ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Association of Delayed Vitamin D Supplementation and Low Thyroxine Levels with Bronchopulmonary Dysplasia Severity in Preterm Infants

Prematüre Bebeklerde D Vitamini Takviyesinin Gecikmesi ve Düşük Tiroid Hormon Seviyelerinin Bronkopulmoner Displazi Şiddetiyle İlişkisi

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Abstract

Introduction: The development of bronchopulmonary dysplasia (BPD) is multifactorial, and the extent to which individual risk factors influence its development may vary. The aim of this study is to analyse the risk factors for BPD and to determine preventive future approaches for them.

Materials and Methods: This study was conducted on newborns with a gestational age ≤32 weeks. admitted to the neonatal intensive care unit, Antenatal, natal, and postnatal risk factors for premature infants were evaluated by collecting data from patient files using a retrospective cross-sectional descriptive study method.

Results: According to the inclusion criteria, 539 patients were included in the study. BPD was detected in 172 patients (31.9%) at any stage (mild-moderate-severe). Low gestational age, low birth weight, delayed transition to enteral feeding, low free thyroxine levels, delayed initiation of vitamin D supplementation, erythrocyte transfusion and counts, and prolonged respiratory support durationwere found to be risk factors for BPD development ($p<0.05$). According to the results of the multivariate logistic regression analysis, the day of oxygen restriction [odds ratio (OR), 1.332; 95% confidence interval (CI) 1.064–1.667, $p=0.012$] and red blood cell transfusion (OR 41.865, 95% CI 1.337–1310.596, $p=0.034$) were found to be independent risk factors for BPD.

Conclusion: In our study, oxygen support period and erythrocyte transfusion may independent risk factors for BPD development. Additionally, as a significant new finding, we determined that low free thyroxine levels and delayed initiation of vitamin D supplementation may be related to the severity of BPD.

Öz

Giriş: Bronkopulmoner displazinin (BPD) gelişimi çok faktörlüdür ve bireysel risk faktörlerinin gelişimini etkileme derecesi değişebilir. Bu çalışmanın amacı, BPD için risk faktörlerini analiz etmek ve bunlar için gelecekteki önleyici yaklaşımları belirlemektir.

Gereç ve Yöntem: Bu çalışma, gebelik yaşı ≤32 hafta olan ve yenidoğan yoğun bakım ünitesine yatırılan yenidoğanlar üzerinde gerçekleştirilmiş olup, prematüre bebekler için doğum öncesi, doğum sırası ve doğum sonrası risk faktörleri, retrospektif kesitsel tanımlayıcı çalışma yöntemi kullanılarak hasta dosyalarından veri toplanarak değerlendirilmiştir.

Keywords
Bronchopulmonary dysplasia, prematurity, risk factors, vitamin D, free thyroxine

Anahtar kelimeler
bronkopulmoner displazi, prematürite, risk faktörleri, D vitamini, serbest tiroksin

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Bulgular: Dahil edilme kriterlerine göre, çalışmaya 539 hasta dahil edildi. BPD, herhangi bir evrede (hafif, orta, şiddetli) 172 hastada (%31,9) tespit edildi. Düşük gebelik yaşı, düşük doğum ağırlığı, enteral beslenmeye geçişin gecikmesi, düşük serbest tiroksin seviyeleri, D vitamini takviyesinin gecikmeli başlatılması, eritrosit transfüzyonu ve sayımları ve uzun süreli solunum desteği süresi, BPD gelişimi için risk faktörleri olarak bulundu (p<0,05). Çok değişkenli lojistik regresyon analizinin sonuçlarına göre, oksijen kısıtlamasının uygulandığı gün [olasılık oranı (OR), 1,332; %95 güven aralığı (CI) 1,064–1,667, p=0,012] ve kırmızı kan hücresi transfüzyonu (OR 41,865, %95 CI 1,337–1310,596, p=0,034) BPD için bağımsız risk faktörleri olarak bulundu.
Sonuç: Çalışmamızda, oksijen desteği süresi ve eritrosit transfüzyonu, bronkopulmoner displazi (BPD) gelişimi için bağımsız risk faktörleri olabileceği belirlenmiştir. Ayrıca, önemli yeni bir bulgu olarak, düşük serbest tiroksin seviyelerinin ve D vitamini takviyesine geç başlanmasının BPD'nin şiddetiyle ilişkili olabileceğini tespit ettik.

Introduction

Northway and colleagues were the first to observe bronchopulmonary dysplasia (BPD) approximately half a century ago. BPD has been defined as a chronic lung disease resulting in pulmonary fibrosis following mechanical ventilation treatment due to respiratory distress in a relatively larger number of premature infants (1). In time, with the development of treatment strategies aimed at reducing respiratory distress and premature morbidity, smaller premature babies are able to survive. A new clinical presentation is emerging in the alveolar and pulmonary vascular structures of smaller preterm infants due to impaired extrauterine development. Chronic respiratory failure in small preterm infants is currently defined as "New BPD." According to current guidelines, premature infants born before 32 weeks of gestation who require respiratory support by the time they reach the postmenstrual corrected 36th week are diagnosed with BPD at different stages (2).

The maturation of the pulmonary system in premature infants continues even after birth (2). The pathogenesis of BPD in preterm infants involves an inflammatory cascade that leads to impaired alveolarization and abnormal angiogenesis during lung development (3). During the extrauterine pulmonary development period oxygen, invasive respiratory support and numerous prenatal and postnatal factors may increase the risk of BPD development. Nevertheless, the most important known risk factors for BPD development are low gestational age and weight at birth (1). The presence of genetic and environmental factors in the development of BPD in preterm infants can further complicate the pathophysiology. The degree of severity of the effects of all other additional risk factors on BPD development may vary between neonatal intensive care units and over time (3).

BPD is the most significant respiratory morbidity in premature infants and methods developed to reduce BPD are primarily based on identifying risk factors, followed by reducing these risk factors and implementing preventive approaches (3,4). Therefore, identifying BPD risk factors is crucial to help prevent BPD (5). There is still a need for current research on the pathophysiology, risk factors and treatment of BPD. As the influence of BPD risk factors differs across neonatal units, ongoing evaluation of changes in these risk patterns over time is necessary (2,6,7).

According to our study hypothesis, identifying BPD risk factors in premature infants in our unit may enable us to develop preventive and therapeutic approaches for potential BPD risk factors in the future. This can lead to improved quality of care for premature infants and a reduction in the severity or frequency of BPD and improved quality of life. Our study aimed to facilitate clinical decision-making by identifying prenatal, natal, and postnatal BPD risk factors in preterm infants born at ≤32 weeks of gestation, enabling early prediction and prevention of BPD.

Materials and Methods

Design and Participants

This study was conducted on premature newborns with a gestational age ≤32 weeks who were admitted to the Neonatal Intensive Care Unit at Ankara Bilkent City Hospital Children's Hospital and Women's Hospital of Health Sciences University between September 1, 2019, and December 31, 2020. The data from our study population were evaluated using a retrospective cross-sectional descriptive study method to identify antenatal, natal, and postnatal risk factors for BPD. Newborns with a gestational age >32 weeks and those with major congenital anomalies were excluded from the study. The criterion of oxygen support requirement on postnatal 28th day was used for staging the severity of BPD in the neonatal period. Therefore, patients born at ≤32 weeks gestation and lost within the first 28 days were excluded from the study.

Ethical approval was obtained before the study commenced from the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Ankara Bilkent City Hospital, Hospital (decision no. E2-21-364, date: 07.04.2021).

The study process was performed by the researchers in accordance with the Helsinki principles.

Demographic and Clinical Characteristics

Patient data were obtained from patient files and the hospital-based electronic data system. The patients' prenatal, natal, and postnatal history, demographic data laboratory results, and treatments were recorded for the study. Patients' gestational age at birth, birth weight, sex, maternal age, preeclampsia, gestational diabetes mellitus, multiple pregnancy, antenatal steroids, chorioamnionitis, mode of delivery, 1. and 5. minute Apgar scores, clinical risk ındex for babies (CRIB) II score, score for neonatal acute physiology perinatal extension (SNAP-PE) II score, delivery room resuscitation (positive pressure ventilation or intubation or cardiac compression), time to start vitamin D supplementation, free thyroxine (fT4) levels, thyroid-stimulating hormone (TSH) levels, time to transition to full enteral feeding, early neonatal sepsis (within the first 3 days of birth) late-onset neonatal sepsis (after the first 3 days), respiratory distress syndrome (RDS), hemodynamically significant patent ductus arteriosus (PDA) requiring medical treatment, (stage ≥2) necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), severe (≥stage 3) intraventricular hemorrhage (IVH), need for erythrocyte transfusion, number of erythrocyte transfusions, total noninvasive ventilation time, mechanical ventilation time, oxygen support time, length of stay, and mortality data were recorded. Vitamin D was administered orally at a dose of 1200 IU/day for each infant. In all our study patients, fT4 and TSH levels were assessed on the 10th postnatal day as a standard procedure. Both early and late neonatal sepsis were defined as sepsis in patients with culture-positive and clinical sepsis. RDS was defined for patients with surfactant deficiency who received surfactant. According to our unit transfusion policy, all erythrocyte transfusions are administered at a dose of 10 ml/kg. Patients were grouped as having no BPD, mild, moderate, and severe BPD and were compared in terms of demographic and clinical characteristics.

Bronchopulmonary Dysplasia Classification

BPD classification is performed for preterm infants born before 32 weeks of gestation at 36 weeks postmenstrual (PM) or at the time of hospital discharge. Premature infants must have received at minimum 21% oxygen support therapy for the first 28 days to be discharged or, if not receiving oxygen support at 36 weeks gestational age, have mild BPD, if the patient requires <30% oxygen support, it is classified as moderate BPD and if the patient requires ≥30% oxygen support or positive pressure ventilation support, it is classified as severe BPD (2).

Statistical Analysis

The number (n) and percentage (%) values were used to show the distribution of the individuals in the demographic information. The normality of the continuous variables included in the study was assessed graphically and using the Shapiro-Wilk test. Median (minimum-maximum) values were used in the presentation of descriptive statistics. According to the BPD status, cross-tables were created for the comparison of categorical variables, and the number (n), percentage (%), and chi-square (χ^2) test statistic were given. Kruskal-Wallis was used to compare continuous variables according to BPD status. Analysis results were presented with Bonferroni correction for paired comparisons. Potential risk factors may be associated with BPD were examined using multivariate logistic regression analyses. Results are presented as odds ratios (Exp (B)] and 95% confidence intervals. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MS-Excel 2007 software was used for statistical analyses and calculations. Statistical significance was defined as $p<0.05$.

Results

A total of 687 preterm infants born at ≤32 weeks gestation during the study period were reviewed. Since patients must survive for at least 28 days to receive a BPD diagnosis, 148 patients who died before the first 28 days were excluded from the study, and statistical analysis was performed on 539 patients.

BPD was not detected in 68.1% (n=367) of the total 539 patients, while it was detected in 31.9% (n=172) at any stage. Of the 172 patients with BPD, 12.6% (n=68) had mild BPD, 9.3% (n=50) had moderate BPD, and 10.0% (n=54) had severe BPD. The prevalence of BPD at any stage was found to be 31.9% (n=172). Of the patients 42.7% (n=220) were female and 57.3% (n=319) male gender. The mean gestational age was determined to be 29.7±2.4 weeks.

There was no significant difference between genders according to BPD stages. BPD severity increased significantly as birth weight and gestational age decreased among groups with birth week ≤28 weeks and >28-32 weeks, and birth weight ≤750 g, 750-1000 g, 1000-1500 g, and >1500 g (Table 1).

Table 1. Comparison of gender, gestational age, and birth weight according to bronchopulmonary dysplasia classification

Variables	Bronchopulmonary dysplasia				p
	None (n=367)	Mild (n=68)	Moderate (n=50)	Severe (n=54)	
	n (%)	n (%)	n (%)	n (%)	
Gender					
Female	166 (45.2)	24 (35.3)	20 (40.0)	23 (43.4)	0.481
Male	201 (54.8)	44 (64.7)	30 (60.0)	31 (56.6)	
Gestational age					
≤28 weeks	51 (13.7)	30 (44.1)	33 (66.0)	36 (66.7)	<0.001*
>28-32 weeks	316 (86.3)	39 (55.9)	17 (34.0)	18 (33.3)	
Birth weight					
≤750 g	9 (2.5)	9 (13.2)	7 (14.0)	14 (25.9)	<0.001*
750-1000 g	28 (7.7)	4 (5.9)	10 (20.0)	14 (25.9)	
>1000-1500 g	117 (32.0)	35 (51.5)	22 (44.0)	21 (38.9)	
>1500 g	213 (57.8)	21 (29.4)	11 (22.0)	5 (9.3	

*Statistically significant p values are highlighted

There were no significant differences between groups in terms of maternal age, preeclampsia, gestational diabetes mellitus, multiple pregnancy, antenatal steroids, chorioamnionitis, cesarean delivery, and TSH levels according to BPD stages (p>0.05). The CRIB II score, SNAP-PE II score, delivery room resuscitation rates, day of starting vitamin D, and transition to full enteral feeding day were found to increase in direct proportion to BPD severity, while the 1. and 5. minute Apgar scores and fT4 levels decreased significantly as BPD severity increased (p<0.05) (Table 2).

Early and late neonatal sepsis, RDS, PDA, NEC, ROP, erythrocyte transfusion frequency, number of erythrocyte transfusions, noninvasive ventilation duration, mechanical ventilation duration, oxygen support duration, and length of stay were found to be significantly increased with BPD severity (p<0.05). Mortality rates were significantly lower in the mild and moderate BPD group compared to the severe and non-BPD group (p=0.001). No significant difference was found between the groups in the frequency of intraventricular hemorrhage (p>0.05) (Table 3).

Logistic regression analysis was performed by controlling for gestational age and birth weight risk factors independently may be associated with an increase in BPD rate. Multivariate logistic regression analysis revealed that the risk of BPD increased by 1.332 times as oxygen support duration increased and by 41.865 times with erythrocyte transfusion (p=0.012 and p=0.034, respectively) (Table 4).

Discussion

In our study analyzing premature infants born at ≤32 weeks gestation, we found that the incidence and severity of BPD increased with gestational age. We observed that increasing BPD severity may be associated with lower Apgar scores and significantly higher CRIB II and SNAP-PE II scores. Increased BPD severity may be associated with increased frequency of other preterm morbidities, excluding IVH. Our findings suggest that low fT4 levels and delayed starting of vitamin D supplementation may be associated with the development of severe BPD. In addition, based on our results following regression analysis, we may state that the primary risk factors for BPD development are the duration of oxygen support and erythrocyte transfusion.

BPD is a common complication of preterm birth and is associated with serious short- and long-term complications (8). BPD is one of the morbidities of prematurity that can cause long-term, destructive consequences in premature infants, affecting multiple organ systems, including adverse effects on lung function and neurodevelopmental outcomes (9).

Table 2. Relationship between bronchopulmonary dysplasia classification and demographic characteristics

Characteristics	Bronchopulmonary dysplasia				p
	None (n=367)	Mild (n=68)	Moderate (n=50)	Severe (n=54)	
Maternal age, years[a]	29.0 (15-44)	27.5 (18-42)	28.0 (16-41)	28.5 (18-41	0.376
Preeclampsia[b]	69 (20.4)	7 (11.7)	9 (21.4)	14 (31.8)	0.095
Gestasyonel diabetes mellitus[b]	30 (9.0)	2 (3.6)	3 (7.0)	2 (4.7)	0.387
Multiple pregnancy[b]	110 (29.9)	25 (36.7)	15 (30)	10 (18.5)	0.491
Antenatal steroid[b]	234 (84.5)	43 (82.7)	26 (72.2)	32 (86.5)	0.291
Chorioamnionitis[b]	12 (21.8)	2 (10.5)	3 (25.0)	4 (33.3)	0.462
Cesarean delivery[b]	327 (89.2)	64 (92.4)	44 (93.6)	45 (84.3)	0.399
1. min Apgar score[a]	6.0 (1-9)	6.0 (0-7)	5.0 (1-7)	4.0 (0-7)	<0.001*
5. min Apgar score[a]	8.0 (0-10)	7.0 (2-9)	7.0 (3-8)	7.0 (2-9)	<0.001*
Resusitation in delivery room[b]	120 (32.6)	33 (48.5)	26 (52)	39 (72.2)	<0.001*
CRIB II score[a]	3.0 (0-17)	6.0 (2-15)	7.0 (0-13)	10.0 (2-14)	<0.001*
SNAP-PE II score[a]	0.0 (0-35)	0.0 (0-35)	0.0 (0-35)	18.0 (0-47)	<0.001*
Day of starting vitamin D, days[a]	11.0 (4-50)	13.0 (7-66)	12.0 (7-59)	15.0 (7-88)	<0.001*
f T4, ng/dL[a]	1.4 (0.2-10.0)	1.2 (0.2-3.1)	1.1 (0.2-8.3)	1.1 (0.6-3.6)	<0.001*
TSH, uIU/L[a]	3.9 (0.3-112.0)	3.8 (0.3-65.3)	3.9 (0.5-5.80)	3.9 (0.6-100.0)	0.692
Full enteral feeding day, days[a]	8.0 (1-53)	14.0 (5-53)	13.0 (7-56)	20.0 (8-121)	<0.001*

*Statistically significant p values are highlighted, [a]median (minimum-maximum), [b]n (%), CRIB: Clinical Risk Index For Babies, SNAP-PE II: Score for Neonatal Acute Physiology Perinatal Extension II, fT4: Free thyroxine, TSH: Thyroid-stimulating hormone

Table 3. Premature morbidity and mortality outcomes according to bronchopulmonary dysplasia stage

Characteristics	Bronchopulmonary dysplasia				p
	None (n=367)	Mild (n=68)	Moderate (n=50)	Severe (n=54)	
Early neonatal sepsis[a]	198 (54.1)	46 (63.2)	39 (80.4)	36 (65.4)	0.004*
Late neonatal sepsis[a]	163 (46.7)	52 (77.6)	44 (91.7)	53 (100.0)	<0.001*
Respiratory distress syndrome[a]	103 (28.2)	42 (63.6)	38 (74.0)	47 (84.6)	<0.001*
Patent ductus arteriosus[a]	44 (12.9)	28 (41.8)	31 (63.3)	32 (61.5)	<0.001*
Necrotizing enterocolitis[a]	13 (3.6)	7 (10.3)	5 (10.0)	9 (16.7)	0.002*
Retinopathy of prematurity[a]	47 (16.4)	30 (45.5)	29 (58.0)	40 (74.1)	<0.001*
Intraventricular hemorrhage[a]	2 (0.5)	1 (1.4)	1 (2)	2 (3.7)	0.315
Erythrocyte transfusion[a]	93 (25.9)	44 (64.7)	47 (95.9)	51 (96.2)	<0.001*
Number of erythrocyte transfusion[b]	2.0 (1-5)	2.0 (1-7)	2.0 (1-9)	5.0 (1-14)	<0.001*
Total non invasive ventilation time, days[b]	2.0 (0-41)	12.0 (1-51)	17.5 (2-51)	17.0 (0-63)	<0.001*
Total mechanical ventilation time, days[b]	1.0 (0-61)	11.5 (0-96)	28.0 (0-95)	73.0 (15-261)	<0.001*
Oxygen support time, days[b]	6.0 (0-61)	37.0 (8-112)	60.0 (4-123)	103.5 (50-185)	<0.001*
Hospital stay, days[b]	31.0 (6-128)	54.0 (32-137)	78.0 (37-169)	134.0 (66-378)	<0.001*
Mortality[a]	34 (9.5)	1 (1.5)	0 (0.0)	7 (11.3)	0.001*

*Statistically significant p values are highlighted, [a]n (%), [b]median (minimum-maximum)

Table 4. Potential risk factors associated with bronchopulmonary dysplasia in the multivariate logistic regression model

Variables	β	Standart error	Wald	p	Exp(B)	95% confidence interval for Exp(B)	
						Low	High
1. min Apgar score	0.657	1.347	0.238	0.626	1.930	0.138	27.035
5.min Apgar score	-3.334	2.013	2.742	0.098	0.036	0.001	1.844
Full enteral feeding day	0.179	0.116	2.369	0.124	1.196	0.952	1.502
CRIB score	0.372	0.543	0.471	0.493	1.451	0.501	4.203
SNAP-PE score	-0.212	0.175	1.464	0.226	0.809	0.574	1.140
Respiratory distress syndrome	3.024	2.110	2.053	0.152	20.566	0.329	1287.048
Total mechanical ventilation time	-0.063	0.120	0.281	0.596	0.939	0.743	1.186
Total non invasive ventilation time	-0.283	0.165	2.939	0.086	0.754	0.546	1.041
Oxygen support time	0.287	0.114	6.274	0.012*	1.332	1.064	1.667
Late neonatal sepsis	0.062	1.994	0.001	0.975	1.063	0.021	52.988
Retinopathy of prematurity	2.721	1.900	2.052	0.152	15.202	0.367	629.367
Erythrocyte transfusion	3.734	1.757	4.517	0.034*	41.865	1.337	1310.596

*Statistically significant p values are highlighted, CRIB: Clinical Risk Index For Babies, SNAP-PE II: Score for Neonatal Acute Physiology Perinatal Extension II

BPD development is associated with many risk factors that appear during the prenatal, natal, and postnatal periods. Identifying the main risk factors and indicators in premature babies who will develope significant respiratory problems after birth and be diagnosed with BPD at 36 weeks is one of the most challenging research topics today. The aim of studies is often to identify the target group of BPD patients who will benefit most from specific treatment alternatives in the early postnatal (2,8). In this context, units strive to identify risk factors for BPD development and, based on the results obtained, are able to develop BPD prevention strategies (1,2,8). In our study, we aimed to reduce the risk factors for BPD development and identify preventive methods for BPD by determining our unit conditions and risk factors for BPD.

Low gestational age and birth weight are the main risk factors for BPD due to extrauterine immature lung development (8,9). Compared to full-term infants, the prevalence of BPD in infants born at ≤32 weeks of gestation ranges from 21% to 47% (9). The incidence of BPD in preterm infants with a gestational age of less than 32 weeks is 29.2%, and in those born before 28 weeks, it can increase to 47.8% (10). This frequency may varies across countries and between units. It is thought that variability in clinical care standards and genetic factors are primarily responsible for the changing prevalence of BPD (9). Our results appear to be consistent with these informations. Maternal illnesses, infections, prenatal and natal characteristics may negatively affect BPD development (5,11). In our results, maternal diseases, mode of delivery, multiple pregnancy, chorioamnionitis, and frequency of antenatal steroid administration were not significant risk factors affecting the BPD incidence. The reason for the varying effects of antenatal and natal factors on BPD may stem from the variability in BPD risks or risk-reducing procedures in the databases of different studies. Furthermore, the genetic, epigenetic, and immunological characteristics of the study groups may be the key factors in the development of BPD (8,9,12). The increased severity of BPD in our results appears to be associated with increased CRIB II, SNAP-PE II, and low Apgar scores, a high need for resuscitation, a longer time to transition to full enteral feeding, and the fact that patients with severe BPD were born at a lower gestational age (5,8,9,12).

A premature baby born with immature lungs, due to a lower birth week and weight, faces significant respiratory support treatment and impaired lung development. Increased incidence of RDS associated with immature lungs, increased

infections due to immature immune systems, prolonged hospital stays, high mortality, and other morbidities of prematurity such as PDA and NEC are associated with low gestational age and increased BPD severity, as reported in our study (2,8,9,11).

All newborn babies are given vitamin D supplementation unless there is a gastrointestinal contraindication, in according with the national nutrition protocol. The timing of initiation of vitamin D supplementation due to lack of sunlight, low cord blood vitamin D levels, and low maternal milk vitamin D levels, and its effect on BPD are unknown (13). An important and novel finding of our study is that delayed initiation of vitamin D supplementation increases the severity of BPD. Vitamin D, with its anti-inflammatory properties, affects the inflammatory process in BPD development and also regulates alveolar signaling pathways that support perinatal lung maturation (14). These effects of vitamin D may explain the result in our findings that early vitamin D supplementation reduces the severity of BPD. Animal studies on vitamin D have found that vitamin D has a protective effect against neonatal lung injury caused by hyperoxia, a major factor in the development of BPD (15). Based on experimental data and our findings, there is a need for new studies to test the role of vitamin D in preventing BPD in premature infants. Ge et al. (16) administered 800 IU of vitamin D supplementation to small premature infants at 32 weeks of gestation within the first 48 hours after birth. They showed a significant reduction in the incidence of BPD in the vitamin D supplemented group compared to the control group. Vitamin D may bind to vitamin D receptors to regulate inflammatory response, immune response, and hormone secretion. During lung development and maturation, vitamin D may increase the expression of alveolar epithelial-mesenchymal differentiation agents, improve the proliferation of alveolar and vascular endothelial cells, and promote the synthesis of alveolar surfactants. Ge et al. (16) demonstrated that the positive effect of vitamin D on BPD development was due to the reduction of inflammatory cytokines.

Premature babies often require long-term supplemental oxygen to ensure adequate oxygenation due to their immature lungs. In this situation, exposure to hyperoxia leads to oxidative stress, impaired lung development, and the development of BPD as a result of pulmonary fibrosis (5,17). In our patients, longer oxygen support duration was strongly associated with BPD severity; however, this finding should be interpreted cautiously because oxygen requirement is part of the diagnostic definition of BPD. Despite improvements in the survival rates of more premature infants and advances in medical care, BPD remains a significant cause of morbidity in premature infants. Therefore, there is still a need to study new mechanisms that mediate oxidative stress and lung development in newborns (17,18).

We found that fT4 levels were significantly reduced in patients with severe BPD. Regarding the effect of thyroid hormones on lung development, it has been reported that thyroid hormones, including T4 and triiodothyronine play a role in regulating fetal lung development and that serum T4 levels decrease in hyperoxia-exposed mice (19,20). Reducing oxidative stress-induced mitochondrial dysfunction through thyroid hormones deficiency and thyroid hormone supplementation may be a useful strategy for reducing neonatal lung injury and BPD (17). However, based on limited evidence, systemic thyroid hormone supplementation has been shown to provide minimal respiratory beneficial effects on BPD (21). In this context, based on our results and limited literature data, it remains unknown whether thyroid hormones can improve hyperoxic lung injury and reduce the risk of BPD in preterm infants. Therefore, the effect of thyroid hormones on BPD appears to be a pathophysiological issue that has not been sufficiently elucidated and needs to be clarified through further studies.

Erythrocyte transfusion has been shown to be an independent risk factor for BPD severity in our patient population. The transfusion of erythrocyte may increase the risk of oxidative damage, infection, and other complications (22). Increased oxidative damage with erythrocyte transfusion, increased transferrin-unbound iron, and inflammatory mediators present in transfused blood products are implicated as possible mechanisms of transfusion's effect on the development or severity of BPD (9,23). Before now, the relationship between blood transfusions and BPD has not been clearly distinguished in terms of causality (5). Our study brings to mind the need for a more detailed examination of the relationship between erythrocyte transfusion and BPD.

Study Limitations

The main limitations of our study can be considered to be its retrospective design and the limited data available from a single unit. We were unable to provide more detailed data on thyroid hormones monitoring, red blood cell transfusion data, maternal and umbilical cord vitamin D levels, and neurodevelopmental outcomes.

Conclusion

Our study reiterates the negative effect of hyperoxia on the development of BPD. Limited and guideline-compliant applications, instead of liberal oxygen and red blood cell transfusion practices, may have a positive effect on BPD development. In addition, our study found that starting vitamin D supplementation later and having low fT4 levels may increase the severity of BPD. Furthermore, our study reported a potential association between late initiation of vitamin D supplementation, low fT4 levels, and increased BPD severity. Our current findings may offer an additional perspective on BPD development and a new perspective for further studies.

Ethics

Ethical Approval: Ethical approval was obtained before the study commenced from the Clinical Research Ethics Committee of Health Sciences University Ankara Bilkent City Hospital, Hospital (decision no. E2-21-364, date: 07.04.2021). The study process was performed by the researchers in accordance with the Helsinki principles.

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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