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Is There a Relationship Between Carbon Dioxide Fluctuations and Intraventricular Hemorrhage in Preterm Infants?

Gülsüm Kadıoğlu Şimşek, Betül Siyah Bilgin, Şeyma Bütün Türk, Nihan Tufan, H. Gözde Kanmaz Kutman, Fuat Emre Canpolat

Ankara City Hospital, Clinic of Neonatology, Ankara, Turkey

What is known on this subject?

Previous studies on premature babies have revealed different relationships between carbon dioxide (CO_2) levels and cranial pathologies. An association between periventricular leukomalacia and hypocarbia was reported in older articles. Although a more recent study found no association between changes in blood gases and cranial hemorrhages in the neonatal intensive care unit, the same data found a correlation between end-tidal CO_2 levels in the delivery room and intraventricular hemorrhages.

What this study adds?

According to the results of this study, keeping CO_2 levels within the normal range is extremely important for controlling intracranial hemorrhage in preterm infants.

ABSTRACT

Objective: This study aimed to examine the association between hypo/hypercapnia and fluctuations in carbon dioxide (CO_2) levels and severe intraventricular hemorrhage (IVH) during the initial 72 hours of life among preterm infants.

Material and Methods: A retrospective study of premature infants with birth weights between 750 and 1.250 g and gestational ages of 30 weeks who required respiratory support. Blood gas measurements were collected during the first 3 days of life. Multivariate analyses were performed to assess the association between hypercapnia and carbon dioxide pressure (pCO_2) fluctuations and IVH.

Results: Our cohort included 376 patients with a median gestational age of 28 weeks and a median birth weight of 920 g. After controlling for gestational age and birth weight, histologic chorioamnionitis and pCO_2 fluctuations remained significantly associated with severe IVH.

Conclusion: Fluctuations in pCO_2 over a short period may have a stronger association with severe IVH than the mere occurrence of hypo- or hypercapnia.

Keywords: Hypercapnia, hypocapnia, preterm infant, intraventricular hemorrhage

Introduction

It is known that there is a relationship between carbon dioxide (CO_2) levels and intracranial hemorrhage in premature babies (1). In particular, previous studies have supported a link between low CO_2 levels and periventricular leukomalacia and that excessive ventilation increases neurodevelopmental problems in premature babies (2). While some studies suggest that this relationship is related to CO_2 fluctuations

Address for Correspondence: Gülsüm Kadıoğlu Şimşek MD, Ankara City Hospital, Clinic of Neonatology, Ankara, Turkey
Phone: +90 505 389 28 46 **E-mail:** glsmkadioglu@gmail.com **ORCID ID:** orcid.org/0000-0003-4831-8950
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rather than CO_2 levels, others argue that acidosis is a more valuable predictor of cranial hemorrhage than gas pressure in blood gases (2,3). Premature babies cannot maintain the intracranial vascular circulation balance. In these babies, the response of the vascular bed to the amount of blood CO_2 is inadequate (4). As a result of this physiological deficiency, blood gas fluctuations result in severe neurological morbidity. Given these different results in the literature (5,6), we wondered whether this relationship existed in our patient population. In this study, we aimed to investigate the potential relationship between CO_2 levels during the first 3 days and severe intraventricular hemorrhage (IVH) in preterm infants.

Material and Methods

All babies born at less than 30 weeks of gestation, with a birth weight between 750 and 1.250 g, who required respiratory support in the first hours of life and were admitted to the Neonatal Intensive Care Unit at Ankara Bilkent City Hospital between January 2020 and December 2022, were included in the study. Respiratory support was defined as the need for continuous positive airway pressure (CPAP) or mechanical ventilation. Early death, defined as death occurring within the first 3 days of life, congenital anomalies, or missing data were excluded from the analysis. The resuscitation history of the babies in the delivery room, birth weight, gestational age, whether they received surfactants, type of respiratory support, and the results of the first transfontanel ultrasonography were recorded.

We divided and compared the infants into two groups based on cranial ultrasound findings: the first group consisted of infants with grade 3 or 4 cranial bleeding, while the remaining infants formed the second group. Blood gas parameters, data on the first admission to the ward, and other blood gas values within the first 3 days were included in the study data. At least two different blood gas results were recorded per day. Because most of our patients had venous blood gas samples, partial venous carbon dioxide pressure (pCO_2) data in this study were generated by comparing only venous blood gases to avoid confusion. A small number of patients with only arterial and no venous blood gas samples were not included in the study.

Considering that >90% of intracranial hemorrhages in premature babies occur within the first 72 hours of life and that early CO_2 changes are also associated with this problem, we evaluated the relationship between the values in the first 72 hours and early ultrasonography results specifically for this study.

Data analyzed included the main prenatal and neonatal characteristics that have previously been shown to be associated with severe IVH (7), including birth weight, gestational age, preeclampsia, hypertension, premature prolonged rupture of membranes, antenatal steroid (ANS) use, histologic chorioamnionitis (8), 1- and 5-minute Apgar scores, use of nasal CPAP or nasal intermittent positive pressure ventilation, and use of invasive intermittent mechanical ventilation. In addition, data were collected on severe IVH [grades 3 and 4 parenchymal bleeding according to the classification described by Papile et al. (9)], and the infants were divided into two groups according to ultrasound findings. The highest and lowest pCO_2 values were determined from blood gas results obtained during the first 72 hours of life. Measures of pCO_2 dispersion for each patient, including the maximum to minimum range (difference in pCO_2), were calculated. Hypercapnia was defined as any pCO_2 level >65 mmHg within the first 3 days of life. Hypocapnia was defined as any pCO_2 35 mmHg. Normocapnia was defined as maintaining all pCO_2 levels between 35 and 64 mmHg during the first 3 days of life. pCO_2 fluctuation was defined as the difference between two consecutive pCO_2 measurements 6-h apart for each infant. The 6-h interval was selected empirically to assess relatively rapid changes in pCO_2 levels among patients. A difference of more than 20 mmHg between two consecutive pCO_2 levels was considered a prominent fluctuation.

Our hospital is one of the largest healthcare centers in Turkey, with a birth rate of over 15,000 deliveries per year. Our department has 150 neonatal intensive care unit (NICU) beds with all the facilities needed for preterm infant care, including cardiac surgery, extracorporeal membrane oxygenation, a cardiac angiography laboratory, laser intervention for prematurity retinopathy, and hemodialysis. At our facility, preterm infants are initially resuscitated in the delivery room with blended oxygen, commencing at a concentration of 30%, and adjusted according to pulse oximetry measurements. A T-piece resuscitator is used to administer CPAP or positive pressure ventilation. For surfactant use and indications, our department follows and complies with national guidelines (10). Subsequent doses of surfactant are administered based on the need for supplemental oxygen and high mean airway pressure on the ventilator. We use less-invasive surfactant applications when the infant is on non-invasive respiratory support and requires surfactant. Ventilator adjustments are based on blood gas measurements, which are typically performed every 6-12 hours unless there is an additional need for closer monitoring.

This retrospective study was approved by the Ethics Committee and Institutional Review Board no. 2 of Ankara Bilkent City Hospital, (decision number: E2-21-553, date: 02.06.2021).

Statistical Analysis

Descriptive statistics were computed using SPSS for Windows® version 22.0 (SPSS Inc., Chicago, IL). The data were presented as mean (± standard deviation), median (range), or frequency (percentage) as applicable. Continuous variables were analyzed using the t-test, non-parametric data were analyzed using the Mann-Whitney U test, and categorical variables were analyzed using the chi-square test for bivariate analysis of hypercapnia levels and fluctuations. A logistic regression model was used to investigate the relationship between pCO_2 fluctuations and the occurrence of severe IVH, adjusting for potential confounders such as gestational age, ANS administration, gender, 5-min Apgar score, and hypercapnia. Previous studies have identified higher gestational age and ANS use as factors linked to decreased risk of IVH (11). Additionally, the regression model accounted for the 5-min Apgar score and hypercapnia as an indicator of respiratory compromise. Statistical significance was determined using a p value threshold of <0.05.

Results

During the study period, a total of 483 babies were born in our hospital with a birth weight between 750 and 1.250 g and a gestational age of 30 weeks. Data for 427 babies were accessed, of which 22 died in the early period; data for 29 patients could not be accessed. The study data were created using the results and information from 376 patients. The median gestational age was 28 weeks (range 25-30), and the median birth weight was 910 g (range 750-1250). The baseline characteristics of the study population are summarized in Table 1.

Table 1. Demographic and clinical characteristics of the study population

Total number of infants	376
Gestational age, (weeks)*	28 (25-30)
Birthweight (grams)*	910 (750-1250)
Gender, male	191 (50)
Complete course of antenatal steroids	236 (62)
Cesarean section	244 (65)
Histologic chorioamnionitis	157 (42)
Apgar score of 5 min <5	75 (20)
Delivery room intubation	168 (44)
Number of blood gas samples during the first 72 h	10 (8-14)
Hypocapnia	169 (45)
Hypercapnia	86 (23)
Both hypocapnia and hypercapnia	56 (15)
pCO_2 fluctuation	105 (28)

**Median (minimum maximum) or n (%), pCO_2: Carbon dioxide pressure*

When we divided and compared the infants into two groups based on cranial ultrasound findings, one group comprised infants with grade 3 or 4 cranial bleeding, while the remaining infants comprised the control group. Significant differences were observed between these groups in terms of gestational age, ANS use, histologic chorioamnionitis, 5th-min Apgar score, hypocapnia, and CO_2 fluctuations (Table 2). After adjusting for gestational age and birth weight, logistic regression analysis revealed that ANS use, histologic chorioamnionitis, and CO_2 fluctuations were independent factors associated with intracranial hemorrhage (Table 3).

Discussion

Our study data supported the existence of a relationship between early fluctuations in CO_2 levels in blood gas and intracranial hemorrhage in premature infants. This study showed that very low and very high CO_2 levels were independently correlated with the severity of cranial hemorrhage, and fluctuations in CO_2 levels were associated with IVH.

Table 2. Factors associated with intracranial hemorrhage

Variable	Grade 3-4 IVH (n=58)	No and grade 1-2 (n=318)	p value
Gestational age in weeks*	27±1.5	28.2±2	<0.01
Birth weight, grams*	872±190	890±210	0.32
Antenatal steroids	23 (40)	213 (66)	<0.01
Histologic chorioamnionitis	34 (60)	123 (38)	<0.01
Apgar score @5 min <5	26 (45)	49 (15)	<0.01
Hypercapnia	18 (31)	68 (21)	0.107
Hypocapnia	39 (67)	130 (40)	<0.01
pCO_2 fluctuation	38 (65)	67 (21)	<0.01

**Mean ± SD, others n (%), IVH: Intraventricular hemorrhage, pCO_2: Carbon dioxide pressure, SD: Standard deviation*

Table 3. Logistic regression results of intracranial hemorrhage

Variable	Odds ratio	95% confidence interval	p value
Gestational age	0.8	0.62-1.02	0.06
Antenatal steroids	0.3	0.2-0.52	<0.01
Histologic chorioamnionitis	1.4	1.05-1.9	0.02
Apgar score @5 min <5	1.2	0.56-2.34	0.7
Hypocapnia	1.15	0.43-3.03	0.65
pCO_2 fluctuations	2.5	1.2-5.4	0.014

pCO_2: Carbon dioxide pressure

Previous studies on premature babies have revealed varying relationships between CO_2 levels and cranial pathologies. An association between periventricular leukomalacia and hypocarbia was previously demonstrated (12). Subsequent publications have emphasized the relationship between CO_2 fluctuations and IVH, highlighting the need to closely monitor blood CO_2 levels in preterm infants (13). Although a more recent study found no association between changes in blood gases and cranial hemorrhages in the NICU, the same data revealed a correlation between end-tidal CO_2 levels in the delivery room and IVHs (3).

Our team conducted a retrospective neurodevelopmental study on 230 premature babies, which revealed a relationship between very low and very high CO_2 levels in blood gases taken in the first days of life and neurodevelopmental disorders. A difference of >20 mmHg in pCO_2 measured in blood gases was also associated with abnormal motor skills in premature babies. In the multinomial logistic regression analysis of the same study's data, which included birth weight, gestational age, and duration of ventilator use, the risk of a ≥20 mmHg difference in pCO_2 values between the two blood gas samples and the risk of any developmental index being below 75 was found to be statistically significant [odds ratio: 4.64 (1.58-13.6 95% confidence interval), p=0.005] (14).

In the most comprehensive multicenter randomized controlled study conducted on this subject, targeting high CO_2 levels and maintaining them within normal limits were compared, and it was revealed that these two targets did not affect neurodevelopmental outcomes in premature babies (15).

In a study conducted by Altaany et al. (7), which is very similar to our research, it was concluded that there may be a relationship between fluctuations in CO_2 levels and cranial hemorrhages.

Study Limitations

Our study has some limitations. The first of these is that it was conducted retrospectively, and we do not yet have the long-term results of the patients. We could not determine the independent effects of early ventilation methods/modes applied to premature babies on blood gases. Additionally, we may not have included all factors that could contribute to cranial hemorrhage in the analysis. However, our patient sample size is sufficient, and the data we collected and accessed are reliable.

Conclusion

In conclusion, according to the results of this study, maintaining CO_2 levels within the normal range is extremely important for controlling intracranial hemorrhage in preterm infants. Planned prospective studies to examine the effects of different ventilation methods on CO_2 levels in premature babies will provide new insights into this subject.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Ethics Committee and Institutional Review Board no. 2 of Ankara Bilkent City Hospital, (decision number: E2-21-553, date: 02.06.2021).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: H.G.K.K., Concept: H.G.K.K., Data Collection or Processing: Ş.B.T., N.T., Analysis or Interpretation: F.E.C., Literature Search: G.K.Ş., Writing: B.S.B.

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