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Factors Associated with Neurodevelopmental Retardation in Preterm Infants: A Single-center Experience

Preterm Bebeklerde Nörogelişimsel Gerilik ile İlişkili Faktörler: Tek Merkez Deneyimi

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ABSTRACT

Objective: Today, the survival rate of low-birth-weight infants has increased thanks to supportive care. However, various permanent health problems, especially neurodevelopmental retardation, can be seen in these infants. This study investigates the risk factors associated with neurodevelopmental retardation, especially hypocarbia, in this patient group.

Methods: All patients who were hospitalized in our neonatal ıntensive care unit between January 1 and December 31, 2016, with a gestational age of less than 32 weeks, without congenital anomalies, and who came for regular follow-up were included in this study. Demographic, clinical and laboratory data were obtained retrospectively from file records. The neurodevelopment of the patients was evaluated between 18 and 24 months with the Bayley Scales of Infants and Toddler Development, Second Edition (Bayley-II).The demographic, clinical and laboratory parameters of the patients with and without neurodevelopmental retardation were compared.

Results: Neurodevelopmental retardation was observed in 9 (16.1%) of the 56 patients included in the study. No neurodevelopmental retardation was detected due to cerebral palsy, hearing impairment or visual impairment. When the patient groups with and without neurodevelopmental retardation were compared in terms of demographic, clinical and laboratory parameters, birth weight and first and fifth-minute Apgar scores were lower in patients with neurodevelopmental retardation, while mechanical ventilation requirement, reintubation, convulsion, patent ductus arteriosus treatment, hypotension, bronchopulmonary dysplasia, asphyxia, hyperglycemia and hypocarbia rate were higher ($p<0.05$).

Conclusion: While providing mechanical ventilation support, in addition to the negative effects of hypercarbia on neurodevelopment, the negative effects of hypocarbia on neurodevelopment should also be kept in mind.

Keywords: Bayley Scale, hypocarbia, infant, neurodevelopmental retardation, preterm

ÖZ

Amaç: Günümüzde yenidoğan bakımındaki gelişmeler sayesinde düşük doğum ağırlıklı bebeklerin hayatta kalma oranları artmıştır. Ancak bu bebeklerde başta nörogelişimsel gerilik olmak üzere çeşitli kalıcı sağlık sorunları görülebilmektedir. Bu çalışma, bu hasta grubunda başta hipokarbi olmak üzere nörogelişimsel gerilik ile ilişkili risk faktörlerini araştırmayı amaçlamaktadır.

Yöntem: 1 Ocak-31 Aralık 2016 tarihleri arasında yenidoğan yoğun bakım ünitemizde yatan, 32 haftadan küçük, doğumsal anomalisi olmayan ve düzenli takibe gelen tüm hastalar bu çalışmaya dahil edildi.

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Demografik, klinik ve laboratuvar verileri dosya kayıtlarından geriye dönük olarak elde edildi. Hastaların nörogelişimleri 18-24 ay (düzeltilmiş yaş) arasında Bayley Scales of Infants and Toddler Development, Second Edition (Bayley-II) ile değerlendirildi. Nörogelişimsel geriliği olan ve olmayan hastaların demografik, klinik ve laboratuvar parametreleri karşılaştırıldı.

Bulgular: Çalışmaya alınan 56 hastanın 9'unda (%16,1) nörogelişimsel gerilik gözlendi. Serebral palsi, işitme veya görme bozukluğuna bağlı nörogelişimsel gerilik saptanmadı. Nörogelişimsel geriliği olan ve olmayan hasta grupları demografik, klinik ve laboratuvar parametreleri açısından karşılaştırıldığında, nörogelişimsel geriliği olan hastalarda doğum ağırlığı ve birinci ve beşinci dakika Apgar skorları daha düşük iken mekanik ventilasyon gereksinimi, yeniden entübasyon, konvülziyon, patent duktus arteriosus tedavisi, hipotansiyon, bronkopulmoner displazi, asfiksi, hiperglisemi ve hipokarbi oranı yüksekti (p<0,05).

Sonuç: Mekanik ventilasyon desteği sağlanırken hiperkarbinin nörogelişim üzerindeki olumsuz etkilerinin yanı sıra hipokarbinin nörogelişim üzerindeki olumsuz etkileri de akılda tutulmalıdır.

Anahtar Kelimeler: Bayley Skoru, hipokarbi, yenidoğan, nörogelişimsel gerilik, prematüre

INTRODUCTION

Infants born prematurely have lower survival rates compared to term infants. Additionally, a significant proportion of survivors must struggle with some health problems throughout their lives.[1,2] In these infants in particular, intraventricular bleeding (IVB) and bronchopulmonary dysplasia (BPD) are common in the neonatal period, and neurodevelopmental retardation is common in later years.[3,4] These health problems increase exponentially, especially in very low-birth-weight preterm infants.[5] recently, survival rates have increased considerably with antenatal steroid treatment applied to the mothers of these patients before birth, surfactant treatment applied to infants after birth, and noninvasive mechanical ventilation support.[6] However, some undesirable results may occur due to these supportive treatments. Periventricular leukomalacia due to hypocarbia seen during mechanical ventilation support due to respiratory distress is one of these results.[7,8]

Very low-birth-weight infants in particular should be followed up for neurodevelopment. Patients with neurodevelopmental retardation in the early period benefit more from early intervention due to the high incidence of cerebral plasticity cases in the early period of life. The Bayley Scales of Infants and Toddler Development, Second Edition (Bayley-II), which is frequently used to evaluate the neurodevelopment of preterm infants, consists of cognitive, language and motor parameters.[9,10] In a study conducted in our country, it was reported that this scale has a sensitivity of 91% and a specificity of 49%.[11]

In this study, it was aimed to determine the risk factors associated with neurodevelopmental retardation, especially hypocarbia, by evaluating the neuromotor development of infants with a gestational age <32 weeks and treated and followed in our neonatal intensive care unit at 18-24 months (corrected age) with the Bayley-II test.

METHODS

All patients, who were hospitalized in the Neonatal Intensive Care Unit of the Health Sciences University, Dr. Behcet Uz Child Disease and Surgery Training and Research Hospital between January 1 and December 31, 2016, with a gestational age of less than 32 weeks, without congenital anomalies, and who came for regular follow-up were included in this study. Patients with congenital anomalies, without regular follow-ups, and where data were incomplete, were excluded from the study. The study was conducted with the approval of Dr. Behcet Uz Child Disease and Surgery Training and Research Hospital, dated 20.06.2019 and numbered 2019/300.

Demographic characteristics of patients such as antenatal steroid therapy, mode of delivery, gender, gestational age, birth weight, intrauterine growth retardation, clinical follow-up data such as the need for mechanical ventilation, Apgar score, Respiratory distress syndrome (RDS), surfactant therapy, phototherapy therapy, transfusion therapy, sepsis, apnea, presence of patent ductus arteriosus (PDA) requiring medical treatment, presence of convulsions, presence of hypotension requiring inotropes, necessity of reintubation, IVB, BPD and necrotizing enterocolitis (NEC) and laboratory findings such as C-reactive protein (CRP), hyperglycemia, hypocarbia, and asphyxia data were obtained retrospectively from the files of the patients.

A pCO_2 value of less than 40 mmHg in 2 consecutive capillary blood gases taken 6 h apart in the first 72 h after birth was considered hypocarbia. Low-birth-weight for age was defined as height or weight for age <-2 standard deviation (SD). Babies of mothers who received at least two doses of steroids at least 24 h before birth were considered to have received antenatal steroids.

The mental development index (MDI) and psychomotor development index (PDI) were measured by the developmental pediatrician with the Bayley Developmental Assessment Scale II for Infants, which was adapted to Turkish children at the age of 18-24 months (adjusted age). Additionally, all patients were examined by a pediatrician, and children with pathological neurological findings were evaluated by a pediatric neurologist. European guidelines were taken as reference for the diagnosis of cerebral palsy.[12] In the hearing and ophthalmological evaluations

made by otolaryngologists and ophthalmologists, the report of the British Society of Perinatal Medicine was taken as a reference for the definitions of vision and hearing disorders.[13] The presence of any following criterion was accepted as an indicator of neurodevelopmental retardation: cerebral palsy, hearing impairment, visual impairment, MDI or PDI score <70.[14]

Statistical Analysis

The Statistical Package for the Social Sciences 25.0 (IBM Corporation, Armonk, New York, United States) program was used in the analysis of the variables. The conformity of data to a normal distribution was evaluated with the Shapiro-Wilk test and homogeneity of variance was evaluated with the Levene test. The independent-samples t-test was used together with the Bootstrap results, while the Mann-Whitney U test was used together with the Monte Carlo results in the comparison of two independent groups according to the quantitative data. The Jonckheere-Terpstra test with the results of the Monte Carlo simulation technique was used to compare more than two groups with each other according to the quantitative data. In the comparison of categorical variables with each other, the Pearson chi-squared and Fisher exact tests were used together with the exact results, while the Fisher-Freeman-Holton test was used together with the Monte Carlo Simulation technique. Quantitative variables were shown as mean±SD and median (minimum/maximum), and categorical variables as n (%). Variables were analyzed at 95% confidence level and the p value was considered significant when it was <0.05.

RESULTS

It was wished to include 74 patients in the study. However, only 56 patients could be included in the study, since 6 of them had died during the follow-up, 3 of them had congenital anomalies, and 9 of them did not come for regular control. Of the patients, 26 (46.4%) were male and the gestational age of 33 (58.9%) patients was 29-32 weeks, while 23 (41.1%) were <28 weeks. Ten (17.9%) patients were delivered by vaginal delivery and 46 (82.1%) of them were delivered by emergency cesarean section. Birth weight was <1000 g in 13 patients (23.2%), 1001-1500 g in 31 (55.4%) and more than 1500 g in 12 (21.4%) patients. Neurodevelopmental retardation was observed in 9 (16.1%) patients. Neurodevelopmental retardation was not detected in any patient due to cerebral palsy, hearing impairment or visual impairment. The general characteristics of the patients are summarized in Table 1.

Patient groups with and without neurodevelopmental retardation were compared in terms of demographic, clinical and laboratory parameters. When the patients were compared in terms of demographic characteristics, the birth weight of the patients with neurodevelopmental retardation was lower (p<0.05).

Table 1. General characteristics of the patients

	n (%)
Gender (male)	26 (46.4)
Gestational age (week)	
29-32	33 (58.9)
<28	23 (41.1)
Mode of delivery	
Vaginal delivery	10 (17.9)
Emergency cesarean section	46 (82.1)
Birth-weight (g)	
<1000	13 (23.2)
1001-1500	31 (55.4)
>1500	12 (21.4)
Antenatal steroid therapy	32 (80.0)
IUGR	5 (8.9)
Apgar score 1st min*	5.65±1.73
Apgar score 5th min*	7.09±1.27
Mechanic ventilation	
CPAP	42 (75.0)
Intubated	14 (25.0)
RDS	32 (57.1)
IVH	18 (32.1)
Surfactant therapy	30 (53.6)
Apnea	45 (80.4)
Phototherapy	43 (76.8)
Sepsis	35 (62.5)
PDA treatment (medical)	16 (28.6)
Transfusion	39 (69.6)
Convulsion	4 (7.3)
Reintubation	11 (19.6)
BPD	9 (16.1)
NEC	1 (1.8)
Hypotension	8 (14.3)
Asphyxia	5 (8.9)
Hyperglycemia	5 (8.9)
Hypocarbia	30 (53.6)
Bayley MDI (<70)	5 (8.9)
Bayley PDI (<70)	6 (10.7)
Neurodevelopmental retardation	9 (16.1)

*Mean±standard deviation.

IUGR: Intrauterine growth retardation, RDS: Respiratory distress syndrome, IVH: Intraventricular hemorrhage, BPD: Bronchopulmonary dysplasia, NEC: Necrotizing enterocolitis, MDI: Mental development index, PDI: Psychomotor development index, PDA: Patent ductus arteriosus

When a comparison was made in terms of clinical findings, the first and fifth-minute Apgar scores of patients with neurodevelopmental delay were found to be lower, while the rate of patients receiving mechanical ventilation support, the rate of patients undergoing reintubation, the rate of patients with convulsions, the rate of patients receiving medical treatment for PDA treatment, and the rate of patients requiring inotropic therapy and the rate of patients with hypotension and the rate of patients with BPD were statistically significantly higher ($p<0.05$). In terms of laboratory findings, the rate of patients who developed asphyxia, hyperglycemia and hypocapnia in the patient group with neurodevelopmental retardation was statistically higher ($p<0.05$). There was no difference between the two groups in terms of gender, gestational age, mode of delivery, intrauterine growth retardation, antenatal steroid treatment, surfactant treatment, phototherapy treatment, blood transfusion, sepsis, apnea, IVB, RDS and NEC parameters ($p>0.05$) (Table 2).

DISCUSSION

In this study, it was shown that the development of hypocarbia in the early period (within the first 72 h after birth) in infants with a gestational age of <32 weeks is a risk factor for neurodevelopmental retardation. Additionally, as previously reported in the literature, low birth-weight, low Apgar score, the need for mechanical ventilation, the need for reintubation, asphyxia, convulsion, hypotension, hyperglycemia, the presence of PDA requiring medical treatment, and BPD were also associated with neurodevelopmental retardation in the current study.

In the study by Bulbul et al.[15], it was reported that cerebral palsy was seen in 11.5% of infants with a gestational age of <34 weeks, and when evaluated with the Bayley-III scale, 13% had cognitive retardation and 31% had neuromotor developmental retardation. In a meta-analysis by Pascal et al.[16], however, when low or very lowbirth-weight infants were evaluated at the corrected age of 2 years, it was reported that neurodevelopmental retardation was found in approximately 20.6% of them. In a review study by Palumbi et al.[17], it was reported that 32.4% of late preterm infants had retardation in language development. In the study by Agarwal et al.[18], neurodevelopmental retardation was found at a rate of 20% in very low-birth-weight infants around 2 years of age. However, none of the patients included in the current study developed cerebral palsy, nor had hearing or visual impairments. Neurodevelopmental retardation was found in 16% of the patients, consistent with the literature.

It has been reported that periventricular leukomalacia develops in infants who develop hypocarbia with early mechanical ventilation support applied to very low-birth-weight infants and who are exposed to hypocarbia for one hour.[7,8] In a study by Murase and Ishida[19], it was reported that periventricular leukomalacia developed due to hypocarbia in this group of patients, and cerebral palsy developed mostly in these patients in the follow-up. Thome et al.[20], however, reported that 16% of very low- birth-weight infants developed hypocarbia, and there was no difference

Table 2. Comparison of demographic, clinical and laboratory findings of patients with and without neurodevelopmental retardation

	Neurodevelopmental retardation		p
	Absent (n=47)	Present (n=9)	
Gender (male)	22 (46.8)	4 (44.4)	0.999[f]
Gestational age (week)**	30 (24/32)	27 (24/32)	0.119[u]
Birth-weight (g)*	1275±297	927±418	**0.026[t]**
Mode of delivery (caesarean section), n (%)	39 (83)	7 (77.8)	0.999
IUGR	3 (6.4)	2 (22.2)	0.178[f]
Antenatal steroid therapy, n (%)	27 (81.8)	5 (71.4)	0.336[fh]
Apgar score** 1st min 5th min	6 (1/9) 8 (5/10)	5 (1/6) 7 (3/7)	**0.003[u]** **0.006[u]**
Ventilator support	8 (17)	6 (66.7)	**0.005[f]**
Surfactant therapy, n (%)	25 (53.2)	5 (55.6)	0.999f
Phototherapy, n (%)	34 (72.3)	9 (100.0)	0.098f
Transfusion, n (%)	32 (68.1)	7 (77.8)	0.707f
Sepsis, n (%)	28 (59.6)	7 (77.8)	0.459f
Convulsion, n (%)	0 (0.0)	4 (44.4)	**<0.001[f]**
Hypotension, n (%)	4 (8.5)	4 (44.4)	**0.017[f]**
Hyperglycemia, n (%)	3 (6.4)	3 (33.3)	**0.046[f]**
Apnea, n (%)	28 (59.6)	2 (22.2)	0.066[f]
Asphyxia	2 (4.3)	3 (33,3)	**0.025[f]**
Reintubation	6 (12.8)	5 (55.6)	**0.010[f]**
PDA closure, n (%)	10 (21.3)	6 (66.7)	**0.012[f]**
Hypocarbia, n (%)	1 (3.8)	8 (26.7)	**0.029[f]**
IVB, n (%)	13 (27.7)	5 (55.6)	0.129[f]
RDS, n (%)	26 (55.3)	6 (66.7)	0.718[f]
BPD, n (%)	3 (6.4)	6 (66.7)	**<0.001[f]**
NEC, n (%)	1 (2.1)	0 (0.0)	0.999[f]

[P]Pearson chi-squared test (exact), [F]Fisher's exact test, [FH]Fisher-Freeman-Halton test (Monte Carlo), [T]Independent samples t-test (Bootstrap), [U]Mann-Whitney U test (Monte Carlo), [W]Wilcoxon signed-rank test (Monte Carlo).

**Median (minimum/maximum), *mean±standard deviation.

IUGR: Intrauterine growth retardation, RDS: Respiratory distress syndrome, IVB: Intraventricular bleeding, BPD: Bronchopulmonary dysplasia, NEK: Necrotizing enterocolitis, PDA: Patent ductus arteriosus

in neurodevelopment between patients with hypocarbia and normocarbic patients. In this study, it was determined that neurodevelopmental retardation was more common in infants who developed hypocarbia within the first 72 h after birth. To the best of our knowledge, no such data have been reported in the literature before.

Birth weight and gestational age play an important role in both survival and neurodevelopmental outcomes.[21] Additionally, it has been reported that the duration of mechanical ventilation support has a negative effect on neurodevelopment in low and very low-birth-weight infants.[1] In a study by Bulbul et al.[15], it was reported that birth-weight, gestational age, Apgar score, duration of oxygen therapy, duration of mechanical ventilation support, and need for resuscitation in the delivery room were associated with neuromotor development retardation in infants with a gestational age of <34 weeks. In a study by Zambrana et al.[22], however, an inverse correlation was reported between gestational age and cognitive retardation. Similar to the literature, low birth-weight, low Apgar score, asphyxia, the need for mechanical ventilation and the need for reintubation were associated with neurodevelopmental retardation in this study.

In a study by Asztalos et al.[23], BPD, NEC, and severe neurological damage were reported to be strongly associated with neurodevelopmental retardation. Similar to the literature, neurodevelopmental retardation was found to be more common in patients with BPD in the current study. However, no association was found between NEC and neurodevelopmental retardation. This is thought to be because we only had one patient who developed NEC.

In a study by Agarwal et al.[18], it was reported that there is a relationship between non-administration of antenatal steroids to the mother, male gender, the presence of hypotension requiring inotropes and cognitive neurodevelopment retardation. Wong et al.[24], however, reported no relationship between antenatal steroid use and neurodevelopmental retardation. In a meta-analysis by Sotiriadis et al.[25], it was reported that the use of steroids even once during the antenatal period helps prevent the development of neurodevelopmental retardation. Similar to the literature, a relationship between the presence of hypotension requiring inotropes and neurodevelopmental retardation was demonstrated in the current study. However, there was no relationship between antenatal steroid use and neurodevelopmental retardation. This difference is thought to be due to the small number of patients included in the study.

Gonzalez Villamizar et al.[26] Reported that the neurodevelopment of infants with a gestational age of <32 weeks, who had hyperglycemia after birth, was lagged. Gudmundsdottir et al.[27], however, reported that PDA increases the risk of neurodevelopmental retardation in very low-birth-weight infants, whether treated surgically or medically. In this study, in parallel with the literature, it was shown that there is a relationship between the presence of hyperglycemia in the neonatal period and the presence of PDA requiring medical treatment, and neurodevelopmental retardation.

Study Limitations

The study has some limitations. First, the findings cannot be generalized because the study was single-center. The second limitation is the small number of patients included in the study, while the third limitation is the retrospective nature of the study. It is thought that these limitations of the study will not change the results obtained.

CONCLUSION

In conclusion, currently, the rate of survival for low and very low-birth-weight infants is high thanks to supportive treatments such as antenatal steroid therapy, surfactant therapy, and mechanical ventilation support. However, a significant proportion of these patients have neurodevelopmental retardation compared to their peers. It is vital for normal neurodevelopment to protect those patients, who need respiratory support, especially in the early neonatal period, from hypocarbia and from hypercarbia.

Ethics

Ethics Committee Approval: The study was approved by the Dr. Behcet Uz Child Disease and Surgery Training and Research Hospital Local Ethics Committee (date: 23.05.2019, protocol no: 2019/300).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: R.Ç., M.K., Ş.Ç., T.G.Y., Design: R.Ç., M.K., Ş.Ç., T.G.Y., Data Collection or Processing: R.Ç., S.A.Ö., Analysis, or Interpretation: R.Ç., E.Y.E., Literature Search: R.Ç., E.Y.E., Writing: R.Ç.

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