The application of nasal synchronized intermittent mandatory ventilation in primary apnea of prematurity

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We aimed to evaluate the efficacy of nasal synchronized intermittent mandatory ventilation (nSIMV) in preterm infants with primary apnea of prematurity (AOP). Forty-four preterm infants with AOP were divided into the nSIMV group or nasal continuous positive airway pressure (nCPAP) group. Clinical symptoms, signs and blood gas results following nSIMV or nCPAP were compared between the two groups. Infants receiving nSIMV had a greater reduction in apneic spells and a greater decrease in bradycardia than those receiving nCPAP. Compared with the nCPAP group, the nSIMV group had a lower incidence of respiratory support failure (9.1% vs. 27.3%; p<0.05), a lower incidence of hypercarbia (4.5% vs. 18.2%; p<0.05) and a lower incidence of gastrointestinal complications (4.5% vs. 13.6%; p<0.05). This study showed that nSIMV was more effective in respiratory support in preterm infants with AOP.

Key words: primary apnea of prematurity, nasal synchronized intermittent mandatory ventilation, nasal continuous positive airway pressure ventilation.

Apnea is a common clinical symptom of prematurity, especially in low birth weight preterm infants. Apnea in preterm infants is usually related to immaturity of the central nervous system and is called apnea of prematurity (AOP)[1]. AOP is related inversely to gestational age, with 25% of preterms below 34 weeks needing either pharmacological or ventilatory support for repeated apneic episodes[2,3]. Recurrent apnea can cause respiratory failure, pneumorrhagia, intracranial hemorrhage, and hypoxic-ischemic brain damage in preterm infants[4,5]. Nasal ventilation is increasingly used to reduce complications associated with invasive mechanical ventilation in preterm infants[6,7]. Nasal continuous positive airway pressure (nCPAP) is the most common form of noninvasive respiratory support used in these infants. However, studies have shown important failure rates of nCPAP in preventing invasive ventilation or after extubation in the smaller infants[8,9]. Nasal synchronized intermittent mandatory ventilation (nSIMV) as a mode of synchronized nasal ventilation has been widely applied in preterm infants[10,11]. In this study, we compared the efficacy of nSIMV and nCPAP in the management of apnea in preterm infants.

Material and Methods

Subjects

This study was conducted in the Neonatal Intensive Care Unit (NICU) of the Second Affiliated Hospital of Dalian Medical University, and was approved by the hospital research and ethics committees. Written parental consent was obtained prior to enrollment. The enrollment criteria complied with the following conditions: 1) gestational age <34 weeks; 2) birth body weight <1600 g; and 3) exclusion of secondary causes of apnea before a diagnosis of AOP is made.

All neonates with apnea were investigated to exclude common causes of secondary apnea. The investigations included blood glucose, hematocrit, electrolytes, septic screen, blood culture, arterial blood gas, chest X-ray, ultrasound of the head, and other investigations (computed tomography [CT] or magnetic resonance imaging [MRI]) depending on the history and physical examination. The apneas began 2 to 3 days after birth. Infants with respiratory distress syndrome (RDS),

pneumonia, congenital anomalies, ongoing sepsis, severe perinatal asphyxia, or intracranial hemorrhage were excluded. Among those infants, nine infants with RDS received surfactant therapy. The enrolled infants were divided into the nCPAP group and the nSIMV group with 22 cases in each. No significant difference was observed between the two groups of preterm infants with respect to gender, gestational age, body weight, apnea onset age, and Apgar score (Table I).

Respiratory Management

The infants were treated uniformly in accordance with standard routine in our NICU. All patients were monitored using electrocardiography. The patients who responded to aminophylline therapy were excluded. If nasal respiratory support was indicated, the mode was nCPAP or nSIMV. There was no difference in the amount of oxygen required or the frequency of apnea between the two groups at entry to the respiratory support therapy. Both nCPAP and nSIMV were delivered through silicone binasal prongs by a commercial neonatal ventilator (NEWPORT150, American). The nCPAP was set at 4-6 cm H_2O, and the nSIMV was set at a synchronized mode, rate of 25-30 breaths/min (according to partial pressure of carbon dioxide in arterial blood [$PaCO_2$]), inspiratory time of 0.6-0.8 seconds, positive end expiratory pressure (PEEP) of 3-4 cm of water, and positive peak inspiratory pressure (PIP) of 15-20 cm of water according to chest excursion and the infant's weight. Fraction of inspired oxygen (FiO_2) was adjusted to keep oxygen saturation by pulse oximetry between 88%-92%. Synchronization was achieved by manipulation of trigger sensitivity and rate. Other conventional treatments were consistent between the nCPAP and nSIMV groups. For example, all cases were warmed at a moderate temperature after hospitalization, and intravenous access was established to maintain blood pressure stability and to maintain the perfusion of the heart, brain, and other vital organs. In addition, acidosis was corrected, and partial or complete intravenous nutrition was administered.

Apneic spells were detected by NEO-TRACK Neonatal Monitor. Before and after 4 hours of the nasal respiratory support treatment, arterial blood gases were measured, and the levels of pH, oxygen saturation (SaO_2), partial pressure of oxygen in arterial blood (PaO_2), and $PaCO_2$ were analyzed. The SaO_2, $PaCO_2$, heart rate, respiratory rate, blood pressure, and arterial blood gases were monitored during the respiratory support treatment. When clinical symptoms disappeared and breathing stabilized, the ventilator parameters were gradually reduced. When apnea disappeared over 12 hours, the nasal respiratory support was removed.

Assessment of the Effectiveness of nCPAP and nSIMV

The frequency of apnea and bradycardia was assessed. The outcome measure was the percent of infants in whom nasal respiratory support failed and who needed endotracheal ventilation. The criteria for failure of nasal support were: continuation of significant apneas, hypercarbia, hypoxia, or abdominal distension requiring cessation of feeds.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 11.0 software. The *t* test was performed to analyze the baseline data of patients, the frequency of apnea and bradycardia, and the blood gases. χ^2 test was performed to analyze the incidence of failed nasal support, hypercarbia, hypoxia, and gastrointestinal complications. Differences were considered significant if the p value was <0.05. Data are expressed as the means ± SD (standard deviation).

Results

The clinical features of preterm infants with AOP are summarized in Table I. There was no difference between groups in gender, gestational age, body weight, apnea onset age, or Apgar score.

The Infants' Responses to nCPAP or nSIMV Treatment

After four hours of the treatment, the frequency of apnea and bradycardia was significantly reduced with both forms of treatment. However, the reduction in apneic spells was significantly greater in the nSIMV group compared to the nCPAP group. A similar tendency was observed in the episodes of bradycardia. Following four hours of the nasal respiratory support, there was a tendency for increase in the mean PaO_2 and SaO_2 in both groups, although no significant differences were observed. There was no difference in the improvement in $PaCO_2$,

Table I. Comparisons of Clinical Features of Preterm Infants between the nCPAP and nSIMV Groups

Group	Cases	Gender		Gestational age (weeks)	Birth weight (g)	Onset age of apnea (d)	Apgar score	
		Male	Female				1 min	5 min
nCPAP	22	12	10	31.1±2.4	1396±214	3.3±1.3	8.1±2.0	8.7±1.6
nSIMV	22	13	9	30.9±2.3	1378±227	3.1±1.5	8.2±1.8	8.8±1.3

Data are expressed as the means ± SD. nCPAP: Nasal continuous positive airway pressure. nSIMV: Nasal synchronized intermittent mandatory ventilation. SD: Standard deviation.

Table II. The Infants' Responses to nCPAP or nSIMV Treatment

	nCPAP		nSIMV	
	Before	After 4 h	Before	After 4 h
Apnea spells (times/h)	2.9 (2.2-5.6)	1.3 (0.0-4.3) *	3.1 (2.1-6.2)	0.7 (0.0-3.5)* #
Bradycardia (times/h)	2.1 (0.3-3.2)	0.8 (0.0-2.1) *	2.3 (0.3-3.4)	0.4 (0.0-2.2) * #
pH	7.29±0.09	7.31±0.07	7.28±0.08	7.32±0.08
$PaCO_2$ (mmHg)	50.46±11.02	49.67±7.68	51.49±10.45	48.32±9.10
PaO_2 (mmHg)	60.08±14.54	67.56±14.12	59.78±11.43	68.51±13.02
SaO_2 (%)	0.78±0.13	0.85±0.11	0.77±0.14	0.89±0.09

*$p<0.05$ vs. before treatment; #$p<0.05$ vs. nCPAP group.
nCPAP: Nasal continuous positive airway pressure. nSIMV: Nasal synchronized intermittent mandatory ventilation.

Table III. The Efficacy of nCPAP and nSIMV in Preterm Infants with AOP

Group	Time to stop nasal support (d)	Failed nasal support (%)	CO_2 retention (%)	Hypoxemia (%)	Gastrointestinal complications (%)
nCPAP	3.7±1.2	27.3（6）	18.2（3）	9.1（2）	13.6 （4）
nSIMV	3.5±1.4	9.1*（2）	4.5*（1）	4.5（1）	4.5*（1）

*$p<0.05$ vs. nCPAP group.
AOP: Primary apnea of prematurity. nCPAP: Nasal continuous positive airway pressure. nSIMV: Nasal synchronized intermittent mandatory ventilation.

PaO_2 or SaO_2 between the nCPAP and nSIMV groups (Table II).

The Efficacy of nCPAP and nSIMV in Preterm Infants with AOP

There was no difference in the time of nasal support between the nCPAP and nSIMV groups. However, the nSIMV group had lower incidences of respiratory support failure, hypercarbia and gastrointestinal complications (Table III).

Discussion

Apnea of prematurity (AOP) is almost universal in infants who are born before 34 weeks' gestation. nCPAP is a useful method of respiratory support, which reduces the incidence of apnea. This mode provides a certain positive pressure for infants with autonomous respiration in the entire respiratory cycle of expiratory and inspiratory phases to maintain the airway in a certain dilated status. The effects of CPAP include an increase in functional residual capacity (FRC), thus improving PaO_2 and decreasing airway resistance. Our study showed that the frequencies of apnea and bradycardia were significantly reduced after four hours of the nCPAP mode. However, apneic infants managed with nCPAP sometimes require endotracheal intubation with its attendant morbidity and cost. With excessive CPAP, $PaCO_2$ may increase as tidal volume decreases and dead space increases. Our results showed that the failed rate of the nCPAP mode was 27.3%. Among 22 infants managed with nCPAP, hypercarbia occurred in 4 (18.2%) infants.

The nSIMV is a mode of noninvasive respiratory support and has been shown to be more effective than nCPAP in the treatment of RDS[12]

and AOP[13]. nSIMV can provide ventilation support for infants at the specified respiratory frequency through a noninvasive manner. The negative pressure of autonomous respiration of infants can trigger the ventilator to conduct synchronous positive pressure ventilation, and can supply stable PIP and PEEP noninvasively. During synchronized mechanical ventilation, positive airway pressure and spontaneous inspiration coincide. Synchronization can reduce spontaneous breathing effort, improve chest wall stability and reduce asynchrony[14,15]. In this study, trigger sensitivity was adjusted in each patient to achieve synchronous ventilation. We observed that synchronous ventilation can be achieved in apneic infants, which is consistent with the previous reports that adequate synchrony between the ventilator cycle and spontaneous inspiration was achieved in stable preterm infants[16]. The infants receiving nSIMV for four hours had a greater reduction in apneic spells and a greater decrease in bradycardia than those receiving nCPAP. We also found that the nSIMV group had a lower incidence of failed respiratory support and a lower incidence of hypercarbia, which is consistent with the previous reports[17]. In addition, thoracoabdominal asynchrony is common in preterm infants. If ventilator breaths were delivered in synchrony with laryngeal opening, gastrointestinal side effects might be reduced[18]. Our study showed that the nSIMV group had a lower incidence of gastrointestinal complications.

In conclusion, this study showed that nSIMV was more effective in providing respiratory support for premature apnea, as it improved the rate of respiratory support failure and reduced the complications of nCPAP.

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