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Usefulness of DuoPAP in the treatment of very low birth weight preterm infants with neonatal respiratory distress syndrome

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Abstract. – OBJECTIVE: This study examined the usefulness of nasal Duo positive airway pressure (DuoPAP) in the treatment of very low birth weight preterm infants with neonatal respiratory distress syndrome (NRDS).

PATIENTS AND METHODS: Eighty-five very low birth weight preterm infants with NRDS were randomly divided into two groups. Forty-five infants were treated with DuoPAP, while 40 infants were treated using nasal continuous positive airway pressure (nCPAP). The study outcomes were pH, $PaCO_2$, PaO_2, oxygenation index (PaO_2/FiO_2), and the number of failure cases at 1, 12, and 24 hours after non-invasive respiratory support.

RESULTS: At all studied time points, after non-invasive respiratory support, $PaCO_2$, PaO_2 and oxygenation index were significantly ($p < 0.05$) better in the nasal DuoPAP group compared with nasal CPAP group. In addition, rates of failure of assisted ventilation (respectively, 4.44% vs. 22.50%) and the occurrence of apnea (13.33% vs. 32.50%) were significantly ($p < 0.05$) better in the nasal DuoPAP group. Other parameters (such as duration of noninvasive ventilation, number of retinopathies of premature children, intraventricular hemorrhages, or periventricular leukomalacias) were comparable between both non-invasive regimen.

CONCLUSIONS: Nasal DuoPAP better improves oxygenation, reduces CO_2 retention, and diminishes the need for invasive mechanical ventilation and complications in the treatment of NRDS.

Key Words:

Duo positive airway pressure, Continuous positive airway pressure, Neonatal respiratory distress syndrome, Very low birth weight, Premature infant.

Abbreviations

DuoPAP = Duo positive airway pressure; NRDS = neonatal respiratory distress syndrome; nCPAP = nasal continuous positive airway pressure; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure.

Introduction

NRDS and repeated apnea often occur in premature infants due to immature respiratory and nervous systems. Immature lungs produce inadequate amounts of pulmonary surfactant. Surfactant deficiency leads to extensive alveolar collapse and decreased lung compliance. This is an important cause of death and a significant determinant of quality of life of premature infants. Respiratory support therapy is commonly used in these infants. The INSURE ("intubate-surfactant-extubate to continuous positive airway pressure") procedure can reduce the use of tracheal intubation for mechanical ventilation[1]. Our Department uses nasal Duo positive airway pressure (airway pressure release ventilation; DuoPAP) to treat NRDS in order to reduce the use of invasive mechanical ventilation and to lower the occurrence of apnea in premature infants. The objective of our study is to examine the usefulness of DuoPAP in the treatment of very low birth weight preterm infants with NRDS.

Patients and Methods

Patients

Our study included infants with NRDS treated in the neonatal ICU of our Hospital from January 2013 throughout February 2014. All children met the diagnostic criteria for NRDS[2]. The children, who gave up DuoPAP or CPAP treatment and left the hospital, are considered as exclusion criteria and not included in the statistics.The gestational age at birth was < 37 weeks, birth weight of < 1500 g, and age of ≤12 hours. The X-ray exam after admission showed NRDS grade I-II. The exclusion criteria were gestational age at birth of

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< 28 weeks, birth weight of < 1000 g, death within 24 hours after admission, discontinued treatment or spontaneous discharge during the administration of nasal DuoPAP or nasal CPAP treatment, complications (cyanotic heart disease, meconium aspiration syndrome, diaphragmatic hernia and congenital respiratory abnormalities, etc.), tracheal intubation and invasive mechanical ventilation after admission, neonatal pulmonary hemorrhages, absence of effective spontaneous breathing after recovery from respiratory paralysis, and cardiac or respiratory arrest due to nervous system diseases or muscle diseases. If disease progresses during the DuoPAP or CPAP treatment, intubation will be replaced by mechanical ventilation. This was considered as noninvasive ventilation failure cases in the statistics. What we studied was the noninvasive assisted ventilation, deaths occurred after intubation and mechanical ventilation was not included in the study.The study design was a randomized trial. A total of 85 premature infants were included. The randomization was performed using a random number table, with 45 infants in the nasal DuoPAP group and 40 infants in the nasal CPAP group. There were no significant differences between the groups in the gender, 1 min Apgar scores, gestational age, birth weight, use of corticosteroids from 24 hours prenatally to 7 days after birth, use of INSURE procedure, or administration of pulmonary surfactant (Table I).

Ventilator Application

In the nasal DuoPAP group, ventilation was applied as follows. Neonatal and pediatric ventilator (Fabian, Hirzel, Switzerland) was used in the noninvasive DuoPAP mode. Initial parameters were: PEEP 5 cm H_2O (1 cm H_2O = 0.0981 kPa), PIP 8 cm H_2O, FiO_2 0.4, time for high pressure 0.5 sec, pressure-switching frequency 30-40/min. According to blood gas analysis and SpO_2 regulation parameters (upper limit: PEEP ≤ 8 cm H_2O, PIP ≤ 15 cm H_2O, FiO_2 ≤ 0.6), SpO_2 was maintained at 88-93% and not higher than 95%, PaO_2 > 50 mm Hg, $PaCO_2$ < 50 mm Hg. If parameters decreased (FiO_2 ≤ 0.3, PEEP ≤ 3 cm H_2O, PIP ≤ 5 cm H_2O), the infant was considered as not having repeated apnea. If blood gas analysis was normal for subsequent 24 hours, then the infant was weaned off the ventilator and moved to an oxygen hood. Neonatal air-oxygen mixture was used, with FiO_2 of 0.3-0.4 and flow of 5 L/min.

In the nasal CPAP group, non-invasive CPAP

Table I. Demographic and clinical data in study groups.

Group	Gender, male/female, number	Apgar score		Gestational age, weeks	Birth weight, kg	Age, hours	Prenatal use of hormone, absolute numbers (%)	Use of pulmonary surfactant, absolute numbers (%)
		1 min	5 min					
Nasal DuoPAP group	25/20	4.81 ± 1.33	7.04 ± 2.01	30.96 ± 1.65	1.31 ± 0.12	6.72 ± 2.34	21 (46.7)	32 (71.1)
Nasal CPAP group	21/19	4.93 ± 1.44	7.33 ± 1.95	31.01 ± 1.57	1.33 ± 0.20	7.11 ± 3.12	17 (42.5)	29 (72.5)
p	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

Footnote: Data are presented as mean ± SD or as indicated in the table. N.S.: not significant.

device (Stephanie, Hamburg, Germany) was used. The initial parameters were: PEEP 5 cm H_2O, flow 4-8 L/min, FiO_2 0.4. The parameters were adjusted according to blood air analysis and SpO_2: upper limit PEEP ≤8 cm H_2O, FiO_2 ≤0.6, SpO_2 was maintained at 88 – 93% and not higher than 95%, PaO_2 > 50 mm Hg. If parameters decreased (FiO_2 ≤0.3 and PEEP ≤3 cm H_2O), the infant was considered as having no repeated apnea. As above, if blood gas analysis was normal for subsequent 24 hours, then the infant was weaned off the ventilator and moved to an oxygen hood. Neonatal air-oxygen mixture was used, with FiO_2 of 0.3-0.4 and flow of 5 L/min.

In addition, infants in two study groups received bovine pulmonary surfactant therapy. The INSURE procedure was used: tracheal intubation, infusion of bovine pulmonary surfactant through the tracheal catheter, followed by the use of nasal DuoPAP or nasal CPAP after extubation. Sputum suctioning was not allowed within 6 hours after administration of bovine pulmonary surfactant therapy. Routinely, stomach tube was removed in all infants to reduce the occurrence of abdominal distension.

If the infant's condition has not improved significantly or has even exacerbated after nasal DuoPAP or nasal CPAP therapy, then the indications for tracheal intubation and mechanical ventilation were the following. If FiO_2 > 0.6 was needed, and the infant's condition has not improved significantly, PaO_2 < 50 mm Hg (or SpO_2 < 85%), $PaCO_2$ > 70 mm Hg, and pH < 7.25, tracheal intubation and mechanical ventilation were needed due to occurrence of repeated apnea[3]. In addition, intubation with mechanical ventilation was applied situations like neonatal pulmonary hemorrhage or in infants without effective spontaneous breathing after recovery from respiratory paralysis, cardiac or respiratory arrest due to nervous system diseases or muscle diseases.

The study outcomes were infant's heart rate, breathing rate, blood pressure, SpO_2, blood gas analysis, chest X-ray, oxygenation index (calculated as PaO_2/FiO_2), weaning time, number of tracheal intubations for mechanical ventilation due to failure of non-invasive ventilation, number of infants with apnea, air leak syndrome, bronchopulmonary dysplasia or retinopathy of prematurity, number of intraventricular hemorrhage and periventricular leukomalacia in premature infants, who received conventional cranial B-ultrasonography 3 days after birth.

Statistical Analysis

The statistical analysis was performed using SPSS, version 13.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were presented as mean ± SD, and the *t* test was used for intergroup comparisons. Qualitative data were presented as percent, and the chi-square test was used for intergroup comparison. The *p* value of < 0.05 was considered statistically significant.

Results

Blood Gas Analysis Before and After Treatment

Two study groups showed comparable parameters of blood gas analysis at 0 hours (Table II). After respiratory support therapy, there was a significant difference in $PaCO_2$, PaO_2, and oxygenation index after 1, 12, and 24 hours of treatment. Blood pH value increased with a similar magnitude in both study (Table II).

Efficacy and Outcome

The time of non-invasive nasal ventilation did not differ between infants on nasal DuoPAP or CPAP (Table III). The number of failures of non-invasive ventilation and apnea episodes was lower in the nasal DuoPAP group (p < 0.05; Table III), while numbers of pneumothoraxes, bronchopulmonary dysplasias or retinopathies of prematurity were similar between both study groups (Table III). Furthermore, the rate of intraventricular hemorrhages and periventricular leukomalacias in premature infants, determined by cranial B-ultrasonography at 3 days after birth, was comparable between both groups (Table III).

Discussion

Synthesis of pulmonary surfactant increases only after 35 weeks of gestational age, leading to more frequent NRDS in the neonates with very low birth weight. Therapy with pulmonary surfactant for neonate NRDS, using INSURE therapy, can reduce the use of invasive mechanical ventilation[1]. The CPAP non-invasive ventilation can provide positive pressure to the child with spontaneous breathing during the inspiration and expiration phases of respiratory cycle to improve the ventilation/perfusion ratio and promote oxygenation[3]. However, the number of failures of non-invasive ventilation was higher in the nasal CPAP group compared with nasal DuoPAP

Table II. Blood gas parameters in study groups.

A) Group	pH				$PaCO^2$, mm Hg			
	0 hour	1 hour	12 hours	24 hours	0 hour	1 hour	12 hours	24 hours
Nasal DuoPAP group	7.27 ± 0.11	7.29 ± 0.08	7.34 ± 0.10	7.36 ± 0.05	53.37 ± 2.36	47.91 ± 3.24	43.22 ± 3.88	41.25 ± 3.14
Nasal CPAP group	7.26 ± 0.10	7.27 ± 0.07	7.33 ± 0.09	7.35 ± 0.07	54.22 ± 3.55	50.12 ± 2.83	45.74 ± 2.62	43.31 ± 2.23
p	N.S.	N.S.	N.S.	N.S.	N.S.	< 0.05	< 0.05	< 0.05
B) Group	PaO_2, mm Hg				Oxygenation index, mm Hg			
	0 hour	1 hour	12 hours	24 hours	1 hour	12 hours	24 hours	
Nasal DuoPAP group	45.23 ± 1.95	54.66 ± 2.67	55.67 ± 2.32	57.27 ± 2.66	119.91 ± 4.17	121.15 ± 4.65	142.51 ± 7.68	
Nasal CPAP group	45.82 ± 2.88	53.13 ± 1.39	53.84 ± 2.63	54.88 ± 3.67	115.71 ± 2.26	118.43 ± 5.25	136.33 ± 6.61	
p N.S.	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05		

Footnote: Data are presented as mean ± SD. N.S.: not significant.

Table III. Efficacy of assisted ventilation in study groups.

Group	Time of invasive ventilation	Number of failures, absolute numbers (%)	Number of apneas, absolute numbers (%)	Number of pneumothoraxes, absolute numbers (%)	Number of bronchopulmonary displasias, absolute numbers (%)	Number of retinopathies of prematurity, absolute numbers (%)	Number of intraventricular hemorrhages, absolute numbers (%)	Number of periventricular leukomalacias, absolute (%)
Nasal DuoPAP group	3.61 ± 0.97	2 (4.44)	6 (13.33)	2 (4.44)	1 (2.22)	1 (2.22)	14 (31.11)	5 (11.11)
Nasal CPAP group	3.44 ± 1.18	9 (22.50)	13 (32.50)	1 (2.50)	1 (2.50)	2 (5.00)	13 (32.50)	3 (7.50)
p N.S.	< 0.05	< 0.05	N.S.	N.S.	N.S.	N.S.	N.S.	

Footnote: Data are presented as mean ± SD or as indicated in the table. N.S.: not significant.

group, indicating that premature infants are still at risk of respiratory failure after nasal CPAP therapy and may still require tracheal intubation for mechanical ventilation. Common reasons were apnea and development of lung disease[4].

Our study found that $PaCO_2$, PaO_2, and oxygenation index improved better in infants on nasal DuoPAP. DuoPAP is a novel respiratory support mode combining two CPAP regimen. The PEEP is shown in the ventilator as fundamental CPAP pressure, while PIP is the upper limit of intermittently superimposed pressure[5,6]. The frequency (RR) is the number of superimposed PIP per minute. The switch from PIP to PEEP depended on time, and the infant could breathe freely under two pressures. Therefore, it was similar to the biphasic positive airways pressure (BIPAP) mode[7]. The respiratory support was stronger in nasal DuoPAP than in nasal CPAP. The former ventilation regimen also added a frequency of intermittent positive pressure ventilation to CPAP, increased mean airway pressure, tidal volume and ventilation volume per minute. This improved hypoxemia and CO_2 retention[8-10], while maintaining dilatation of the respiratory tract and preventing a small airways collapse and reducing the work of breathing. It was similar to a nasal intermittent positive pressure ventilation mode, and the efficacy was similar to that of nasal synchronized intermittent mandatory ventilation[11].

Our study also found that nasal DuoPAP more efficiently than nasal CPAP decreased the occurrence of tracheal intubation in infants with NRDS and reduced appearance of apnea. Thereby, nasal DuoPAP demonstrated a better suitability for the treatment of NRDS.

Conclusions

When nasal CPAP or DuoPAP were used, infants breathed through nasal mask or rhinobyon. Conventional blood gas analysis should be carried out during ventilation. As the flow sensor is not used, an alternative warning system (e.g., impedance respiration measurement) should be used for detection of asphyxia. Further studies are needed to determine whether nasal DuoPAP is beneficial for transitional treatment after extubation after invasive mechanical ventilation.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, Saugstad OD, Simeoni U, Speer CP, Vento M, Halliday HL. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants--2013 update. Neonatology 2013; 103: 353-368.
2) Shao XM, Ye HM, Qiu XS. [Practical pediatrics]. People's Medical Publishing House, Beijing, 2011. in Chinese.
3) Zhou XG, Xiao X, Nong SH. [Neonatal mechanical ventilation--Therapeutics]. People's Medical Publishing House, Beijing, 2011. in Chinese.
4) Meneses J, Bhandari V, Alves JG, Herrmann D. Noninvasive ventilation for respiratory distress syndrome: a randomized controlled trial. Pediatrics 2011; 127: 300-307.
5) Bhandari V. Nasal intermittent positive pressure ventilation in the newborn: review of literature and evidence-based guidelines. J Perinatol 2010; 30: 505-512.
6) DiBlasi RM. Neonatal noninvasive ventilation techniques: do we really need to intubate? Respir Care 2011; 56: 1273-1294; discussion 1295-1277.
7) Xie LX, Liu YN. [Question about the conceptual issues between BiPAP and BIPAP]. Chin J Tuberc Respir Dis 2005; 28: 208. in Chinese.
8) Dumpa V, Katz K, Northrup V, Bhandari V. SNIPPV vs NIPPV: does synchronization matter? J Perinatol 2012; 32: 438-442.
9) Owen LS, Morley CJ, Dawson JA, Davis PG. Effects of non-synchronised nasal intermittent positive pressure ventilation on spontaneous breathing in preterm infants. Arch Dis Child Fetal Neonatal Ed 2011; 96: F422-428.
10) Ramanathan R. Nasal respiratory support through the nares: its time has come. J Perinatol 2010; 30 Suppl: S67-72.
11) Demirel G, Uras N, Celik IH, Canpolat FE, Dilmen U. Nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure for transient tachypnea of newborn: a randomized, prospective study. J Matern Fetal Neonatal Med 2013; 26: 1099-1102.