Randomized, controlled trial of nasopharyngeal continuous positive airway pressure in the extubation of very low birth weight infants

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We conducted a prospective, randomized controlled trial to determine whether extubation of very low birth weight infants was facilitated by the use of nasopharyngeal continuous positive airway pressure (CPAP). Eligible infants included patients weighing 600 to 1500 gm at birth who required tracheal intubation within 48 hours of birth and who met specific predetermined criteria for extubation by day 14 of life. We also sought to determine whether varying the duration of nasopharyngeal CPAP influenced the likelihood of successful extubation. Infants underwent random assignment to receive nasopharyngeal CPAP until resolution of lung disease (n = 40), 6 hours of nasopharyngeal CPAP (n = 42), or oxygen supplementation delivered by hood (n = 42). Extubation failure was predefined as a requirement for ≥80% oxygen, pH ≤7.20, severe apnea, or predefined clinical deterioration, and extubation success was predefined as the ability to remain free of a requirement for mechanical ventilation for 7 days and a 66% reduction in the need for supplemental oxygen. Each group was similar with regard to race, sex, and birth weight. Extubation was successful in 62%, 61%, and 60% of infants. After stratification by birth weight, there were no significant differences in the rates of successful extubation among the treatment groups. We conclude that nasopharyngeal CPAP does not improve the likelihood of successful extubation of very low birth weight infants who are ready for extubation within the first 2 weeks of life. (J PEDIATR 1994;124:455-60)

Continuous positive airway pressure, which utilizes the delivery of continuous airway pressure through catheters, prongs, or endotracheal tubes placed in the nares or nasopharynx, has several effects that might facilitate the transition from positive-pressure ventilatory support to oxygen supplementation by hood in neonates. Positive effects of CPAP on oxygenation,[1-7] respiratory rate,[4] and the need for mechanical ventilation[8] have been described in patients with respiratory distress syndrome; positive effects in patients with periodic breathing[9] and apnea of prematurity[10] have also been reported. In the postextubation period, CPAP positively affects oxygen pressure,[11] carbon dioxide pressure,[12] apnea,[11] pulmonary compliance,[11] pulmonary resistance,[11] respiratory rate,[12] and oxygenation as assessed by the alveolar-arterial oxygen pressure gradient.[12] However, potential negative effects on pulmonary and cardio-

CPAP	Continuous positive airway pressure
VLBW	Very low birth weight

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vascular function have also been documented, including decreased lung compliance,[4, 13] decreased tidal volume,[9] decreased minute ventilation,[4, 9] decreased pulse pressure,[4] and decreased central venous pressure.[4] In at least one study, nasopharyngeal CPAP administered soon after birth was associated with subsequent development of more severe respiratory distress and an increased incidence of death.[14]

To investigate the hypothesis that nasopharyngeal CPAP would facilitate the extubation of very low birth weight infants who received mechanical ventilation, we compared the likelihood of successful extubation among infants whose endotracheal tubes were removed with one of three therapies: oxygen supplementation by hood, nasopharyngeal CPAP for 6 hours after extubation, and continuation of nasopharyngeal CPAP until a substantial improvement in respiratory status occurred. To obtain a homogeneous population and exclude patients with chronic lung disease, we limited our study population to infants up to 2 weeks of age.

METHODS

We sought to investigate the hypothesis under the conditions usually encountered in intensive care nurseries (management trial design). For this reason the study design allowed for a defined degree of clinical decision making by the patient care team. Clinical examinations that are not widely available in level 3 nurseries, such as preextubation pulmonary function testing, were not used.

All inborn and transferred infants admitted to the neonatal intensive care unit at the Medical University of South Carolina, Children's Hospital, were considered for participation in this trial. Eligibility criteria included (1) birth weight of 600 to 1500 gm, (2) endotracheal intubation within 48 hours of life for respiratory support, (3) eligibility for extubation by day 14 of life, and (4) a stable or improving clinical course. Exclusion criteria included chromosomal anomalies, neuromuscular diseases, congenital anomalies or other conditions requiring surgery in the neonatal period, or a decision not to resuscitate. A patient was considered eligible for extubation when the following criteria were achieved: fraction of inspired oxygen $\leq$50%, pH $\geq$ 7.25, peak inspiratory pressure $\leq$16 cm H_2O, and ventilatory rate $\leq$15 breaths per minute. In addition, patients were required to be in medically stable or improving condition when enrolled. After informed consent was obtained, patients were randomly assigned by means of opaque, sealed envelopes (placed in random order with a random number table) to one of three treatment groups. Cards for randomization were prepared in blocks of nine to ensure approximately equal numbers in each therapy group. Randomization was stratified by birth weight into 600 to 750 gm, 751 to 1000 gm, and 1001 to 1500 gm groups. Concurrent studies in the nursery during this period included an open enrollment surfactant replacement therapy protocol. For this reason, random patient assignment was also stratified within each weight group by the use of surfactant replacement therapy (yes/no) for a total of six strata.

Infants underwent one of three treatment regimens: (1) nasopharyngeal CPAP until substantial clinical improvement, as manifested by the achievement of predefined goal criteria, was noted (CPAP group); (2) nasopharyngeal CPAP for 6 hours after extubation, followed by treatment with oxygen delivered by hood (short-CPAP group); and oxygen supplementation by hood (hood group). All patients received aminophylline before extubation. Nasopharyngeal CPAP was administered through a nasotracheal tube inserted under direct visualization into the nasopharynx. Patients treated with nasopharyngeal CPAP received 6 cm H_2O distending pressure with humidified air or oxygen delivered by a pressure-cycled infant ventilator (Seachrist [Seachrist Industries Inc., Anaheim, Calif.] or model BP-200 [Bear Medical Systems, Riverside, Calif.]) with flow rates of approximately 6 to 8 L/min. The fraction of inspired oxygen was adjusted to maintain oxygen saturations of 90% to 96%, or arterial oxygen pressure of 50 to 80 mm Hg. Patients enrolled in the CPAP group received nasopharyngeal CPAP until prespecified goal criteria were reached; the criteria included a 66% reduction in supplemental oxygen requirement (i.e., the amount of oxygen required in excess of 21%) and resolution of clinical evidence of respiratory distress, including intercostal and substernal retractions, tachypnea, and nasal flaring. Goal criteria were chosen as a measure of resolution of respiratory disease; that is, the trial was designed to preclude judgment of successful extubation before resolution of respiratory disease. After a patient in the CPAP group had resolution of respiratory disease, nasopharyngeal CPAP was discontinued, although reinstitution was allowed by the protocol. Success was defined as the ability of the patient to remain free of the need for mechanical ventilation for 7 days after extubation and achievement of goal criteria, as defined above. If a patient had an oxygen requirement of 80% or more, pH of $\leq$7.20, severe apnea and bradycardia (defined as six or more episodes per hour of a heart rate less than 100 beats/min, necessitating physical stimulation, or any episode unresponsive to bag and mask ventilation), or clinical deterioration, extubation was considered to have failed and the patient was considered in need of mechanical ventilation. In such cases further management was at the discretion of the health care team. Clinical deterioration was determined by progressive worsening of physical examination findings, including level of activity, respiratory rate, depth of retractions, and onset of grunting and flaring, with evidence of deterioration of blood gas values. Because objective criteria

Table I. Patient characteristics at birth

Characteristic	Group		
	CPAP (n = 40)	Short CPAP (n = 42)	Hood (n = 42)
Preterm labor	21 (52)	28 (67)	20 (48)
ROM >24 hours	7 (18)	12 (29)	10 (24)
Maternal use of steroids	5 (12)	7 (17)	2 (5)
Pregnancy–induced hypertension	11 (28)	8 (19)	10 (24)
Chorioamnionitis	1 (2)	3 (7)	2 (5)
Apgar score at 1 min	4	4.5	4*
Apgar score at 5 min	6*	6	6.5
Cesarean section	25 (62)	22 (52)	26 (62)
Inborn	33 (82)	37 (88)	36 (86)
Nonwhite	24 (60)	30 (71)	29 (69)
Male	16 (40)	20 (47)	16 (38)
EGA (wk)	29.3 ± 8.6	28.0 ± 2.3	28.3 ± 2.2
Birth weight (gm)	1090 ± 250	1102 ± 256	1037 ± 239

There were no significant differences in characteristics at birth between groups. Numbers in parentheses represent percentages.
ROM, Rupture of membranes; *EGA*, estimated gestational age by obstetric criteria.
*One data point is missing as a result of assignment errors.

Table II. Patient characteristics at extubation

Characteristic	Group		
	CPAP (n = 40)	Short CPAP (n = 42)	Hood (n = 42)
Days receiving ventilation	3 ± 2	3 ± 2	3 ± 2
Surfactant therapy	29 (72)	29 (69)	30 (71)
Respiratory distress syndrome	35 (88)	32 (76)	34 (81%)
Patent ductus arteriosus[a]	8 (20)	4 (10)	14 (33)
Extubation weight (gm)	1051 ± 269	1054 ± 268	997 ± 243
pH	7.38 ± 0.05	7.38 ± 0.07	7.40 ± 0.06
Mean airway pressure at extubation (cm H_2O)	4.6 ± 0.8*	4.7 ± 0.7†	4.7 ± 0.8
Maximal P_{CO_2}[b] (mm Hg)	52.4 ± 10.8	56.7 ± 17.9	49.0 ± 9.4
P_{CO_2} at extubation	35.8 ± 5.2	35.7 ± 6.9	34.7 ± 5.8
Maximal mean airway pressure (cm H_2O)	8.5 ± 2.4*	9.1 ± 2.4*	8.9 ± 2.0

Numbers in parentheses represent percentages.
P_{CO_2}, Carbon dioxide pressure.
*Data missing for one patient.
†Data missing for two patients.
[a] $p < 0.05$.
[b] $p < 0.05$.

for extubation failure were stringent, we believed that the inclusion of a category of respiratory failure associated with clinical deterioration was necessary.

All data were collected prospectively except mean airway pressure at extubation, which was collected by chart review. The primary outcome variable was successful extubation, as defined above. Secondary outcome variables included rates of bronchopulmonary dysplasia (supplemental oxygen requirement on day 28 of life) and death.

On the basis of expected rates of successful extubation of 30% in the hood group and 60% in the nasopharyngeal CPAP groups, an α level of 0.05, and a balanced distribution of patients among groups (resulting from a 1:2 allocation ratio between hood delivery of oxygen and nasopharyngeal CPAP of any duration), it was estimated that 40 patients would be required in each group to achieve 80% power in comparing hood delivery of oxygen with nasopharyngeal CPAP of any duration. In addition, comparison of either nasopharyngeal CPAP treatment arm (CPAP or short-CPAP groups) with the hood group would result in 75% power, with the mentioned above assumptions. Data were compared by means of a chi-square test for categoric variables and analysis of variance for continuous variables. Data are presented as means ± SD, except for Apgar scores, which are presented as medians. Apgar scores were compared by means of the nonparametric medians test.

This investigation was approved by the Medical University of South Carolina Human Research Board, and informed consent was obtained from parents or guardians. Before beginning this protocol, all physicians in the division agreed to enroll patients into the study. The attending staff did not change during the study period.

RESULTS

From Aug. 2, 1990, through Aug. 3, 1992, a total of 216 potentially eligible infants were admitted to the neonatal intensive care unit. Of these, 126 were enrolled in our study and randomly assigned to a treatment group. The remaining 90 infants born during the study period were not enrolled for the following reasons: presence of congenital anomalies, 4; inability to obtain consent or consent refused, 18; infant death before eligibility, 31 (including 2 infants for whom a decision not to resuscitate was made); ventilation duration longer than 14 days, 25; occurrence of self-extubation, 7; study team not notified of eligibility, 3; and study termination before eligibility, 2. Of the 126 infants enrolled, two infants were withdrawn from the trial (one at the parent's request and one because of the diagnosis of neuromuscular disease) and excluded from analysis; a total of 124 infants completed the study. No patient was excluded by physician request. There were no significant differences in characteristics at birth among the three groups (Table I). At the time

Table III. Results

Result	Group CPAP (n = 40)	Short CPAP (n = 42)	Hood (n = 42)
Death	1 (3)	1 (2)	1 (2)
Success	25 (62)	25 (61)	25 (60)
At goal	26	31	30
At 7 days	27	25	25
BPD	15 (38)	17 (42)	20 (48)

There were no significant differences in outcome variables between groups. There was also no significant difference in likelihood of successful extubation between patients treated with hood oxygen compared with patients treated with nasopharyngeal-CPAP of any duration. Numbers in parentheses represent percentages.
BPD, Bronchopulmonary dysplasia.

Table IV. Subgroup analysis

Subgroup	Group CPAP	Short CPAP	Hood
600-1000 gm			
n	15	16	19
Success	6 (40)	6 (38)	9 (47)
1001-1500 gm			
n	25	26	23
Success	19 (76)	19 (73)	16 (70)

There were no significant differences in likelihood of successful extubation between groups when data were stratified by birth weight strata. Numbers in parentheses represent percentages.

of extubation (Table II), there was a significant difference in the number of infants who had a patent ductus arteriosus that had been diagnosed by two-dimensional, color flow Doppler echocardiography at any time before extubation (20%, 10%, and 33% in the CPAP, short-CPAP, and hood groups, respectively). However, in all cases, patients with patent ductus arteriosus were treated before extubation and had clinical or echocardiographic evidence of closure before enrollment. In addition, the maximal carbon dioxide pressure observed before extubation was significantly different among groups at the time of extubation (52.4, 56.7, and 49.0 mm Hg in the CPAP, short-CPAP, and hood groups, respectively). However, partial pressure of carbon dioxide at the time of extubation did not differ. There were no other significant differences among groups at the time of extubation.

There were no significant differences among groups with regard to the primary outcome variable (successful extubation). There were no significant differences in rates of success between those infants who received nasopharyngeal CPAP of any duration compared with those treated with oxygen delivered by hood. Similarly, there were no significant differences in secondary outcome variables (Table III).

Although patient assignments were made in three birth weight strata, because of the small number of patients in the 600 to 750 gm stratum, birth weight strata of 600 to 1000 gm and 1001 to 1500 gm were used for the purposes of analysis. There were no significant differences in the likelihood of successful extubation between groups in each stratum (Table IV).

In eight patients extubation was considered to have failed because of clinical deterioration alone (CPAP group, one patient; short-CPAP group, three patients; hood group, four patients). We reviewed seven available charts to document deterioration in blood gas values or physical examination. In five patients, blood gas values or physical examination criteria compatible with respiratory failure (but not yet meeting stringent study criteria) were documented, including respiratory rate >90 breaths/min or pH $\leq$7.25, in addition to physical examination evidence of progressively worsening respiratory distress. The sixth patient had a respiratory rate of >80 breaths/min and a pH of 7.27. In all cases this represented significant worsening during the postextubation period. The seventh patient had an endotracheal tube inserted because of worsening oxygen saturation values with systemic signs of sepsis. One chart was unavailable for review. Because of concerns that the inclusion of clinical deterioration as a criterion for extubation failure might bias the results in favor of one study group, we analyzed the data, including the data on all infants in whom extubation was considered to have failed because of clinical deterioration but in whom there was no objective evidence of failure, in the successful extubation category. There were no significant differences in the rates of successful extubation groups (65%, 67%, and 69% for the CPAP, short-CPAP, and hood groups, respectively) when the data were analyzed in this manner. Furthermore, to investigate a "worst case" situation, we included patients in whom nasopharyngeal CPAP failed in the successful extubation category but without changing the classification of patients in whom extubation to hood oxygen failed. We were unable to demonstrate benefit of nasopharyngeal CPAP in this situation (65%, 67%, and 60%, respectively).

DISCUSSION

Beneficial effects of CPAP on the clinical courses of patients with respiratory diseases and its effects on obstructive and mixed apnea are well known.[1-8, 10, 12, 15, 16] These clinical observations, supported by measurable effects on pulmonary function and mechanics that indicate the prevention of atelectasis, recruitment of small airways, increased

airway diameter, and improved reflex-mediated respiratory responses,[6, 7, 11, 15, 17] suggest a therapeutic role in the support of VLBW infants after extubation. Only two studies[12, 18] have addressed the use of CPAP as an adjunct therapy to facilitate extubation. In both studies, improvement in the likelihood of successful extubation was demonstrated. However, only one of these[18] specifically addressed the use of CPAP in the extubation of VLBW infants. We sought to determine whether the use of nasopharyngeal CPAP improved the likelihood of successful extubation of VLBW infants when endotracheal tubes were removed early in the hospital course. Extubation criteria were predetermined and intentionally liberal to allow for the extubation of infants in an aggressive manner. The bias of the investigating team was that use of CPAP would improve the likelihood of successful extubation and allow for more aggressive extubation criteria. However, we were unable to demonstrate this benefit. This was also true when data were analyzed by birth weight strata, but a reduction in power because of the smaller sample size of individual strata limits this analysis.

These data differ from previously published reports regarding the use of nasopharyngeal CPAP.[12-18] There are several potential explanations for such discrepancies, including the method of delivery for CPAP, the criteria for extubation, and the age of the infants when extubation occurs. One important point to consider in a comparison of our results with those of previous reports is the rate of successful extubation in the control group. In our study, successful extubation was achieved in 60% of control infants, substantially more than in control populations reported by Higgins et al.[18] (21%) and Engelke[12] (33%). This may reflect differences in reintubation thresholds or population characteristics, coupled with the beneficial effects of administration of aminophylline in reducing obstructive apnea, one mechanism by which nasopharyngeal CPAP might improve rates of successful extubation. Our study population included all patients who required intubation for reasons other than resuscitation or transport, that is, a minimal duration of ventilation or a specific respiratory diagnosis was not required for study eligibility. This resulted in the inclusion of infants whose endotracheal tubes were removed during the first several days of life. Such infants may represent a unique population, resulting in a high rate of successful extubation in the control (hood) group. The mean ages at extubation in the study by Higgins et al. were 10.1 and 12.3 days, significantly older than our population, in whom endotracheal tubes were removed after a mean of less than 4 days of mechanical ventilation. Our investigation limited enrollment to infants aged 14 days or less and thus might address the efficacy of nasopharyngeal CPAP in a population different from that studied by Higgins et al. Thus these studies might be considered complementary rather than contradictory. The overall incidence of respiratory distress syndrome was 81%, and 71% of infants in this study qualified for (by the surfactant study protocol) and received surfactant replacement therapy. However, it is possible that CPAP is a more effective adjunct to extubation for infants who are ready for extubation later in their hospital courses. This is of importance in making management decisions regarding VLBW infants with favorable responses to surfactant replacement therapy—particularly prophylactic therapy—and who are ready for extubation within the first several days of life. Use of CPAP has been shown to have little effect on central apnea, but CPAP and administration of methylxanthines both reduce obstructive apnea. However, because methylxanthines were routinely administered before extubation in both studies, the use of aminophylline in our study does not account for the disparate results.

Another potential criticism of our study is the inclusion of clinical criteria to determine extubation failure. However, we believed that inclusion of clinical criteria for extubation failure was necessary to prevent potential harm to patients who were in respiratory distress, with worsening clinical examination findings, but who had not yet satisfied stringent reintubation requirements regarding pH and fractional inspired oxygen. This approach also was most compatible with our goal of investigating the use of nasopharyngeal CPAP under management conditions likely to be encountered in practice. Therefore we decided that the reduction in precision and objectivity that occurred by including clinical decision making in the trial was justified and in our patients' best interest. To determine whether the use of clinical criteria resulted in bias that might have altered the outcome of this investigation, we analyzed the data after reclassifying the outcome of all patients in whom extubation failed for clinical reasons alone as being successful. Furthermore, we analyzed the data after classifying only patients in whom nasopharyngeal CPAP failed as having successful extubation. The latter analysis would result in the best possible outcome for patients assigned to receive nasopharyngeal CPAP and the worst possible outcome for patients who received oxygen by hood. In both cases, the results of this investigation were not altered, which effectively eliminates the possibility that bias with regard to this point influenced our results.

In addition to introducing subjective criteria for extubation failure, CPAP might influence airway patency and receptor-mediated reflexes, thereby altering physical examination findings.[15, 17] In this trial a single pressure (6 cm H_2O) was used. The changing pulmonary mechanics characteristic of the first days of postnatal life may have influenced physical examination findings in patients treated with

nasopharyngeal CPAP by altering airway reflexes and airway diameter.

We were unable to demonstrate a beneficial effect of nasopharyngeal CPAP in the extubation of VLBW infants who required intubation for reasons other than resuscitation and were ready for extubation by day 14 of life. Therefore we cannot recommend its use in such a population. It is possible that nasopharyngeal CPAP might have a beneficial effect of smaller magnitude than could be detected by this investigation. It is also possible that nasopharyngeal CPAP may be beneficial in other populations or for other indications.

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