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Diagnostic and Therapeutic Methods

Efficacy of Nasal Intermittent Positive Pressure Ventilation in Treating Apnea of Prematurity

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Summary. The efficacy of nasal intermittent positive pressure ventilation (NIPPV) in treating apnea of prematurity was evaluated. Apneic preterm infants were randomly assigned to receive either NIPPV or continuous positive airway pressure (NCPAP) for 4 hr when they failed to respond to conservative therapy. The amount of reduction in apneic spells and bradycardia in the two groups after treatment was compared. Thirty-four infants (18 with NIPPV, 16 with NCPAP) were enrolled. Their birth weights ranged from 590–1,880 g (mean, 1,021 g) and gestational ages from 25–32 weeks (mean, 27.6 weeks).

The baseline characteristics were comparable in the two groups. Frequency of apnea and bradycardia was reduced during both forms of treatments. However, the infants receiving NIPPV had a greater reduction of apneic spells ($P = 0.02$) and a tendency to greater decrease in bradycardia ($P = 0.09$) than those receiving NCPAP. We conclude that NIPPV is more effective than NCPAP in reducing apnea in preterm infants. NIPPV may reduce bradycardia; however, this needs to be validated by a larger number of observations. **Pediatr Pulmonol. 1998; 26: 349–353.**

Key words: preterm infants; apnea; nasal intermittent positive pressure ventilation; randomized controlled trial.

INTRODUCTION

Apnea occurs in approximately 25% of preterm infants during the first 10 days of life.[1] Its incidence increases with decreasing gestational age.[2] The diagnosis of apnea of prematurity (AOP) is made when no known cause for apnea other than prematurity can be identified. Apnea is classified into obstructive (10–20%), central (10–55%) and mixed (33–71%) types.[3–5] Infants with intractable apnea may require endotracheal intubation and mechanical ventilation. This procedure is invasive and has been associated with complications such as subglottic stenosis, tracheal stenosis, endotracheal tube displacement, and infection.[6,7] Therefore, an alternative treatment modality would be preferable if it could prevent the infants from requiring endotracheal intubation. Moretti et al.[8] successfully treated 10 preterm infants with intractable apnea with nasal intermittent positive pressure ventilation (NIPPV). However, it was an uncontrolled trial, and the definition of apnea was not mentioned.[8] Furthermore, 70% of the apneic infants had sepsis in that study. Apnea in septic infants should be distinguished from idiopathic apnea, and sepsis requires special treatment in addition to management of apnea. In a randomized crossover control study, Ryan et al.[9] compared the efficacy of NIPPV with nasal continuous positive airway pressure (NCPAP) in infants with idiopathic apnea, and they concluded that NIPPV had no advantage over NCPAP. Unfortunately, the criteria for enrollment of their subjects were not clear, which may have affected their results.

NIPPV creates intermittently higher pharyngeal pressure than NCPAP[9] and, by intermittent inflation of the

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pharynx during airflow, it may activate the dilator muscles of the pharynx and respiratory drives to abort the apneic spells.[8,10] We, therefore, hypothesized that NIPPV would be more effective than NCPAP in reducing the incidence of apnea in preterm infants. The study here reported is an open and randomized controlled trial to answer this question.

SUBJECTS AND METHODS

Study Design

Premature infants admitted to the neonatal intensive care unit (NICU) of our hospital were attached to cardiorespiratory monitors (Hewlett-Packard, Boeblingen, Germany). Apneic spells were detected by the monitor with a standard thoracic impedance technique and confirmed visually by an assigned nurse. Heart rate was measured by the same monitor. Arterial oxygen saturation was monitored constantly by a pulse oximeter (Biox 3700, or 3760, Ohmeda, Boulder, CO) and maintained between 85–95%. Apnea was defined as the absence of respiratory efforts for more than 20 sec, or less than 20 sec when associated with bradycardia (heart rate <100/min) or with hypoxemia (O_2 saturation <85%). The cessations of respiratory movements or bradycardia occurring during nursing care were not included. Apnea with no known etiology except prematurity was termed ''AOP.'' We observed the apneic infants for 4 hr. The 4-hr observational period was selected because it provided better means of enumeration of episodes of apnea and bradycardia from hard copies provided by the monitors. Each infant with apnea was evaluated for the following etiologies: patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), hypoglycemia, hypocalcemia, electrolyte imbalance, anemia, and sepsis. PDA and IVH were confirmed by echography, and chest X-rays were performed to identify possible pulmonary diseases. Environmental temperature was controlled to remain within the range of a neutral thermal environment. Informed consent was obtained from the parents prior to the study.

Only infants who had apneic episodes more than twice per hour in the preceding 4 hr and who failed to respond to the following treatments were included: 1) tactile stimulation and oxygen supplementation, which was administered via oxygen hood; and 2) aminophylline therapy. Aminophylline was administered intravenously at a loading dose of 5 mg/kg. Its serum levels were determined 30 min later and maintained within the range of 5–15 mg/L. Infants with apnea related to IVH, sepsis, electrolyte imbalance, or congenital anomalies were excluded.

Infants meeting the enrollment criteria received a number sealed in an envelope drawn by an administrative assistant and were randomly assigned to either the NIPPV or the NCPAP treatment group. Thorough nasal and oral suction was performed before the application of either NCPAP or NIPPV, and repeated oral suction was done as needed during the study period. NCPAP[11] was delivered at a constant pressure of 4–5 cm H_2O. NIPPV was started at the peak pressure of 12 cm H_2O and increased progressively to 20 cm H_2O until the excursion of the chest wall became observable. End-expiratory pressure was maintained at 4–5 cm H_2O; ventilation rate was set at 20 per min and flow rate at 8 L/min. Both methods were administered by the Bear-Cub Infant Ventilator (Bear Medical Systems, Inc., Riverside, CA) through nasal prongs of various sizes (Hudson RCI, Infant Nasal CPAP Cannula, Temecula, CA) according to the size of the infants. The ventilator pressure settings were calibrated with an RT-200 calibration analyzer (Allied Healthcare Products, Inc., St. Louis, MO), and the pressure was determined at the proximal part of the nasal prongs. Attempt was made to maintain the arterial oxygen saturation levels between 85–95%. All infants had an orogastric tube placed for gastric decompression, and they were not fed during the 4-h study period. They stayed in a supine position, and the mandible was held with a strap to prevent air leakage.

Abbreviations

AOP	Apnea of prematurity
Fi,O_2	Fraction of inspired oxygen
IVH	Intraventricular hemorrhage
NCPAP	Nasal continuous positive airway pressure
NIPPV	Nasal intermittent positive pressure ventilation
PDA	Patent ductus arteriosus

Sample Size Calculation

Based on a frequency of apneic episodes of 3–4 per hour, we determined that 17 infants in each group were needed to achieve 80% statistical power to demonstrate a 40% difference in the reduction of the incidence of apnea or bradycardia between the two groups. Type I error was set at 5%.

Outcome Variables

Arterial or arterialized capillary blood gas tensions were determined at time 0 and 4 hr after the start of treatment. The frequencies of apneic spells and bradycardia over 4 hr before and after the therapy were recorded by the cardiopulmonary monitors and printed out by a think-jet printer (Hewlett-Packard, Singapore). The hard copy of the heart rates and apneic spells were evaluated by one of the authors, who was blinded to the randomization.

TABLE 1—Clinical Characteristics of Infants Treated With Either Nasal Intermittent Positive Pressure Ventilation (NIPPV) or Continuous Positive Airway Pressure (NCPAP)[1]

	NIPPV (N = 18)	NCPAP (N = 16)	*P* values*
BW (g)	1020 ± 327	1022 ± 174	NS
GA (weeks)	27.8 ± 2.2	27.3 ± 1.4	NS
Age at entry (days)	15.5 ± 10.1	15.7 ± 10.2	NS
Fi,O_2 at entry	0.35 ± 0.16	0.31 ± 0.07	NS
Hb (g/dL)	12.8 ± 5.1	12.3 ± 2.6	NS
Theophylline (μg/mL)	7.9 ± 2.3	7.7 ± 3.4	NS

[1]N, case number; BW, birth weight; GA, gestational age; Fi,O_2, fraction of inspired oxygen; data were expressed as mean ± SD.
*Between-group comparisons were made using Wilcoxon rank sum test.

Statistical Analysis

Continuous variables such as gestational age, birth weight, age at enrollment, whole-blood Hb levels, theophylline levels, and fraction of inspired oxygen (Fi,O_2) at entry were compared between the NIPPV and NCPAP groups by the Wilcoxon rank sum test. Changes in episodes of apneic spells and bradycardia before and 4 hr after treatment were compared between the two groups, using analysis of covariance. Log transformation of the data was performed before conducting the analysis due to the skewed nature of the data. Unless indicated otherwise, data were expressed as means ± 1 SD. A *P* value of less than 0.05 was considered significant.

RESULTS

Ninety infants were observed during the study period, 24 of whom were excluded due to coexisting conditions such as sepsis (11 cases), PDA (9 cases), IVH (3 cases), and respiratory failure (1 case). Thirty-two (49%) responded to aminophylline therapy and were excluded, leaving 34 infants (18 in NIPPV group, 16 in NCPAP group) who were enrolled in this randomized trial. Their clinical features are summarized in Table 1. The birth weights ranged from 590–1,880 g (mean, 1,021 g), gestational ages ranged from 25–32 weeks (mean, 27.6 weeks), and mean age at entry to this study was 15.6 days (3–36 days). There was no difference in the amount of oxygen required or the hemoglobin levels between both groups at entry to the study. The average theophylline concentrations were maintained within the therapeutic range in both groups; two infants, one in the NIPPV group, and the other in the NCPAP group, had theophylline concentrations lower than 5 mg/L, requiring booster doses to maintain the appropriate blood level before they entered the study. One infant receiving NCPAP therapy was noted to have a mild nasal abrasion during the study period.

Table 2 shows the infants' responses to treatment. The reduction in apneic spells (times/hour) was significantly greater in the NIPPV group compared to the NCPAP group ($P = 0.02$). A similar tendency was observed in the episodes of bradycardia ($P = 0.09$). There were no time effects on the response to therapy in either group. One infant receiving NCPAP failed to respond as his P_{CO_2} rose to 65 mm Hg, thus requiring endotracheal intubation (see Fig. 2). All infants started with values within reasonable ranges; there was an increase in the mean P_{O_2} by 14.9 mm Hg and 10.4 mm Hg in the NIPPV and NCPAP groups, respectively. However, the difference in the increments in P_{O_2} was not significant between both groups.

TABLE 2—Comparison of Responses Between Infants Treated With Either Nasal Intermittent Positive Pressure Ventilation (NIPPV) or Continuous Positive Airway Pressure (NCPAP)[1]

	NIPPV (N = 18)	NCPAP (N = 16)	*P* values*
Apneic spells (times/hour)			0.02
Before	3.5 (2.3–6.8)	2.6 (2.3–9.0)	
After	0.8 (0.0–5.0)	1.5 (0.0–6.5)	
Bradycardia (times/hour)			0.09
Before	2.6 (0.3–3.8)	2.3 (0.3–3.8)	
After	0.5 (0.0–2.3)	1.1 (0.0–4.8)	
PCO_2 (mm Hg)			NS
Before	49.5 ± 11.5	51.8 ± 9.4	
After	50.2 ± 13.3	49.4 ± 9.6	
PO_2 (mm Hg)			NS
Before	50.3 ± 14.1	49.2 ± 10.4	
After	65.2 ± 29.4	59.6 ± 19.5	

[1]N, case number. All continuous data were expressed as either median (range) or mean ± SD.
*Analysis of covariance was performed to compare the therapeutic effects of NIPPV and NCPAP.

A biphasic response was observed in infants treated with NIPPV, which indicates that a positive pressure breath may induce sighing (Fig. 1). Figure 2 shows the respiratory impedance of an infant who gradually failed on NIPPV. The chest wall movements were noted during NIPPV, but the tracing progressively diminished in amplitude and finally led to apnea.

DISCUSSION

Henderson-Smart et al.[12] reported that one third of preterm infants have bradycardia, with apnea spells defined as cessation of breathing lasting longer than 20 sec. Smaller preterm infants may develop hypoxemia or bradycardia even with shorter cessation of respiratory movements.[1] With the monitor used in this study, we were unable to differentiate which types of apnea the infants had. However, with concomitant monitoring of heart rate, respiratory impedance, and arterial oxygen saturation at bedside, we could detect significant apneic episodes irrespective of type. Aminophylline is effective against central and some mixed types of apnea that started with a central element. Since we only enrolled infants who did not respond to aminophylline therapy,

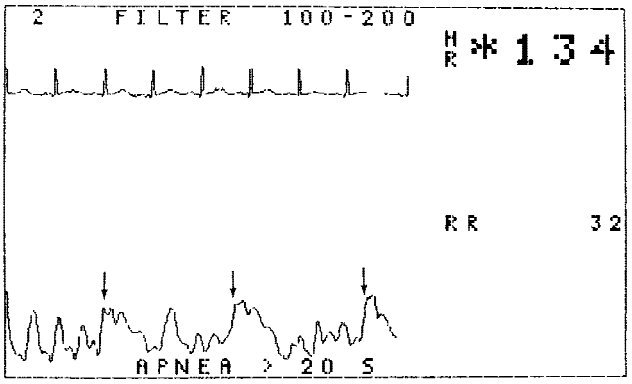

Fig. 1. Respiratory impedance of an infant receiving nasal intermittent positive pressure ventilation (NIPPV). There is a biphasic wave after the positive pressure breath. Arrows indicate administration of NIPPV.

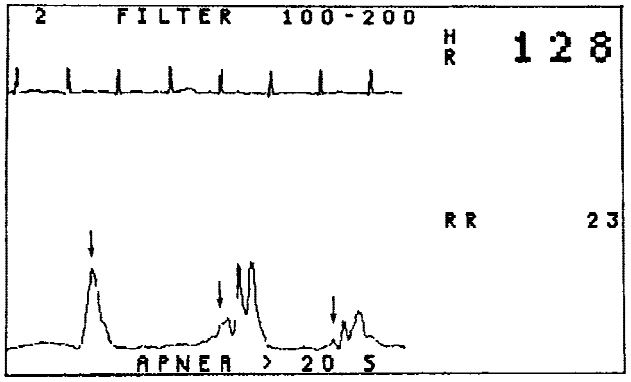

Fig. 2. Respiratory impedance measurements of chest wall excursions indicate that nasal intermittent positive pressure ventilation (NIPPV) fails to maintain adequate ventilation. The tracing progressively diminishes in amplitude. Arrows indicate administration of NIPPV.

we might have studied infants who primarily had obstructive apneas.

Apneic episodes associated with severe bradycardia may induce fluctuation in the blood pressure[13,14] and have potential deleterious hypoxic-ischemic effects on the brain.[14] For example, severe apnea and bradycardia may well be related to the higher incidence of abnormal neurologic status observed at follow-up.[15] Therefore, more aggressive treatment is recommended when infants have frequent apnea, especially when it is accompanied by bradycardia.[1,4,16,17] NCPAP administered by nasal prongs is an effective method to reduce the frequency of mixed or obstructive apnea in preterm infants.[4,5,16] However, in 18 preterm infants with clinical conditions similar to those enrolled in the present study, Kattwinkel et al.[16] demonstrated that the frequency of apnea could only be reduced by 70% following application of NCPAP.

Miller et al.[4] proved that NCPAP is selectively effective in reducing the incidence of mixed and obstructive apneas. NCPAP splints the airway throughout the respiratory cycle, increases functional residual capacity, eliminates the Hering-Breuer reflex, and stabilizes the chest wall of the infant.[18–20] Its application reduces the need and duration of mechanical ventilation as well as the mortality rate of the infants.[19,21] Our study shows that NIPPV is more effective than NCPAP in treating apnea. We speculate that NIPPV may provide infants with higher airway pressure than NCPAP, and this may also contribute to the higher response rate in the former. Since the duration of observations was relatively short, a follow-up study is warranted to reveal the long-term outcome of these infants.

Dransfield et al.[22] monitored a group of preterm infants recovering from respiratory distress syndrome and reported that all types of apnea are associated with bradycardia. There was a close relationship between bradycardia, apneic spells, and hypoxemia.[23] Therefore, a tendency to decrease bradycardia in the NIPPV infants in our study may be related to the decrease in apneic spells and improvement in oxygenation. The failure to observe statistically significant decreases in bradycardia is likely due to the small number of infants and a small decrease in bradycardia. A larger number of observations will probably make the observed trend significant.

In contrast to our results, Ryan et al.[9] reported that NIPPV had no significant edge over NCPAP in reducing the incidence of apnea. The peak pressure they used (20 cm H_2O) was similar to our settings, yet was lower than those (20–35 cm H_2O) used in the study of Moretti et al.[8] It has been noted that higher flow rate may produce a fast rise in the airway pressure so that the soft palate could be pushed against the tongue and seal the oral cavity.[8] In both Moretti et al.[8] and our present study, NIPPV was delivered at a flow rate of 8 L/min. The flow rate in Ryan, et al.[9] however, was not defined. In addition, infants in the present study had more frequent episodes of apnea and bradycardia than in Ryan et al.,[9] which could also have contributed to the discrepancy in results.

Increase in chest wall excursions and sigh breathing were observed when the infants responded to NIPPV. Sighs were not noted in infants given NCPAP. Rigatto and Brady[24] reported that the frequency of sighs increased during hypoxia or airway occlusion. Sighs may play a physiologic role in inflating atelectatic areas of the lungs.[25,26]

The evidence that a sigh was induced by NIPPV suggests that sighing is one of the mechanisms involved in making NIPPV an effective treatment. NIPPV could influence the tracing of thoracic impedance and reduce apneic episodes in NIPPV infants. However, we observed gradual airway closure in those infants who failed NIPPV treatment. Gauda et al.[27] evaluated the function of the genioglossus dilator muscle of the upper airway and the diaphragm during the apneic episodes. They found that all types of apnea were associated with a

reduction in the contraction of the diaphragm and dilator muscles of the upper airway.

Vocal cords dilate during inspiration so that positive pressure can be effectively transmitted to the distal airway. If NIPPV is delivered in the expiratory phase it may increase the work of breathing. Furthermore, it may adversely induce high airway pressure and result in pneumothorax.[28] Administration of NIPPV that works in synchrony with the infant's inspiratory drive may reduce the work of breathing[23] and improve pulmonary function.[29] Amitay et al.[30] showed that there is an improvement in tidal volume and minute ventilation, and less variability in arterial blood pressure during synchronous ventilation. We did not have a device that could deliver NIPPV synchronized with the infant's respiration. Its application may further increase the success of NIPPV in reducing apneic episodes.

In summary, the evidence, though not conclusive, is highly suggestive that NIPPV benefits infants with AOP. However, the duration of observations was too short to extrapolate long-term outcome. The mechanisms for effectiveness of NIPPV may be related to the triggering of sigh. Failure to prevent closure of the upper airway may be the cause of occasional failure to NIPPV. NIPPV may reduce the frequency of bradycardia; however, this can only be validated with larger numbers of observations.

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