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Relationship Between Early Respiratory Support and Neurodevelopment in Extremely Low Birth Weight Infants

Aşırı Düşük Doğum Ağırlıklı Bebeklerde Erken Dönem Solunum Desteğinin Nörogelişimsel Sonuçlarla İlişkisinin İncelenmesi

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ABSTRACT

Objective: This study investigated relationship between early respiratory support and neurodevelopmental outcomes in extremely low birth weight infants.

Methods: Our study included infants born before 32 weeks' gestation at a birth weight of 750-1000 g that were admitted to the neonatal intensive care unit and underwent a neurodevelopmental evaluation at the corrected age of 24 months. Two hundred-twelve infants were divided into 3 groups by determining the predominant type of respiratory support required in the first 3 days of life. Infants who received supplemental oxygen therapy group 1, those who received nasal continuous positive airway pressure and/or nasal intermittent mandatory ventilation were in group 2, and intubated infants were included in group 3. Differences between the groups and relationships between neurodevelopment scores [mental development index (MDI); psychomotor development index (PDI)] were examined.

Results: The patients mean birth weight was 887±73 g and mean gestational age was 27±1.9 weeks. MDI and PDI values were below 70 in the intubated patient group (68 and 66, respectively). Patients who received noninvasive ventilation or supplemental oxygen therapy for the first 3 days of life had significantly higher MDI and PDI values. In terms of morbidities of prematurity, intubated infants had higher rates of bronchopulmonary dysplasia, patent ductus arteriosus, intraventricular hemorrhage, and retinopathy of prematurity.

Conclusion: Restrictive invasive ventilation policies can be applied to preterm infants and may improve neurodevelopmental outcomes. The results of this study suggest that every additional day of invasive mechanical ventilation should be avoided if possible.

Keywords: Extremely low birth weight, mechanical ventilation, neurodevelopmental outcomes, prematurity

ÖZ

Amaç: Bu çalışmanın amacı aşırı düşük doğum ağırlıklı bebeklerde erken dönem solunum desteği ile nörogelişimsel sonuçların ilişkisini araştırmaktır.

Yöntem: Yenidoğan yoğun bakım ünitesinde yatmış, doğum ağırlığı 750-1000 gram arasında ve gebelik haftası 32 haftadan küçük, çalışma sırasında düzeltilmiş 24 aylık nörogelişim muayenesini 2018 Kasım ayı itibarı ile tamamlamış bebekler çalışmaya dahil edildi. İki yüz on iki bebeğin yaşamının ilk üç gününde hangi solunum desteğine ihtiyaç duyduğu belirlenerek üç ayrı grup oluşturuldu. Ağırlıklı serbest oksijen alan bebekler 1., nazal sürekli pozitif hava yolu basıncı ve/veya nazal aralıklı zorunlu ventilasyon alanlar 2., entübe izlenen bebekler ise 3. gruba alınarak gruplar karşılaştırıldı. Bu üç grup arasındaki farklar ve nörogelişim skorları [mental gelişim indeksi (MDI); psikomotor gelişim indeksi PDI)] arasındaki ilişkiler incelendi.

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Bulgular: Hastaların ortalama doğum ağırlığı, 887±73 gr, gebelik haftası 27±1,9 hafta idi. Mekanik ventilatörde entübe izlenen hastaların MDI ve PDI değerleri <70 idi (sırasıyla; 68, 66) idi. İlk üç günde ağırlıklı olarak non-invaziv modda veya serbest oksijen desteği ile takip edilen hastaların MDI ve PDI değerleri daha yüksek saptandı ve istatistiksel olarak anlamlı kabul edildi. Prematüre morbiditeleri açısından analiz edildiğinde ise entübe takip edilen grupta bronkopulmoner displazi, patent duktus arteriozus, intraventriküler hemoraji ve prematüre retinopatisi daha yüksek oranda bulundu.

Sonuç: Erken doğmuş bebeklerde kısıtlayıcı invaziv ventilasyon politikası uygulanabilir ve nörogelişimsel sonuçları iyileştirebilir. Bu çalışmanın sonuçları göz önüne alındığında; ilave her invaziv mekanik ventilasyon günü mümkün olduğunca önlenmelidir.

Anahtar Kelimeler: Aşırı düşük doğum ağırlığı, mekanik ventilasyon, nörogelişimsel sonuçlar, prematürelik

INTRODUCTION

Recent advances in perinatal and neonatal care have reduced mortality rates among high-risk newborns. Progress made in this area includes a more widespread use of antenatal steroids and the incorporation of surfactant into the current treatment approach in the late 1980s. However, it is irrefutable that while these advances reduce mortality, they also increase early and late morbidity rates.[1]

With increased morbidity, many factors were found to influence neurodevelopmental outcomes in long-term follow-up. In the literature, the prevalence of neurodevelopmental problems in preterm infants weighing less than 750 and 1500 grams has been reported as 50% and 10-20%, respectively, with birth weight and gestational age identified as the main factors determining neurodevelopmental outcomes.[2,3]

One cause of morbidity in low birth weight infants is respiratory support practices. The relationship between early respiratory support and neurodevelopmental outcomes is still unclear. Long-term mechanical ventilation has been associated with poor neurodevelopmental outcomes in previous studies. The use of noninvasive ventilation practices in preterm infants was reported to reduce neurodevelopmental impairment at the corrected age of 24 months.[4]

Considering these data, we aimed in this study to investigate the relationship between early respiratory support practices used and the neurodevelopmental outcomes of extremely low birth weight infants.

METHODS

The study included preterm infants who were born in our hospital at a gestational age of less than 32 weeks and birth weight of 750-1000 g, were monitored in our neonatal intensive care unit and underwent developmental assessment tests at the corrected age of 24 months. The patients' medical records were accessed using their Republic of Turkey identification numbers and hospital registration numbers, and pertinent maternal data related to antenatal follow-up such as a history of hypothyroidism, gestational diabetes, preeclampsia, assisted reproduction techniques, chronic disease, or drug use were recorded. A single course of antenatal steroid was defined as the administration of 2 doses of betamethasone to the mother at least 24 h before birth. Need for resuscitation at birth was recorded. The patients' medical data and treatment were analyzed retrospectively; methods of early respiratory support and parameters that may affect neurodevelopmental outcomes were recorded.

The patients were divided into 3 groups based on the predominant type of respiratory support received in the first 3 days (at least 48 of the first 72 h): Supplemental oxygen therapy (group 1); nasal continuous positive airway pressure and/or nasal intermittent mandatory ventilation (group 2); and intubation and mechanical ventilation (group 3).

Spontaneously breathing patients were stabilized in the delivery room and transferred to the neonatal intensive care unit with 6-8 cmH_2O positive end-expiratory pressure delivered by a T-piece device (Neopuff Infant Resuscitator; Fisher and Paykel, Auckland, NZ). For all patients in the study, a mechanical ventilator with both invasive and non-invasive modes was used (SLE 5000, London, UK). Non-invasive mode was used for spontaneously breathing patients supported with nasal continuous positive airway pressure or nasal intermittent mandatory ventilation without intubation, whereas invasive mode was used for patients who were intubated. A short binasal prong was used as the interface for patients who received non-invasive respiratory support.[5] Initial settings for nasal continuous positive airway pressure were defined as positive end-expiratory pressure: 5-8 cmH_2O and flow: 7-10 L/min. Initial settings for nasal intermittent mandatory ventilation were positive end-expiratory pressure: 5-6 cmH_2O, peak inspiratory pressure: 15-25 cmH_2O, inspiratory time <0.5 s, respiratory rate: 10-40/min, flow: 6-10 L/min. Fraction of inspired oxygen was monitored with target postductal oxygen saturation of 89-94% measured by pulse oximetry. Capillary measurements were used to monitor blood gas parameters, thus minimizing iatrogenic blood loss. Failure criteria for noninvasive respiratory support were blood gas findings of pH <7.2 and $PaCO_2$ ≥60 mmHg (respiratory acidosis), 3 or more instances of bradycardia or desaturation or 1 episode of apnea requiring positive pressure support by bag valve mask in the previous 1-2 h,

and requiring fraction of inspired oxygen more than 40% and respiratory rate >70/min to maintain target saturation. Patients receiving noninvasive respiratory support were intubated if they met at least one of these failure criteria despite mechanical ventilator settings being adjusted to the maximum level in the previous 12 h. Volume-targeted ventilation (4-6 mL/kg) was preferred for infants who required intubation for stabilization or failed nasal continuous positive airway pressure/nasal intermittent mandatory ventilation. Mechanical ventilation parameters were adjusted based on clinical follow-up and blood gas results.

Chest X-rays were obtained for every patient included in the study and were repeated during follow-up for patients who had apnea requiring positive pressure ventilation, were intubated, had more than 50% increase in the required fraction of inspired oxygen, or had suspected air leak. Patients who required surfactant according to radiological and clinical findings were diagnosed with respiratory distress syndrome. Turkish Neonatal Society guidelines were used to manage respiratory distress syndrome and assess the need for surfactant.[6] Surfactant was administered endotracheally to patients who required intubation in the delivery room and using less invasive surfactant administration, Take Care, or INtubate, SURfactant, Extubate methods to patients who received noninvasive support.[7] Patients in our study received one of two different surfactant preparations, either poractant alfa (Curosurf, Chiesi, Parma, Italy) or beractant (Survanta, Abbott Laboratories, Chicago, IL, USA). As per recommendations, the initial surfactant dose was 200 mg/kg poractant alfa or 100 mg/kg beractant. If the fraction of inspired oxygen required for target saturation exceeded 40% during the follow-up, a second dose (100 mg/kg) of surfactant was administered after at least 6 h.

Apnea of prematurity was defined as the cessation of breathing that lasted longer than 20 seconds or shorter cessation of breathing accompanied by bradycardia and/or low saturation. In the first hours of life, all infants were administered caffeine citrate intravenously as prophylaxis. A loading dose of 20 mg/kg for 24 h was followed by a maintenance dose of 5 mg/kg/day.

During the follow-up, all patients underwent regular ultrasound examination performed by an experienced pediatric radiologist. All patients were evaluated by the same physician during follow-up for the presence of intraventricular hemorrhage (according to Papile staging criteria) and periventricular leukomalacia status was recorded. In echocardiography performed by a pediatric cardiologist, ductus diameter >1.4 mm/kg and left atrium-to-aorta ratio >1.4 mm were considered hemodynamically significant patent ductus arteriosus and pharmacological therapy was initiated. If the clinical findings persisted after two courses of pharmacotherapy, surgical ligation was planned. Patients who were classified as having mild, moderate, and severe bronchopulmonary dysplasia according to the diagnostic criteria, received medical treatment, and were discharged with a mechanical ventilator or oxygen concentrator were noted. Proven sepsis was defined as clinical findings of sepsis with positive blood culture. All patients were screened for retinopathy of prematurity. The first was examined by experienced ophthalmologists at the corrected age of 31 weeks for patients born before 27 weeks of gestation and at postnatal week 4 for patients born after 27 weeks of gestation. Patients who had retinopathy and underwent laser photocoagulation was recorded.

During the study period (July 2016-November 2018), patients were examined by a developmental pediatrician and child development specialists in the developmental pediatric outpatient clinic when they reached the corrected age of 24 months. Using the Bayley Scales of Infant and Toddler Development, 2nd edition, the patients' mental and psychomotor development were evaluated. Mental development index and/or psychomotor development index values below 70 was neurodevelopmental impairment.[8] Periodic hearing screening and vision examinations were also performed. Patients who had a major congenital anomaly or history of perinatal hypoxia, or were small for gestational age were excluded from the study. Study protocol was approved by the Zekai Tahir Burak Women's Health Training and Research Hospital Ethical Committee and ethical approval obtained (protocol no: 24/2018, date: 29.05.2018).

Statistical Analysis

All data used in the study were transferred to computer and analyzed retrospectively using Statistical Package for the Social Sciences (SPSS®) version 22.0 software. Collected data were entered into the SPSS software and the differences in mental development index and psychomotor development index values between the different respiratory support groups were analyzed using one-way ANOVA. Categorical variables were compared using chi-square test; continuous variables were compared using t-test. Relationships between neurodevelopmental impairment and gestational age, birth weight, and the predominant type of respiratory support within the first 3 days of life were evaluated using multinominal logistic regression analysis. The infants were classified as having good or poor neurodevelopment and compared based on risk factors. Risk factors that were significant according to the chi-square test were included in the logistic regression analysis.

RESULTS

In this study we evaluated the neurodevelopmental data of 240 patients who were born in our hospital between July 2016 and November 2018 at less than 32 weeks of gestation and a birth weight of 750-1000 g and had reached a corrected age of 24 months by November 2018. After excluding patients whose family did not provide consent, those who had congenital anomaly, and those with morbidities requiring surgery, the study included 212 patients. The patients' mean birth weight was 887±73 g and mean gestational age was 27±1.9 weeks. Cesarean section was the most common mode of delivery in all three patient groups. The rate of antenatal steroid administration was similar between the groups. The surfactant requirement was more common (86%) among patients who received invasive ventilator support. Mental development index and psychomotor development index values were below 70 in the intubated patient group (68 and 66, respectively). The patients who received noninvasive ventilation or supplemental oxygen therapy also had mental development index and psychomotor development index values below 70 but significantly higher psychomotor development index value. In terms of preterm morbidities, patients who were intubated had significantly higher rates of bronchopulmonary dysplasia, patent ductus arteriosus, intraventricular hemorrhage, and retinopathy of prematurity (Table 1).

Comparison based on the presence or absence of neurodevelopmental impairment showed that lower birth weight and a longer duration of invasive mechanical ventilation were correlated with neurodevelopmental impairment. Patients who received predominantly noninvasive ventilation for the first 3 days of life had higher mental development index and psychomotor development index values. The prevalence of bronchopulmonary dysplasia was higher among patients with neurodevelopmental impairment. Patients with and without neurodevelopmental impairment were similar in terms of postnatal steroid use (Table 2).

DISCUSSION

Despite the increased use of noninvasive respiratory support, preterm infants require invasive mechanical ventilation at some point in their lives. Approximately 65% of preterm infants with a birth weight less than 1500 g is supported with invasive mechanical ventilation during admission to the neonatal intensive care unit and/or in the delivery room.[9] Physicians should be aware that mechanical ventilation, which is a preferred method when providing ventilator support, leads to severe neurodevelopmental consequences in this sensitive patient population.

Table 1. Demographic characteristics of patients

	Total cohort (n=212)			p value
	Supplemental oxygen therapy (n=62)	Non-invasive mechanical ventilation (n=78)	Invasive mechanical ventilation (n=72)	
Gestational age, weeks±SD	27.2±2	27.6±1.9	27.1±2	0.137*
Birth weight, g±SD	891±73	905±70	863±75	0.281*
Any antenatal steroids, n (%)	47 (76)	57 (74)	56 (78)	0.452#
PPROM, n (%)	10 (13)	11 (15)	9 (12)	0.729#
Chorioamnionitis, n (%)	5 (8)	8 (10)	8 (11)	0.833
C/S, n (%)	46 (75)	62 (80)	50 (70)	0.368
Male gender, n (%)	32 (51)	39 (50)	36 (50)	0.977
Surfactant, n (%)	45 (72)	60 (76)	62 (86)	0.142
PDA, n (%)	41 (67)	54 (70)	52 (72)	0.747
BPD¥, n (%)	20 (32)	27 (35)	29 (40)	0.602
Postnatal steroids, n (%)	19 (30)	25 (32)	28 (39)	0.545
Grade 3-4 IVH, n (%)	8 (12)	8 (10)	10 (13)	0.781
Sepsis, n (%)	15 (24)	18 (23)	20 (27)	0.789
ROP, need laser n (%)	5 (8)	8 (10)	9 (12.5)	0.702
MDI, median IQR	74 (30)		68 (27)	0.283$
PDI, median IQR	78 (28)		66 (28)	0.001$

*ANOVA; #chi-square; $non-parametric test; ¥moderate and severe only; sepsis, late onset and proven only.

PPROM: Preterm premature rupture of membranes, C/S: Caesarean section, PDA: Patent ductus arteriosus, BPD: Bronchopulmonary dysplasia, IVH: Intraventricular hemorrhage, ROP: Retinopathy of premature, MDI: Mental development index, PDI: Psychomotor development index, SD: Standard deviation

Table 2. Comparison of neurodevelopmental outcomes			
	NDI score >70 (n=172)	**NDI score <70 (n=40)**	**p value**
Gestational age, weeks±SD	27.1±2.2	27.2±2.1	0.454*
Birth weight, g±SD	915±76	878±70	0.001*
Resuscitation in delivery room, n (%)	38 (22)	8 (20)	0.772
Surfactant, n (%)	137 (79)	30 (75)	0.517
Caffeine, n (%)	172 (100)	40 (100)	-
Intubation in delivery room, n (%)	65 (38)	15 (37)	0.972
Duration of intubation, <24 h, n (%)	130 (81)	8 (20)	0.001
Duration of intubation, >72 h, n (%)	40 (23)	32 (80)	0.001
nCPAP/nIMV, n (%)	130 (75)	5 (12.5)	0.001
Supplemental oxygen therapy, n (%)	58 (33)	4 (10)	0.002
Duration of mechanical ventilation, hour±SD	9.5±17	12.4±22	0.338*
Moderate/severe BPD, n (%)	46 (27)	30 (75)	0.001
Any antenatal steroids, n (%)	131 (76)	29 (72.5)	0.627
Postnatal steroids, n (%)	47 (27)	25 (62.5)	0.0023

*Student's t-test.

NDI: Neurodevelopmental impairment, nCPAP: Nasal continuous positive airway pressure, nIMV: *Nasal* intermittent *mandatory* ventilation, BPD: Bronchopulmonary dysplasia, SD: Standard deviation

The results of our study indicate that treating extremely low birth weight preterm infants with invasive mechanical ventilation during the first 3 days of life is associated with poor neurodevelopmental outcomes. We can conclude that these infants have a poorer neurodevelopmental course. Invasive mechanical ventilation increases rates of sepsis, other neonatal infections, and bronchopulmonary dysplasia in very low birth weight preterm infants. To reduce these morbidities, providing respiratory support to low birth weight preterm infants using non-invasive methods has been recommended recently based on strong evidence.

Studies have demonstrated that this newly advocated noninvasive mechanical ventilation policy is feasible.[10] Our results follow studies analyzing long-term neurodevelopmental outcomes following non-invasive ventilation.[4]

In another study conducted in Turkey, low birth weight and longer duration of ventilation were found to be independent risk factors for neurodevelopmental impairment, which is a finding that supports our study.[11]

Walsh et al.[12] studied the effect of the duration of invasive mechanical ventilation on neurodevelopmental impairment outcomes of 3041 patients born in 1995-1998 at a birth weight of 500-1000 g. They determined that the entire patient cohort received invasive mechanical ventilation support for a mean of 18 days, while the surviving babies at the corrected age of 18 months had a mean invasive mechanical ventilation duration of 23 days. They concluded based on their findings that mechanical ventilation duration is an important risk factor for neurodevelopmental impairment (Odds ratio: 1.18, 95% confidence interval: 1.14-1.22). Respiratory support policies for preterm infants have changed dramatically in the 20 years since that study. Studies indicate that restrictions to the use of invasive mechanical ventilation have improved the long-term outcomes of preterm infants.[13,14] However, it is still unclear how such an approach affects the relationship between invasive mechanical ventilation and neurodevelopmental impairment. Several hypotheses can be put forth on this subject. First, invasive mechanical ventilation may be an indicator of disease severity. It is conceivable that invasive mechanical ventilation is needed by the most critical patients, who have the highest risk of adverse neurodevelopmental outcomes.[15] Second, patients who are intubated and subjected to invasive mechanical ventilation are at risk of hypocarbia (pCO_2 less than 35 mmHg), which correlates with periventricular leukomalacia and neurodevelopmental impairment.[16]

In our study, mechanical ventilation duration was longer in the neurodevelopmental impairment group than in the group without neurodevelopmental impairment, though the difference was not statistically significant. Even if this increase in invasive mechanical ventilation duration was not statistically significant, our study indicates that there is still a relationship between the duration of invasive mechanical ventilation and unfavorable neurodevelopmental outcomes.

Studies have shown that changes in the ventilation approach used in delivery room practices may impact postnatal mechanical ventilation requirement and long-term outcomes.[17] A comparison of neurodevelopmental outcomes of a patient group with similar characteristics after 5 years revealed better neurodevelopmental outcomes in patients treated with less invasive methods.[18] We also found that patients intubated in the delivery room had poorer neurodevelopmental outcomes.

Bronchopulmonary dysplasia is also known to be associated with unfavorable neurodevelopmental outcomes.[19,20] In this study, the prevalence of bronchopulmonary dysplasia and dysplasia related adverse neurodevelopmental outcomes were consistent with the literature. Meta-analyses on postnatal steroid therapy have indicated a higher risk of neurodevelopmental impairment.[21-23] However, although no difference in postnatal steroid use was found between patients with and without neurodevelopmental impairment in this study, this should not be interpreted as postnatal steroids lacking effect on neurodevelopment.

Study Limitations

This study has certain limitations. Retrospective data collection and our inability to analyze different parameters might have limited the quality of evidence. Because detailed information regarding some factors that affect neurodevelopmental outcomes could not be obtained, they could not be included in the statistical analysis. A consequence of the retrospective study design is that we could not use the Bayley Scales of Infant and Toddler Development, 3rd edition, which has since been introduced. Considering this, we may have determined lower mental development index and psychomotor development index values for the patients than what current assessment scales would yield.[24]

However, as our center is a maternity hospital, the large number of premature infants seen within 2 years was an important contribution to our study. Strengths of our study are that the patients were followed up at a single center and the institutional preference of similar respiratory support strategies established a standard for the analysis of neurodevelopmental disorders.

CONCLUSION

In conclusion, for preterm infants who receive invasive ventilator support, each additional day adversely affects their neurodevelopmental parameters. Transition to noninvasive ventilation should be the therapeutic goal for intubated infants. Restrictions to invasive mechanical ventilation practices may improve neurodevelopmental outcomes. Prospective studies on this subject will provide more reliable data and facilitate the development of recommendations with higher levels of evidence.

Ethics

Ethics Committee Approval: Study protocol was approved by the Zekai Tahir Burak Women's Health Training and Research Hospital Ethical Committee and ethical approval obtained (protocol no: 24/2018, date: 29.05.2018).

Informed Consent: This is a retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: H.G.K.K., Z.Ü., F.E.C., Design: Z.Ü., F.E.C., Data Collection or Processing: E.B., G.K.Ş., M.K.K., M.B., Analysis or Interpretation: Z.Ü., F.E.C., Literature Search: E.B., G.K.Ş., M.K.K., M.B., Writing: E.B.

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