational age).

Prespecified secondary outcomes were the incidence of intubation, reasons for intubation, the need for oxygen treatment at 28 days, the fraction of inspired oxygen (FIO_2) at 36 weeks' gestational age, the incidence of air leaks and intracranial hemorrhages, the duration of ventilation and CPAP, the number of days in the hospital, the number of days to regain birth weight, methylxanthine treatment, treatment with postnatal corticosteroids, and the dose of surfactant.

Data were collected on infants until their death or discharge from hospital. The FIO_2 at 36 weeks' gestational age was recorded for infants treated with oxygen or calculated for infants treated with oxygen by nasal cannula at various flow rates and concentrations.[32]

STATISTICAL ANALYSIS

On the basis of data from the Australian and New Zealand Neonatal Network for 1997 and 1998, we estimated that the rate of the primary outcome for all infants born at 25-to-28-weeks' gestation was 43%.[31] We anticipated a lower rate of bronchopulmonary dysplasia among the infants in our study, since the need for antenatal consent excluded infants who were born outside a hospital, who required urgent delivery, or who were so ill that they required immediate intubation at birth. We estimated that the rate of death or bronchopulmonary dysplasia in infants eligible for the trial would be 30%. For a reduction of one third in this rate (to 20%), 600 infants were needed with a two-tailed type I error rate of 0.05 and a power of 80%.

The analysis was performed according to the intention-to-treat principle. Odds ratios with 95% confidence intervals and chi-square tests were used to compare proportions between the two study groups for the main dichotomous outcomes. Other dichotomous outcomes were compared with the use of Fisher's exact test because some outcomes were rare. All reported P values are two-sided. The Wilcoxon rank-sum test was used to compare continuous outcomes with highly skewed distribution. For the main dichotomous outcomes, adjusted odds ratios and confidence intervals were also estimated with the use of multivariable logistic regression in order to control for potentially confounding effects of center, sex, gestational age, maternal use of antenatal corticosteroids, and multiple births. The analysis for the primary outcome was repeated with the use of the method of generalized estimating equations to account for correlation of outcomes between infants who were part of the same multiple birth, but results were substantially unaffected and are not reported. All analyses were performed with the use of Stata statistical software, version 9.2 (StataCorp).

RESULTS

The numbers of infants who were eligible for the study, who were not enrolled or ineligible, and who were randomly assigned to receive nasal CPAP or intubation and ventilation are shown in Figure 1. A total of 610 infants were enrolled between April 27, 1999, and March 23, 2006: 329 in Australia and New Zealand, 91 in the United States and Canada, and 190 in Europe. The demographic and clinical characteristics at randomization were similar in the two groups (Table 1).

The unadjusted odds ratio for the primary outcome of death or oxygen treatment at 36 weeks' gestation comparing the CPAP group with the intubation group was 0.80 (95% confidence interval [CI], 0.58 to 1.12; P=0.19) (Table 2). The unadjusted reduction in absolute risk was 5% (95% CI, −3 to 13). The comparison was not substantially changed by adjustment with the use of logistic regression, as described. The addition of respiratory support (treatment with CPAP or intubation and ventilation) at 36 weeks' gestational age to the outcome definition made little difference to the estimated effect. For the gestational-age subgroups, the odds ratio for the primary outcome was 0.99 for the group born at 25 or 26 weeks' gestation and 0.72 for the group born at 27 or 28 weeks' gestation in favor of the CPAP group but with no evidence for a true difference in effect between strata (P=0.37 for interaction). There was no significant difference in mortality between the two groups, whether considered as a whole or within the age subgroups; most of the difference between the groups was in the need for oxygen treatment.

At 36 weeks' gestational age, the majority of surviving infants in both groups were treated with no or very little supplemental oxygen. The 75th and 90th percentiles for the inspired oxygen concentration were 22% and 27%, respectively, for the intubation group, as compared with 21% and 28%,

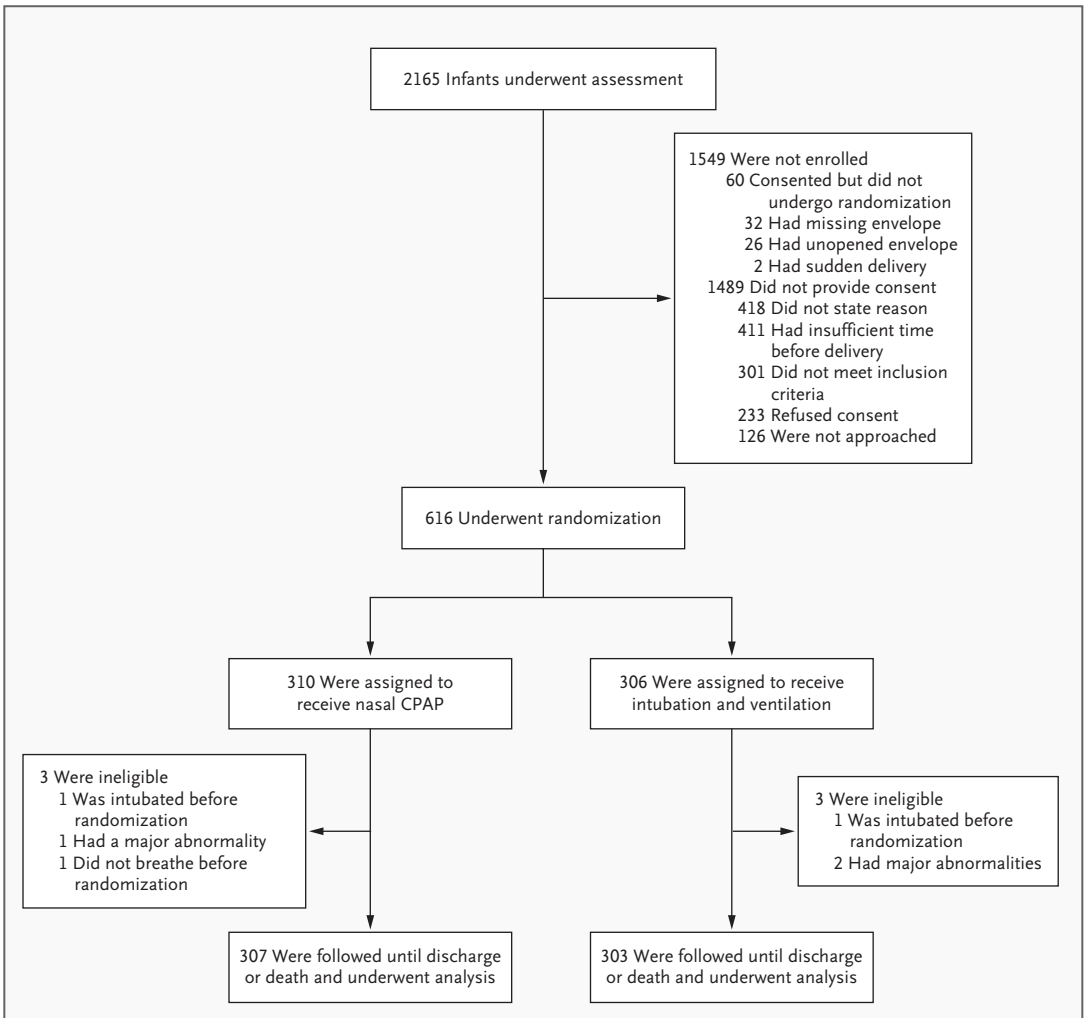

Figure 1. Enrollment and Outcomes.

respectively, for the CPAP group. At 36 weeks' gestational age, an oxygen concentration of 30% or more was received by only 8.8% of the intubation group and 9.4% of the CPAP group (P=0.80), and only 1.3% of the CPAP group and 1.4% of the intubation group received either ventilation or CPAP.

At 28 days of age, the unadjusted odds ratio for death or need for oxygen treatment was 0.63 (95% CI, 0.46 to 0.88; P=0.006) in favor of the CPAP group (Table 3). This result was not greatly altered by adjustment for the above-mentioned covariates (adjusted odds ratio, 0.59; 95% CI, 0.41 to 0.85; P=0.005). The addition of respiratory support at 28 days to this outcome did little to alter the effect. For the gestational-age strata, the unadjusted odds ratios were similar: for infants born at 25 or 26 weeks' gestation, 0.54 (95% CI, 0.27 to 1.08), and for those born at 27 or 28 weeks' gestation, 0.65 (95% CI, 0.44 to 0.96). The 50th, 75th, and 90th percentiles for the inspired oxygen concentration at 28 days were 23%, 29%, and 39%, respectively, for the intubation group and 21%, 25%, and 37%, respectively, for the CPAP group.

Detailed data were collected during the first 5 days of life. The intubation rate for the CPAP group was 46%, with a rate of 55% for infants born at 25 or 26 weeks' gestation and 40% for those born at 27 or 28 weeks' gestation. The median time for intubation was 6.6 hours (interquartile range, 2.2 to 19.3). The reasons for intubation were as follows: a FIO_2 of 0.60 or more (53% of infants), a $PaCO_2$ of more than 60 mm Hg (8.0 kPa) (41%), apneic episodes (38%), or metabolic acidosis unresponsive to treatment (21%); some

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	CPAP (N=307)	Intubation (N=303)	P Value†
Gestational age (wk)	26.91±1.0	26.87±1.0	0.63
Gestational age of 25 or 26 wk (%)	33	35	0.59
Birth weight (g)	964±212	952±217	0.48
Use of antenatal corticosteroids (%)	94	94	0.76
Cesarean section (%)	66	69	0.51
Mother in labor (%)	65	66	0.82
Rupture of membranes (days before birth)			
Median	0	0	0.65
Interquartile range	0–2	0–1	
Male sex (%)	49	56	0.05
Multiple births (%)	35	32	0.57
Resuscitation device used (%)‡			0.13
None	19.5	13.9	
Self-inflating bag	14.7	16.5	
Self-inflating bag plus CPAP	13.0	14.2	
Flow-inflating bag	5.2	6.6	
Neopuff or bubble CPAP	47.2	46.5	
Apgar score at 5 minutes			
Median	9	8	0.001
Interquartile range	8–9	8–9	

* Plus–minus values are means ±SD. CPAP denotes continuous positive airway pressure.
† P values were calculated by the t-test, the chi-square test, or the Mann–Whitney test.
‡ In this category, eight infants (1.3%) were excluded because the resuscitation method was classified as "other."

infants had multiple reasons for intubation. Another 39 patients in the CPAP group (12.7%) were intubated after 5 days of age.

The median daily FIO_2 was approximately 0.21 in both groups during the first 5 days. After day 3, fewer than half the infants in both groups were undergoing ventilation. The lowest and highest $PaCO_2$ levels were similar in both groups during the first 5 days.

Other secondary outcomes are shown in Table 4. The use of surfactant was halved in the CPAP group, as compared with the intubation group. In the CPAP group, the incidence of pneumothorax was significantly increased, with a similar difference between both gestational-age subgroups in the two study groups. There were 28 pneumothoraxes in the CPAP group, with 36% detected on day 0, 43% on day 1, and 18% on day 3. However, this increase did not translate into a need for more respiratory support in the CPAP group. Indeed, days of ventilation were significantly reduced. There was weak evidence of fewer days of supplemental oxygen in the CPAP group (P=0.07). There were no other substantial differences between the groups for other secondary outcomes, nor was there evidence that differences between study groups varied according to gestational-age subgroup.

DISCUSSION

There was no statistical evidence of a difference in the combined outcome of death or bronchopulmonary dysplasia at 36 weeks' gestational age between infants who were assigned to receive early nasal CPAP and those who were assigned to receive intubation. However, at 36 weeks' gestational age, only 9% of infants in each group of survivors were receiving an oxygen concentration of 30% or more. The benefits of CPAP included a lower risk of the combined outcome of death or the need for oxygen therapy at 28 days and fewer days of assisted ventilation. A side effect of CPAP was an increase in the number of pneumothoraxes. Overall, starting early CPAP treatment in very preterm infants was not detrimental.

We randomly assigned infants to study groups after birth rather than antenatally to avoid inappropriate enrollment of infants with apnea in the CPAP group. This procedure reflected clinical practice in which the type of respiratory treatment is determined after observation in the minutes after birth.

The use of surfactant has become standard treatment for very preterm infants.[33,34] However, in these randomized trials of surfactant, infants were electively intubated and rarely received early CPAP; in addition, few of the infants had received antenatal corticosteroid treatment. At the time our trial began, there was increasing observational evidence that very preterm infants who were treated with early CPAP did not require either ventilation or the use of surfactant.[12] We considered that early CPAP needed a randomized trial to define the effects.

Even though only half the infants in the CPAP group received surfactant, there was no difference in FIO_2 or maximum $PaCO_2$ between the study groups during the first 5 days. Infants in the CPAP group required a significantly lower rate of oxygen

Table 2. Death or Need for Oxygen Treatment or Respiratory Support at 36 Weeks' Gestational Age, According to Gestational Age at Birth.*

Outcome	All Infants (25 to 28 Weeks' Gestation)			25 or 26 Weeks' Gestation			27 or 28 Weeks' Gestation		
	CPAP (N=307)	Intubation (N=303)	Odds Ratio (95% CI)	CPAP (N=100)	Intubation (N=105)	Odds Ratio (95% CI)	CPAP (N=207)	Intubation (N=198)	Odds Ratio (95% CI)
	%			%			%		
Death or oxygen treatment	33.9	38.9	0.80 (0.58–1.12)	53.0	53.3	0.99 (0.57–1.71)	24.6	31.3	0.72 (0.46–1.11)
Death, oxygen treatment, or respiratory support	35.2	40.3	0.81 (0.58–1.12)	55.3	55.3	0.99 (0.57–1.72)	25.6	32.3	0.72 (0.47–1.11)
Death before 36 weeks' gestation	6.5	5.9	1.10 (0.57–2.12)	13.0	7.6	1.81 (0.72–4.58)	3.4	5.1	0.66 (0.25–1.76)
Survivors treated with oxygen	29.3	35.1	0.76 (0.54–1.09)	46.0	49.5	0.87 (0.49–1.55)	22.0	27.7	0.74 (0.46–1.17)

* Odds ratios are for the comparison between infants receiving nasal continuous positive airway pressure (CPAP) and those receiving intubation and ventilation.

Table 3. Death or Need for Oxygen Treatment or Respiratory Support at 28 Days of Age, According to Gestational Age at Birth.*

Outcome	All Infants (25 to 28 Weeks' Gestation)			25 or 26 Weeks' Gestation			27 or 28 Weeks' Gestation		
	CPAP (N=307)	Intubation (N=303)	Odds Ratio (95% CI)	CPAP (N=100)	Intubation (N=105)	Odds Ratio (95% CI)	CPAP (N=207)	Intubation (N=198)	Odds Ratio (95% CI)
	%			%			%		
Death or oxygen treatment	53.7	64.7	0.63 (0.46–0.88)	75.0	84.8	0.54 (0.27–1.08)	43.2	54.0	0.65 (0.44–0.96)
Death, oxygen treatment, or respiratory support	64.4	75.6	0.58 (0.41–0.83)	89.0	94.3	0.49 (0.17–1.39)	52.4	65.7	0.58 (0.39–0.86)
Death before 28 days	5.2	5.0	1.06 (0.51–2.18)	11	5.7	2.04 (0.72–5.74)	2.4	4.5	0.52 (0.17–1.58)
Survivors treated with oxygen	51.0	62.8	0.62 (0.44–0.86)	71.9	83.8	0.49 (0.24–1.00)	41.8	51.9	0.67 (0.45–0.99)

* Odds ratios are for the comparison between infants receiving nasal continuous positive airway pressure (CPAP) and those receiving intubation and ventilation.

treatment at 28 days and underwent fewer days of ventilation than did infants in the intubation group, even though the rate of pneumothorax was higher in the CPAP group. These findings suggest that it is possible to initiate CPAP in infants of 25-to-28-weeks' gestation and treat them with surfactant only if they require ventilation. This conclusion is consistent with that of the study by Ammari et al. regarding one hospital's experience with early CPAP.[23] Ammari et al. showed that 76% of infants weighing less than 1251 g and 50% of those weighing less than 751 g did not need to undergo ventilation. In our study, the intubation rate for the CPAP group was determined by the preset criteria for intubation.

Trials have randomly assigned infants to receive elective intubation, followed by treatment with surfactant and then extubation to receive CPAP,[22,35,36] although this regimen was not beneficial in all the trials. The intubation of very preterm infants can be difficult and may destabilize an infant's condition,[37,38] a fact that prompted our investigation into whether it was appropriate to avoid intubation. However, in our study, infants who were intubated were eligible for surfactant use, according to local protocols. The results of our trial corroborate those of Thomson[22] and Escobedo et al.[36] and do not encourage intubation specifically for the use of surfactant for infants in stable condition who are treated with CPAP, although further randomized trials are needed to compare that technique with CPAP.

Table 4. Comparison of Secondary Outcomes.*

Outcome	CPAP (N=307)	Intubation (N=303)	P Value†
Surfactant treatment (%)	38	77	<0.001
Methylxanthine treatment (%)	84	71	<0.001
Days receiving any ventilatory support (no.)			
Median	21	26	0.24
Interquartile range	7–40	7–45	
Days receiving intubation and ventilation (no.)			
Median	3	4	<0.001
Interquartile range	0–11	1–14	
Days receiving CPAP (no.)			
Median	13	16	0.81
Interquartile range	4–30	3–32	
Days receiving oxygen treatment (no.)			
Median	42	49	0.07
Interquartile range	17–71	27–75	
Days until full enteral feeding (no.)			
Median	18	17	0.54
Interquartile range	12–28	11–29	
Days until regaining of birth weight (no.)			
Median	13	13	0.96
Interquartile range	10–16	10–16	
Days in any hospital (no.)			
Median	74	79	0.09
Interquartile range	61–94	65–97	
Complications (%)			
Pneumothorax	9.1	3.0	0.001
Pulmonary interstitial emphysema	5.5	3.6	0.33
Intraventricular hemorrhage grade 3 or 4	8.9	9.3	0.89
Cystic periventricular leukomalacia	2.9	4.0	0.51
Necrotizing enterocolitis grade 2 or 3	3.9	5.0	0.67
Any retinopathy of prematurity	53.1	59.4	0.12
Patent ductus arteriosus	32.4	37.0	0.24
Patent ductus arteriosus ligated	15.2	17.9	0.71
Discharged home treated with oxygen (%)	7.6	9.5	0.46
Late corticosteroid treatment (%)	12.7	13.2	0.81

* CPAP denotes continuous positive airway pressure.
† P values were calculated with the use of Fisher's exact test or the Wilcoxon rank-sum test.

Our finding that infants in the CPAP group had more pneumothoraxes reflects the results of other studies.[16,39,40] Of the infants with a pneumothorax, 96% underwent ventilation. The airway pressure when the pneumothorax was diagnosed was not recorded. The median CPAP pressure on admission was 8 cm of water for infants in whom a pneumothorax developed as well as for those in whom a pneumothorax did not develop. If the pneumothoraxes were associated with the CPAP pressure, it is curious that the incidence was lower in the intubation group, which had higher peak and mean airway pressures. Surfactant treatment has been associated with a reduction in the rate of pneumothorax.[9]

An increased rate of pneumothorax may be a concern because past evidence has suggested that such an increase was associated with increased morbidity.[41] However, in our trial, there was no significant increase in the rate of death, grade 3 and 4 intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, or other adverse outcomes. In addition, the FIO_2 and maximum $PaCO_2$ in the first 5 days did not differ significantly between the study groups.

A CPAP of 8 cm of water was used because a distending pressure is important for maintaining functional residual capacity[42] and for improving lung compliance and oxygenation, and 8 cm of water had been shown to be more effective than a lower pressure.[43] Other studies have used pressures of up to 10 cm of water,[24] and Gregory et al.[39] used a pressure of up to 12 mm Hg.

Data from the first 5 days show that both study groups had relatively good lung function, with a median FIO_2 close to 0.21; the majority of infants in the intubation group were extubated within 3 days, and the median highest and lowest levels of $PaCO_2$ were within the normal range. This good early lung function may be one reason why the study showed a smaller difference than expected between the two groups in the primary outcome.

Our study does not help to identify infants at birth who if treated with CPAP will subsequently require intubation and ventilation. However, it does suggest that starting respiratory support with CPAP does not adversely affect infants even if up to half of them subsequently undergo ventilation, some because of a pneumothorax.

Our study has several limitations. First, since the randomized treatment was not masked, the resuscitation and subsequent care may have been

biased. Second, the consent and enrollment process meant that the infants did not represent all infants born at these gestational ages. Since antenatal consent had to be obtained, there was a lower incidence of acute or serious antenatal complications, and most mothers received antenatal corticosteroids. Also, sick infants who required immediate intubation were excluded. Third, even though more than 600 infants were enrolled, rates of uncommon outcomes were imprecisely estimated. There was a significant imbalance between the groups in the Apgar score at 5 minutes (median score, 9 in the CPAP group and 8 in the intubation group), indicating that infants in both groups were in good condition although those in the CPAP group were rated slightly higher. The randomized treatment was started at the same time, so the Apgar scores may have been affected by the treatment at that time.

In conclusion, infants who were born at 25-to-28-weeks' gestation and were breathing spontaneously were treated with CPAP shortly after birth. Half were subsequently intubated. Infants in the CPAP group had a better outcome at 28 days than did those in the intubation group; the two groups had a similar outcome at 36 weeks' gestational age, but there was an increased incidence of pneumothorax in the CPAP group.

Supported by a grant (148002) from the Australian National Health and Medical Research Council.

Dr. Morley reports being a member of the Australian Resuscitation Council, serving as a coeditor of the Australian Neonatal Resuscitation Guidelines, and serving on the International Liaison Committee on Resuscitation and assisting with the 2005 International Guidelines for Neonatal Resuscitation. No other potential conflict of interest relevant to this article was reported.

We thank Katherine Smith, statistician at the Clinical Epidemiology and Biostatistics Unit, Murdoch Children's Research Institute, Melbourne, for performing the main statistical analysis.

APPENDIX

The following hospitals, investigators, and research nurses participated in the COIN trial, with study sites listed according to the number of infants they enrolled: *Royal Women's Hospital, Melbourne, Australia:* C. Morley, P. Davis, L. Doyle, O. Kamlin, L. Ung, M. Kaimakamis, B. Argus, T. de Paoli, F. Neilsen, B. Mills, K. Callanan; *Maternité Regionale Universitaire, Nancy, France:* J.M. Hascoet, M.-C. Buchweiller, S. Espagne, I. Hamon; *Alexandra Hospital, Athens:* G. Baroutis, M. Dasopoulou; *Royal Brisbane and Women Hospital, Brisbane, Australia:* D. Cartwright, P. Colditz, T. Donovan, V. Smith-Orr, M. Pritchard, J. Horn, T. De Dasselle; *Royal North Shore Hospital, Sydney:* J. Bowen, V. Gallimore; *Albert Einstein College of Medicine, Children's Hospital at Montefiore, Bronx, NY:* L.P. Brion, M. Vega, R. Gray, D. Campbell; *King Edward's Memorial Hospital, Perth, Australia:* K. Simmer, J. Travadi, S. Rao, R. Srinivasjois; *Klinik für Neonatologie, Charité Universitätsmedizin, Berlin:* C.C. Roehr, J. Blank, H. Hammer, R.R. Wauer; *National Women's Hospital, Auckland, New Zealand:* J. Harding, A. Groves, J. Alsweiler, D. Odd, C. West, A. Kennedy, K. Bach, D. Knight; *Ghent University Hospital, Ghent, Belgium:* K. Smets, A. Clabau; *McMaster University Medical Centre, Hamilton, ON, Canada:* B. Schmidt, J. D'Ilario; *Golisano Children's Hospital at Strong, Rochester, NY:* N. Laroia, G. Rowan, R. Jensen; *Jacobi Medical Center, New York:* I. Hand, L. Noble, D. Geiss; *Akershus University Hospital, Oslo:* B. Nakstad, A.M. Hernandez, S. Solheim, M. Johnsrud, M. Karlsen, P. Brevik, L. Egeberg, L. Braendeland, A. Hagensen, T. Farstad; *Center for Pediatrics and Adolescent Medicine, University Hospital, Freiburg, Germany:* R. Hentschel, C. Müller; *Hackensack University Medical Center, Hackensack, NJ:* B. Planer; *Rikshospitalet University Hospital, Oslo:* B. Nakstad, H,R. Kristiansen, M. Grønn, I.E. Silberg.

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