

A Comparative Study of the Effect of Nasal Intermittent Positive Pressure Ventilation and Nasal Continuous Positive Airway Pressure on the Regional Brain Tissue Oximetry in Premature Newborns Weighing <1500 g

Abstract

Background: Near-infrared spectroscopy (NIRS) provides the capability of monitoring oxygenation levels in cerebral microscopic vessels, enabling the operator to observe the spontaneous changes in the levels of hemoglobin concentration in tissue and interpret the resulting fluctuations. The current study tried to investigate whether brain's autoregulatory mechanisms in premature newborns have the potential to prevent the adverse effects caused by asynchronous changes of pressure in the rib cage. Therefore, NIRS method was applied to newborns that were alternatively shifted from nasal continuous positive airway pressure (nCPAP) to nasal intermittent positive pressure ventilation (NIPPV) and vice versa. **Methods:** This study was done as a crossover randomized clinical trial on 30 very low-weight newborns under nCPAP, who had received surfactant as a result of respiratory distress syndrome diagnosis, from April 2015 to April 2016, in Isfahan Shahid Beheshti Educational Hospital. The newborns were 72 h old, experiencing continuous distending pressure (CDP) = 4–6 cmH₂O with FiO₂ = 30%–40%. The respiratory support would alternate from nCPAP to NIPPV and vice versa (with indicators of expiratory PAP (EPAP) = CDP and inspiratory PAP = EPAP + 4 cmH₂O), and the cerebral regional oxygen saturation (CrSO₂) was monitored using NIRS. **Results:** The study results indicated that newborns significantly showed higher levels of CrSO₂ (84.93, $P = 0.005$) and oxygenation (94.63, $P = 0.007$) under nCPAP rather than NIPPV (82.43 and 93.43, respectively). The respiratory rate was also meaningfully slower when newborns were under nCPAP ($P = 0.013$). **Conclusions:** This study revealed that applying NIPPV may have an unfavorable effect on the premature newborn's brain tissue perfusion. However, more studies are needed to ensure solid outcomes.

Keywords: Cerebral regional oxygen saturation, nasal continuous positive airway pressure, nasal intermittent positive pressure ventilation

Introduction

Intracranial hemorrhage (ICH) in premature newborns is a serious damage with potentially irrecoverable effects on the morbidity and mortality rates as well as long-term outcomes of the development of nervous system. During the recent decades, despite the significant improvements in supportive interventional procedures for premature newborns and the resulting decrease in mortality, ICH still presents a significantly harmful risk for these newborns.^[1]

A number of mechanisms cause germinal matrix-intraventricular hemorrhage (GM-IVH), including susceptibility of GM structure to damage, coagulopathy and platelet dysfunctions, genetic factors, cytokines, and finally hemodynamic factors. Hemodynamic factors are influenced by

two interventional systems of intrinsic and extrinsic indicators.^[2]

The fluctuations in cerebral blood flow (CBF), which are caused by the increase in the pressure of cerebral venous drainage during respiratory distress syndrome (RDS), positive pressure ventilation (PPV), out-of-synchrony in PPV, and pneumothorax, are major ground stones for the development of GM-IVH.^[3]

RDS is among the most exclusively challenging conditions for Neonatal Intensive Care Unit (NICUs) and hence needs special management. The most prevalent pathology affecting the newborns <32 weeks of gestational age is RDS. In this regard, a significant portion of the long-term morbidity and mortality cases is ascribed to RDS and its outcomes.^[4,5]

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So far, nasal continuous positive airway pressure (nCPAP) has been considered as the standard care for the management of RDS for more than four decades. nCPAP improves the oxygenation in the newborns involved in the process of RDS through recruitment of pulmonary volumes, prevention of atelectasis, stabilizing the rib cage, alternation of pulmonary compliance, and decreasing the work of breathing. nCPAP decreases the intrapulmonary shunt by enhancing the efficiency of the ventilation to perfusion ratio. Studies have revealed that even in newborns who suffer frequent central apnea, the gas pressure nCPAP imposes on the upper parts of the respiratory system that can prevent the mentioned pauses in respiration through its stimulating effect. Needless to say, nCPAP shows a promising mechanism in maintaining open airways in obstructive apnea.^[6]

Nasal intermittent PPV (NIPPV) was first developed for the primary application of apnea of prematurity control. It has been a while since NIPPV has been introduced as primary mode (when NIPPV is administered for a newborn with RDS, equal or <2 h after birth, either with or without surfactant administration) in NICUs; however, taking this approach to treat RDS has revealed a high level of diversity; as in the U. K., its difference in application ranges from 48% in England to 61% in Ireland.^[7]

Although it is always stressed that the brain's autoregulatory mechanism (though not developed) accompanied by an average systematic blood pressure (BP) above 30 mmHg is enough to maintain the cerebral blood perfusion, Evans *et al.* showed that other factors, such as intrathoracic pressure level, can affect the intracranial blood flow, and interventions involving respiratory support are among those which are markedly accompanied by significant changes in intrathoracic pressure.^[8]

The improvement in our capability to evaluate the changes in cerebral oxygenation levels and the interventional mechanisms affecting the CBF had led to a development of our understanding of these fluctuations and their potential harm to the developing brain tissue. Premature newborns are in danger of developmental delays in "CBF autoregulatory system," and this, in turn, increases the risk of facing unusual perfusion flows (and hence facing unusual levels of oxygenation) during hemodynamic instabilities. So far, very few technologies have been implemented for monitoring CBF in endangered newborns. Near-infrared spectroscopy (NIRS), due to the low thickening of scalp and calvarium in newborns, especially premature newborns, has the capability to monitor oxygenation levels in microscopic vascularity in fact the system monitors the hemoglobin chromophore levels which absorb the wavelength of 700–1000 nm as the basis for its monitoring and also calculates the oxyhemoglobin saturation (StO₂) through differentiating the oxygenated hemoglobin (O₂Hb) from deoxygenated hemoglobin (HHb) using the following formula:

$$\text{StO}_2 = \text{O}_2\text{Hb} + \text{HHb}, \text{ and } \text{tHb} = \text{total Hb}$$

As a result, the operator can relate continuous changes to the changes in tissue hemoglobin concentration (or the blood volume in the tissue, resulting from tissue perfusion and CBF) and interpret its outcome records.^[9]

Due to the concerns regarding the adverse effects related to out-of-synchrony performance in the application of NIPPV, this study tried to challenge this type of respiratory support versus nCPAP through studying the brain tissue oxygenation in newborns that are frequently altered between these two forms of respiratory support.

Methods

Study design and participants

This study is a randomized clinical trial (RCT)-crossover done on very low-weight newborns who were under nCPAP respiratory support in the NICU Department of Isfahan Shahid Beheshti Hospital from October 2015 to May 2016. The newborns who entered the study were diagnosed with RDS (with demonstrations of tachypnea, intracostal retraction, nasal flaring, and grunting^[10] as well as chest X-ray compatible with RDS) and had received surfactant in their first 2 h from birth (Survanta was administered in case FiO₂ ≥30% and continuous distending pressure (CDP) ≥5 cmH₂O was needed to maintain SpO₂ in the range of 89%–95% in the right hand).^[11]

These newborns were placed under nCPAP respiratory support at 72 h from birth (when they entered the study) to maintain SpO₂ in the range of 89%–95% in the right hand with CDP of 4–6 cmH₂O and FiO₂ of 30%–40%.^[12] The exclusion criteria included perinatal asphyxia (5 min Apgar of 0–3, umbilical cord pH of <7, and umbilical cord bicarbonate of <12 mEq/L), congenital malformation,^[13] not receiving surfactant or administration of surfactant later than 2 h from birth,^[14] newborns who revealed evidence of patent ductus arteriosus in echocardiography,^[12] newborns who received inotropic drugs,^[14] newborns who revealed evidence of Grades III to IV GM-IVH in cranial sonogram,^[14] as well as newborns involved in air leak syndrome.^[15]

Variables assessment

Due to the primary goal of the study which included the evaluation and monitoring of cerebral tissue oxygen content, a NIRS transducer (INVOS 4100 Somanetics Corp., Troy, MI, USA) was placed on the scalp of the newborns who realized the conditions of inclusion criteria, right on the frontal region, and the system was activated.^[14] The newborns were monitored for 2 h for the inclusion criteria indicators while they were under BabyFlow Injector (Draeger Medical, Lubeck, Germany) and Babylog 8000 plus ventilator (Draeger Medical, Lubeck, Germany) and were supported with nCPAP respiratory support. The newborns were not fed during that period and

upon 90 min of monitoring the cerebral regional oxygen saturation (CrSO₂), oxygen (O₂) saturation, respiratory rate, and heart rate which was recorded every 30 min; capillary gasometry was done from the newborn's heel through heel stick, and systemic BP evaluation was done on the right hand.

Then, indicators of inspiratory PAP (IPAP) and expiratory PAP (EPAP) were defined for the ventilator (as Ti = 0.5, rate = 30 breath/min, IPAP = EPAP + 4 cmH₂O), and IPPV mode was activated at the end of this initial 2 h period. While under NIPPV support, which was about 2 h, the newborns were not fed, their CrSO₂, O₂ saturation, respiratory rate, and heart rate were monitored every 30 min and after 90 min; gasometry and mean arterial BP tests were done on the newborn.^[15]

Statistical analysis

Considering the 95% confidence interval and the power of 80% with 0.37 error, the data on 30 newborns were analyzed with IBM SPSS statistical software version 18, (Armonk, New York, U.S) using paired samples *t*-test and Pearson's correlation coefficient. Demographics characteristics of newborn are shown in Table 1.

Results

This study was done with a crossover design not to let the participants' physiology interfere with the interventions with nCPAP and NIPPV, as in most RCT trials, in which the physiological conditions are kept similar to study the effect of such mechanisms on brain tissue perfusion regardless of other not intended interfering factors.

Regarding the period effect, 2 h upon birth, the newborn, who had been treated with nCPAP or NIPPV, would be assessed, and the need to administer surfactant would be indicated. Therefore, in case, the newborn did not need to receive surfactant, and it could be concluded that the interventions directed at CDP achieved their optimal effective status during the specified period of treatment.

The studied indicators are shown in Table 2, and the statistical analysis results on correlation and paired samples *t*-test are given in Tables 3 and 4, respectively. The results indicated the respiratory rate was significantly higher under NIPPV (60.96 ± 4.16, *P* = 0.013), and the results from correlation analysis indicated a strong relationship between the method and the respiratory rate (0.722, significant = 0.000) while PCO₂ levels were also higher in NIPPV group but not statistically meaningful (47.34 ± 10.20, *P* = 0.063). Newborns showed significantly lower O₂ saturation (*P* = 0.007) and CrSO₂ (*P* = 0.005) levels when under NIPPV rather than nCPAP. Mean BP and heart rates showed no significant differences between nCPAP and NIPPV groups (*P* = 0.736 and *P* = 0.579, respectively).

Table 1: Demographics characteristics of newborns

Demographic criteria	Value
Gestational age, week (mean±SD)	29.59±2.4
Sex, <i>n</i> (%)	
Male	17 (56.6)
Female	13 (43.4)
Weight, g (mean±SD)	1131±272
Apgar, min (mean±SD)	
1	5.6±1.5
5	7.7±1
ROM ≥18 h, <i>n</i> (%)	7 (23.3)
Maternal steroid administration, <i>n</i> (%)	26 (86.6)
Delivery, <i>n</i> (%)	
Cesarean section	22 (73.4)
Normal vaginal delivery	8 (26.6)

SD=Standard deviation, ROM=Rupture of membrane

Table 2: Clinical outcomes

Item	Mean±SD		
	CPAP	NIPPV	<i>P</i>
CrSO ₂ (%)	84.93±6.19	82.43±7.36	0.005
O ₂ saturation (%)	94.63±2.12	93.43±2.77	0.007
Mean BP (mmHg)	50.30±11.41	49.63±12.85	0.736
RR	59.43±4.38	60.96±4.16	0.013
HR	141±16.42	142.43±19.00	0.579
PCO ₂ (mmHg)	44.52±8.57	47.34±10.20	0.063

SD=Standard deviation, HR=Heart rate, BP=Blood pressure, CPAP=Continuous positive airway pressure, NIPPV=Nasal intermittent positive pressure ventilation, RR=Respiratory rate, CrSO₂=Cerebral regional oxygen saturation, O₂=Oxygen

Table 3: Correlation test results

Paired samples correlations	Paired samples correlations		
	<i>n</i>	Correlation	Significant
Pair 1: CrSO ₂ under CPAP and CrSO ₂ under NIPPV	30	0.793	0.000
Pair 2: O ₂ saturation under CPAP and O ₂ saturation under NIPPV	30	0.601	0.000
Pair 3: BP under CPAP and BP under NIPPV	30	0.615	0.000
Pair 4: RR under CPAP and RR under NIPPV	30	0.722	0.000
Pair 5: HR under CPAP and HR under NIPPV	30	0.791	0.000
Pair 6: PCO ₂ under CPAP and PCO ₂ under NIPPV	30	0.650	0.000

HR=Heart rate, BP=Blood pressure, CPAP=Continuous positive airway pressure, NIPPV=Nasal intermittent positive pressure ventilation, RR=Respiratory rate, CrSO₂=Cerebral regional oxygen saturation, O₂=Oxygen

Discussion

Considering a number of researches done to compare the two approaches of nCPAP and NIPPV respiratory support

Table 4: Paired samples test results

	Paired samples <i>t</i> -test		<i>t</i>	df	Significant (two-tailed)
	Paired differences				
	Mean±SD	SEM			
CrSO ₂ under CPAP and CrSO ₂ under NIPPV	2.50000±4.50096	0.82176	3.042	29	0.005
O ₂ saturation under CPAP and O ₂ saturation under NIPPV	1.20000±2.26518	0.41356	2.902	29	0.007
BP under CPAP and BP under NIPPV	0.66667±10.72327	1.95779	0.341	29	0.736
RR under CPAP and RR under NIPPV	-1.53333±3.19194	0.58277	-2.631	29	0.013
HR under CPAP and HR under NIPPV	-1.20000±11.69851	2.13585	-0.562	29	0.579
PCO ₂ under CPAP and PCO ₂ under NIPPV	-2.82000±7.99122	1.45899	-1.933	29	0.063

SD=Standard deviation, HR=Heart rate, BP=Blood pressure, CPAP=Continuous positive airway pressure, NIPPV=Nasal intermittent positive pressure ventilation, RR=Respiratory rate, SEM=Standard error of mean, CrSO₂=Cerebral regional oxygen saturation, O₂=Oxygen

to treat RDS, it is observed that in the majority of the studies, some of which are referred to in the following, the methodology had not addressed the cerebral function monitoring.

In a study done by Sai Sunil Kishore *et al.*, which lasted from January 2007 to April 2008, nCPAP and NIPPV were compared for the respiratory management of RDS in premature newborns. The newborns had a gestational range of 28–32 weeks, and in case, they had experienced Downes score of equal or higher than 4 in the first 6 h from birth, and they would be randomly assigned to two interventional groups of nCPAP and NIPPV. Around 39 newborns were placed in nCPAP group, and the maximum setup was considered with CDP = 7 cmH₂O and FiO₂ ≤70%. A total of 37 newborns entered the NIPPV group, and the initial setup was rate = 40–50/min, Ti = 0.3–0.35 s, positive end-expiratory pressure (PEEP) = 5 cmH₂O, and peak inspiratory pressure (PIP) = 15–16 cmH₂O; however, regarding the gasometry data, the setup could be raised to rate = 60/min, PEEP = 6 cmH₂O, and PIP = 24–26 cmH₂O. In nCPAP group, at CDP = 4 cmH₂O and FiO₂ ≤30%, the respiratory support would be discontinued, while in the NIPPV group, the respiratory support would be discontinued at rate = 30/min, PEEP = 4 cmH₂O, PIP = 14 cmH₂O, and FiO₂ ≤30%. The need for invasive respiratory support during 48 h and a week from the discontinuation showed a significant increase in the nCPAP group rather than the NIPPV group.^[16]

In another study done by Bhandari *et al.* to compare synchronized NIPPV (SNIPPV) and nCPAP at two hospitals in Yale and San Diego universities, 469 preterm newborns weighing <1250 g, who were under mechanical respiratory support due to RDS, were extubated and entered the two groups of SNIPPV and nCPAP noninvasive respiratory support if during treatment, the ventilator management system indicated PIP ≤16 cmH₂O, PEEP ≤5 cmH₂O, rate = 15–25, and FiO₂ ≤35% to maintain pH = 7.25–7.45, PaCO₂ = 40–55 mmHg, and PaO₂ = 50–80 mmHg. Synchronization management in Infant Star ventilator (invasive or noninvasive) is done through the placement of Graseby capsule on the newborn's abdomen. In this study which lasted from 2002 to 2004, upon extubation,

the newborns who entered the SNIPPV group (*n* = 242) were put under respiratory support with Inca (Infant nCPAP Assembly) and the same invasive ventilation rate, yet PIP was increased 2–4 cmH₂O, and PEEP was set as equal or <6 cmH₂O, and FiO₂ was set to a level to maintain the O₂ saturation in the range of 85%–95%. If FiO₂ of lower than 30% was needed, the newborn was detached from the ventilator (respiratory support). Bronchopulmonary dysplasia prevalence showed a significant decrease in SNIPPV group while PVL prevalence was significantly lower in non-SNIPPV group.^[17]

In a study done by Ramanathan *et al.* in 2012, 110 premature newborns with <30-week gestational age who had RDS and were treated with surfactant within the 1st h from birth entered the two groups of nCPAP and NIPPV treatment and were studied for 7 days (from birth). About 40% of the newborns in the nCPAP group demonstrated a need for mechanical ventilation during 7 days from birth, whereas in the NIPPV group, 7% of the newborns needed mechanical ventilation in the same period.^[18]

Among the few studies done to monitor the brain tissue oximetry for newborns with RDS under nCPAP treatment, we can refer to the one done by Dani *et al.* in 2007. In that study, 14 newborns with RDS and gestational age of <30 weeks were treated with nCPAP. After 12 h from extubation, while nCPAP was administered with FiO₂ ≤40%, CDP was set to 2 cmH₂O for 30 min, followed by a 60-min nCPAP support at CDP = 4 cmH₂O, then a subsequent period of 60 min with CDP of equal to 6 cmH₂O and eventually a final 30-min nCPAP support at CDP = 2 cmH₂O, and the CrSO₂ was monitored throughout the process. The results did not show any significant difference between the CrSO₂s at different levels of CDP.^[12]

In the study done by Lemmers *et al.*, 38 newborns with gestational age of <32 weeks were monitored for CrSO₂ for 72 h upon birth. Among these newborns, 18 were involved in RDS and were supported with conventional mechanical ventilation, and the respiratory management ensured PCO₂ of 40–50 mmHg. The results of this study did not show any significant difference between the two groups of CrSO₂ and fractional tissue oxygen extraction (FTOE); however,

the recorded CrSO₂ and FTOE levels showed a wide and significantly different range of variance at different times in the RDS group.^[14]

Limitations of the study and suggestions for further research

One of the biggest challenges faced by the researcher was the crossover nature of the study. As the number of patients entering the study was limited, the researcher had to perform the study as a crossover. This limited the outcomes of the study, and further studies on this subject are recommended in which a larger population could be studied in a noncrossover approach.

Conclusions

The current study revealed that the newborns showed significantly meaningful lower levels of CrSO₂ while under NIPPV (compared to the time they were under nCPAP). Moreover, by activating the NIPPV mode, the newborns' O₂ saturation levels also decreased significantly. The study done by Bhandari *et al.* revealed that PVL prevalence was significantly lower among newborns in the nCPAP group than those in the NIPPV group. It seems that the results of the current study provide grounds for the outcomes of the study done by Bhandari, as at least part of the background for PVL, more specifically brain tissue ischemia, can be attributed to lower levels of CrSO₂ during NIPPV treatment. Respiratory rate has also been significantly higher in the NIPPV group. The question is whether the decrease in brain tissue oxygen content is due to the decrease in O₂ saturation or the instability in brain tissue perfusion, as the increase in respiratory rate or the increase in CO₂ pressure in blood flow, with their relevant mechanisms of increasing asynchrony and inducing out-of-control pressures in thorax (regarding the increase in respiratory rate), as well as increasing brain tissue perfusion (regarding the increase in PCO₂), may result in fluctuations or CBF. Therefore, it seems necessary to perform a wider range of research (in terms of the magnitude of the samples and the focus on long-term outcomes) before one could consider applying two different pressure levels in an out-of-synchrony fashion in respiratory management of newborns involved in RDS.

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Conflicts of interest

There are no conflicts of interest.

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