ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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An Overview of Intracranial Hemorrhages in Premature Infants, Risk Factors in Low-Grade Hemorrhages, and an Evaluation of Neurodevelopment with the Bayley III Development Scale: Case-Control Study

Prematürelerde İntrakraniyal Kanamalara Bakış, Düşük Evreli Kanamalarda Etken Risk Faktörleri ve Nörogelişimin Bayley III Gelişim Ölçeği ile Değerlendirilmesi: Olgu-Kontrol Araştırması

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This study was prepared based on the findings of Filiz BOLU's thesis study titled "Determining the neurodevelopmental prognosis of preterms with intracranial hemorrhage and the factors affecting the prognosis" (İstanbul: Bakırköy Gynecology and Pediatrics Training and Research Hospital; 2009).

ABSTRACT Objective: Intracranial hemorrhage is a major morbidity in premature infants. We aimed to evaluate the cases with intracranial hemorrhage and to investigate the neurodevelopmental prognosis of prematures with low grade (Grade I-II) hemorrhage and the risk factors affecting it. **Material and Methods:** Fifty-nine of the 80 cases with intracranial bleeding followed-up in the neonatal intensive care unit were evaluated as Grade I-II and 21 as Grade III-IV-periventricular leukomalacia (PVL). Perinatal neonatal problems were investigated in cases with chronological ages of 24-42 months. The effects of risk factors for both Grade I-II and Grade III-IV-PVL were examined at logistic regression analysis. Cognition, language, and motor domain characteristics were determined with the Bayley III Scale. The relationship with risk and retardation was also examined. **Results:** Grade I-II and advanced grade hemorrhage cases were similar in terms of mean gestational week, birth weight or chronological age. Logistic regression analysis showed that the risk of hemorrhage increased with intrauterine growth retardation, sepsis and low Apgar scores. Factors affecting Bayley III scores in cases with Grade I-II were low birth weight and gestational week, intrauterine growth retardation, respiratory distress syndrome, ventilator support requirement, sepsis, seizure, and transport exposure. The motor domain in particular was affected as birth weight and gestational week decreased. Intrauterine growth retardation affected the cognition domain, respiratory problems, seizure, and transport history affected all domains, and sepsis affected the cognition and language domains. The prevalence of cerebral palsy and hydrocephaly was 5%, and that of blindness 1.6%. The advanced grade intracranial hemorrhage group scores were very low in all domains. Cerebral palsy was present at a rate of 33%, hydrocephaly at 23.8%, and blindness at 14.2%. **Conclusion:** Intracranial hemorrhage is an important morbidity of the immature brain in premature infants. Neurodevelopment is adversely affected in both low and advanced grade hemorrhage.

Keywords: Intracranial hemorrhage; neurodevelopmental prognosis; premature

ÖZET Amaç: Preterm bebeklerde intrakraniyal kanama önemli bir sorun olmaya devam etmektedir. Bu çalışmada, intrakraniyal kanama saptanan olguları değerlendirmek ve düşük evre (Evre I-II) kanamalı prematürelerin nörogelişimsel prognozunu ve etkileyen risk faktörlerini araştırmak amaçlandı. **Gereç ve Yöntemler:** Yenidoğan yoğun bakım ünitesinde izlenirken intrakraniyal kanama tanımlanan 80 olgunun 59'u Grade I-II, 21'i Grade III-IV, PVL olarak değerlendirildi. Kronolojik yaşları 24.-42 ay olan olguların perinatal neonatal dönem sorunları irdelendi. Lojistik regresyon analizinde risk etmenlerinin hem evre I-II, hem de evre III-IV-PVL için etkileri irdelendi. Bayley III ölçeği ile bilişsel, dil, motor alanda özellikleri belirlendi. Risk ve gerilik ilişkisi sorgulandı. **Bulgular:** 80 intrakraniyal kanamalı olgunun 59'u Grade I-II, 21'i ileri evre kanamalı idi. Evre I-II ve ileri evre olguların gebelik haftası, doğum ağırlığı, kronolojik yaş ortalamaları arasında istatistiksel fark yoktu. Lojistik regresyon analizinde kanama riski intrauterin büyüme geriliğinde, sepsis ve düşük Apgar skoru varlığında artmış bulundu. Evre I-II kanamalı olguların Bayley III puanlarını etkileyen risk faktörleri düşük doğum ağırlığı ve gestasyonel hafta, intrauterin büyüme geriliği, respiratuvar distres sendromu, ventilatör desteği ihtiyacı, sepsis, konvülziyon geçirme ve transport idi. Doğum ağırlığı ve gebelik haftası azaldıkça özellikle motor alan etkileniyordu. İntrauterin büyüme geriliği bilişsel alanı, solunum sorunları, konvülziyon ve transport öyküsü tüm alanları, sepsis bilişsel ve dil alanını etkilemişti. Serebral palsi ve hidrosefali 5%, sağırlık ve körlük 1,6% sıklıkta idi. İleri evre grubunun tüm alanlarda skoru çok düşüktü. Serebral palsi 33%, hidrosefali 23,8%, körlük 14,2% sıklıktaydı. **Sonuç:** İntrakraniyal kanama prematürelerin immatür beyninin önemli bir morbiditesidir. Hem düşük evre, hem de ileri evre kanamada nörogelişim olumsuz etkilenmektedir.

Anahtar Kelimeler: İntrakraniyal kanama; nörogelişimsel prognoz; prematüre

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Significant advances in perinatal care have been achieved in Türkiye and worldwide since the 1990s in particular. Considerable improvements in technical equipment in neonatal units, trained team working, the wider use of surfactants and antenatal steroids, advances in ventilation therapy, and time-and place-based support practices in the delivery room all increased the chances of survival among high-risk preterms and lowered mortality rates. However, complications arising from both immaturity and the problems experienced in the neonatal period in these very risky preterm infants emerge as severe morbidities at long-term follow-up. Intracranial hemorrhage (ICH) is one of the most important of these morbidities, and impacts adversely on neurodevelopment. ICH rates have been shown to increase as gestational week and/or birth weight decrease. The reported incidence of ICH among <32 week preterms since the 2000s is 25-30%.[1,2]

Various neurological sequelae, particularly cerebral palsy (CP) may be observed in preterm babies. In addition, major neurological sequelae such as hydrocephaly, mental disability, blindness, and deafness may subsequently develop in association with ventriculomegaly developing as a result of hemorrhage. Neurodevelopmental sequelae at long-term follow-up emerge in the form of retardation in movement, perception, and speech, depending on the grade of hemorrhage.[3-6] Severe outcomes are emphasized in research in the follow-up of severe (Grade III-IV) hemorrhage, although neurodevelopmental problems have also been reported in preterms with Grade I-II hemorrhage in recent years.[2,6,7] The present research focused on premature infants experiencing Grade I-II ICH. Risk factors implicated in hemorrhage and the cognitive, linguistic, and motor effects of these factors babies in 36-week preterms were investigated using the Bayley III Scale.[8] We also evaluated major neurological sequelae. This is the first study from Türkiye on the subject to employ the Bayley III Scale.

MATERIAL AND METHODS

Preterm infants born at 26-36 gestational weeks between January 2004 and December 2005, followed-up at the Ministry of Health Bakırköy Women's and Children's Diseases Training and Research Hospital II-III level neonatal intensive care unit (NICU), Türkiye, and diagnosed with Grade I-IV ICH-periventricular leukomalacia (PVL) were included in the study. Risk factors involved in the etiology of ICH in all cases were evaluated using logistic regression analysis. Neurodevelopmental prognosis and affecting factors were investigated in Grade I-II cases. The characteristics of cases diagnosed as Grade III-IV-PVL were summarized. Risks affecting neurodevelopment in low-grade ICH were investigated. Term newborns, babies with any genetic anomaly, and cases of congenital hydrocephaly were excluded.

Date of last menstruation and/or Ballard scores were used to determine gestational age.[9] Growth curves were employed in the evaluation of intrauterine growth.[10] Cases below the 10th percentile on the growth curve were defined as intrauterine growth restriction (IUGR), and those between the 10th and 90th percentiles as appropriate for gestational age (AGA). Premature rupture of membrans (PROM) was defined as tearing of the amniotic membranes 18 h before labor.[11] Töllner's classification, blood culture, and infection markers (C-reactive protein, leukocyte and platelet counts, and the immature/total neutrophil ratio) were used in the diagnosis of sepsis.[12] Respiratory distress syndrome (RDS) was diagnosed based on clinical and radiological findings. Papile et al. and de Vries et al. criteria were employed for the staging of ICH.[13,14] Cranial ultrasonography (US) was routinely performed on all preterms in the first 72 h. Cases with bleeding were identified and placed under weekly US follow-up. Our hospital was a busy Grade III perinatal center, and the neonatologist was inexperienced in cranial US. In addition, due to the fact that our pediatric neurologists have gained experience in cranial US during their fellowship training, the procedure was performed by pediatric neurologist. Suspicious and problematic cases were consulted with radiologists. Cranial US was performed with an Acuson 128XP (Acuson, Mountain View, CA) ultrasound device using a 7.5 MHz multi-frequency probe. Standard coronal and parasagittal sections were examined at transfontanelle evaluation. The grade of hemorrhage was determined.

Chronological age was employed to determine the cases' ages, with a mean range of 24-42 months.

Preterms with a history of transport were defined as those born in our hospital and transferred to an external center or born in an external center and under observation in our unit. Ethics committee approval was received for this study from Bakırköy Obstetrics and Pediatrics Training and Research Hospital's local ethics committee at 24/03/2008 with the record number of 141. Information concerning preterms was retrieved from the intensive care database and clinical observation charts. Families were first contacted by telephone and informed about the study. The study was conducted in accordance with the principles of the Declaration of Helsinki and written consent was obtained from the mother or father on the day of appointment. Cases underwent systemic and neurological examination by the physician performing the research. Bayley III was employed as the neurodevelopmental evaluation scale, being applied by a trained specialist in the field and the physician performing the research. The test room was arranged to resemble a home and play area in which the child could behave in a relaxed manner.

The Bayley III Developmental Assessment Scale measures neurological development at 1-42 months in five domains, cognition, language, motor, social-emotional, and adaptive. The record form contains the cognition, language, and motor domain scales. The cognition scale consists of items aimed at evaluating recall. The language scale consists of receptive language and expressive language sub-tests, while the motor scale consists of gross and fine subtests.[8] Three types of scoring on Bayley III were taken into account-scaled score, composite score, and percentile. Recognized confidence intervals are available for the scales 10±3 for scaled score and 100±15 for composite score. Retinopathy of prematurity (ROP) was defined based on American Academy of Pediatrics and American Academy of Ophthalmology 2006 criteria.[15] CP is defined as a manifestation of hemiplegia, diplegia or tetraplegia, characterized by abnormal muscle tone in at least one extremity, accompanied by posture and/or gait disturbances.[16] Failures associated with hearing and vision were evaluated by an appropriate specialist physician, and the results were recorded as digital data.

STATISTICAL ANALYSIS

The study findings were subjected to statistical analysis on NCSS 2007&PASS 2008 statistical software (Utah, USA) and SPSS 14.0 (SPSS Inc, USA) software. In addition to descriptive statistical methods (mean, standard deviation, and frequency), Student's t-test was applied in the comparison of quantitative data. The Mann-Whitney U test was used to compare continuous variables between two groups, and the Kruskal-Wallis test between multiple groups. Correlation coefficients for relationships between non-normally distributed variables were calculated using Spearman correlation analysis. The chi-square and Fisher's exact tests were used to compare qualitative data. Risk factors affecting ICH were determined using logistic regression analysis. The results were analyzed at a 95% confidence interval, with p values <0.05 being considered statistically significant.

RESULTS

A total of 1,758 preterms were admitted to the NICU between January 2004 and December 2005, 136 (7.73%) of whom were diagnosed with ICH. Twelve patients died during hospitalization and five after discharge home. The families of eight patients refused to take part in the study. The families of 80 of the 119 surviving cases (42 girls and 38 boys) were contacted, and these were enrolled as the study group. The cases enrolled in the study were born at 26-36 gestational weeks (mean 31.81±2.80) with a birth weight of 660-2,500 g (mean 1,358.8±408.72 g). The cases' chronological age during the research was 35.76±5.51 months. Based on intrauterine growth characteristics, 12 (15%) of the 80 cases with ICH were IUGR and 85% were AGA. Grade I ICH was present in 37 (46.25%) cases, Grade II in 22 (27.50%), Grade III in seven (8.75%), and Grade IV in three (3.75%). Eleven (13.75) preterms were under observation due to PVL. PVL was included in the Grade III-IV group due to sequelae of advanced bleeding and/or vasculatory circulation disorder.

No statistically significant difference was observed between the Grade I-II and advanced grade ICH cases in terms of mean gestational week, birth weight, or chronological age. Morbidities capable of

TABLE 1: Distribution of risk factors in preterms with Grade I-II and Grade III-IV hemorrhage.

Risk factors	ICH (Grade I-II) (n=59)	ICH (Grade III-IV, PVL) (n=21)	ICH (+) (n=80)
Gender (female/male)	30/29	12/9	42/38
Birth weight (X±SD)	1351.36±435.50	1379.76±330.45	1358.81±408.72
Gestational week(X±SD)	31.85±2.88	31.71±2.61	31.81±2.79
Chronological age (month)	35.58±5.65	36.26±5.17	35.76±5.51
PROM n (%)	5 (8.5)	3 (14.3)	8 (10)
6≤ Apgar n (%)	3 (5.1)	3 (14.3)	6 (7.5)
Transport n (%)	13 (22)	9 (43)	22 (27.5)
Sepsis n (%)	25 (42.3)	10 (47.6)	35 (43.7)
Convulsion n (%)	2 (3.4)	2 (9.5)	4 (5)
RDS n (%)	23 (39)	15 (71.4)	38 (47.5)
NICU n (%)	33 (56)	21 (100)	54 (55)
Mechanical ventilation n (%)	23 (39)	15 (71.4)	38 (47.5)
IUGR n (%)	9 (15.2)	3 (14.2)	12 (15)

ICH: Intracranial hemorrhage; PVL: Periventricular leukomalacia; SD: Standard deviation; PROM: Premature rupture of membranes; RDS: Respiratory distress syndrome; NICU: Neonatal intensive care unit; IUGR: Intrauterine growth restriction.

causing ICH were investigated in the research (Table 1). Analysis showed that 15.2% of the Grade I-II ICH had IUGR. All the Grade III-IV-PVL cases had been taken for level III intensive care, and 71.4% of these cases had been followed-up on a ventilator due to RDS. Sepsis distributions in the two groups were between 42.3% and 47.6%. Exposure to transport was twice as high in the Grade III-IV cases (Table 1).

Logistic regression analysis applied to determine the effects of the main risk factors on both Grade I-II ICH and advanced ICH revealed that the presence of sepsis increased the risk of hemorrhage 0.437-fold, IUGR increased the risk 0.154-fold, and a low Apgar score increased the risk of hemorrhage 4.23-fold (Table 2). Gestational week and birth weight emerged as independent risk factors in the etiology of ICH.

TABLE 2: Logistic regression analysis of factors thought to cause intracranial hemorrhage.

								95% Confidence interval	
		Coefficient	Standard error	Wald	SD	p value	Odds ratio	Lower	Upper
Threshold	X 1	-2.993	1.669	3.217	1	0.073			
	X 2	-0.434	1.638	0.070	1	0.791			
Location	PROM (-)	0.905	0.526	2.955	1	0.086	2.471	0.881	6.931
	PROM (+)	0[a]	.	.	0	.			
	Sepsis (-)	-0.828	0.410	4.074	1	0.044	0.437	0.196	0.976
	Sepsis (+)	0[a]	.	.	0	.			
	RDS (-)	-0.064	0.440	0.021	1	0.884	0.938	0.396	2.223
	RDS (+)	0[a] 0	.	.	0	.			
	IUGR (-)	-1.870	0.623	9.017	1	0.003	0.154	0.045	0.522
	IUGR (+)	0[a]	.	.	0	.			
	Transport (-)	-0.671	0.472	2.022	1	0.155	0.511	0.203	1.289
	Transport (+)	0[a]	.	.	0	.			
	Convulsion (-)	-1.586	1.102	2.071	1	0.150	0.205	0.024	1.775
	Convulsion (+)	0[a]	.	.	0	.			
	Apgar >7	1.442	0.671	4.618	1	0.032	4.228	1.135	15.745
	Apgar <7	0[a]	.	.	0	.			
	Gestational week >32	-0.595	0.409	2.117	1	0.146	0.552	0.248	1.229
	Gestational week <32	0[a]	.	.	0	.			

a: This parameter is set to zero because it is redundant.
SD: Standard deviation; PROM: Premature rupture of membranes; RDS: Respiratory distress syndrome; IUGR: Intrauterine growth restriction.

TABLE 3: Composite score correlation analysis with the grade of intracranial hemorrhage.

		Cognitive compozite score	Language compozite score	Motor compozite score
Grade of hemorrhage	Correlation coefficient	-0.313	-0.243	-0.348
	p[a]	0.05	0.03	0.002

[a]Spearman correlation analysis.

TABLE 4: Composite score values in different grades of intracranial hemorrhage.

	Grade I n=(37)	Grade II n=(22)	Grade III n=(7)	Grade IV n=(3)	PVL n=(11)	p[a]
Cognitive compozite score (X±SD)	92.8±10.5	88.8±12.7	70.7±33.2	80±18	82.7±16.7	0.053
Language compozite score (X±SD)	94.9±13.7	90.6±14.8	80.8±21.3	80.6±17	83.8±20.6	0.243
Motor compozite score (X±SD)	96.2±13.1	88.3±17.6	77.8±24.6	59±12.4	79.3±24.7	0.017

[a]Kruskal-Wallis test; PVL: Periventricular leukomalacia; SD: Standard deviation.

Evaluation of neurodevelopment according to ICH grades revealed that Bayley III cognition, language, and motor domain composite scores decreased as the degree of hemorrhage increased (Table 3). The difference in the motor domain was significant at subgroup analysis. Mann-Whitney U analysis was used to identify the groups between which this difference was observed. Significant differences were found between Grade I and Grade IV, Grade I and PVL, and Grade II and Grade IV, at z (38)=-2.619, $p<0.01$, z (46)=-2.31, $p<0.05$, and z (23)=-2.14, $p<0.05$, respectively (Table 4).

The purpose of this study was to examine the Grade I-II ICH group of premature infants undergoing ICH and to identify those factors which play a role in neurodevelopment, and to reveal the effect of risk factors on Bayley III cognition, language, and motor domain scores. Accordingly, sex, a low Apgar score, and the presence of PROM were found not to affect Bayley III scores. Sepsis caused a problem in the language domain, while exposure to transport and undergoing seizures caused significant retardation in the cognition, language, and motor domains. Language and motor domain retardation was observed in preterms with Grade I-II ICH followed-up in the intensive care unit and/or receiving mechanical ventilator support. Motor domain scores were significantly low among cases with RDS (Table 5). Thirty-two (37.28%) of the 59 preterms with Grade I-II ICH were born at less than 32 weeks, and 61% weighing less than 1,500 g.

Gestational age and birth weight exhibited a significant impact on Bayley III scores in the motor domain. Scores on the motor domain increased in line with gestational age and birth weight (Table 6). Low scores in all Bayley III domains were observed in preterms with Grade III-IV-PVL (Table 4). In terms of major neurological sequelae, seven of the 10 cases of CP, three of the four cases developing blindness, and five of the eight cases developing post-hemorrhagic hydrocephaly were in the advance hemorrhage group were observed in the form of CP in seven cases.

DISCUSSION

This study investigated factors responsible for bleeding in preterms diagnosed with ICH and the characteristics of cases of Grade I-II ICH by examining their neurodevelopment. Evaluation of all cases of ICH revealed that the presence of sepsis increased the risk 0.437-fold, IUGR increased the risk 0.154-fold, and a low Apgar score increased it 4.23-fold. Gestational week and birth weight emerged as independent risk factors. Grade of ICH was inversely correlated with neurodevelopment. Bayley III cognition, language, and motor domain scores decreased as the degree of bleeding increased. Factors and domains affecting Bayley III scores in preterms who had undergone Grade I-II hemorrhage were investigated; transport, seizure, and receipt of ventilator support were found to lead to retardation in the language and motor domains, IUGR in the language domain, sepsis in the cognition and lan-

TABLE 5: The relationship between Bayley III cognitive, language, motor domain findings with risk factors in Grade I-II ICH (+) prematures.

Risk faktors	Cognitive compozite score (X±SD)	p[a]	Language compozite score (X±SD)	p[a]	Motor compozite score (X±SD)	p[a]
Birth weight						
<1,500 g (n=36)	89.03±13.88	0.074	90.92±6.44	0.124	89.11±17.91	0.019*
≥1,500 g (n=23)	95.00±3.99		97.09±8.67		99.91±6.01	
Gestation week						
<32 (n=22)	89.31±13.99	0.405	90.04±14.90	0.225	88.50±18.43	0.103
≥32 (n=37)	92.56±9.69		95.27±13.50		96.18±12.58	
Female (n=30)	92.17±10.88	0.48	96.07±14.23	0.08	94.07±15.75	0.35
Male (n=29)	90.52±12.13		90.48±13.77		92.55±15.15	
Apgar						
≤6 (n=3)	83.33±20.21	0.45	85.33±15.50	0.30	80.00±18.33	0.2
>6 (n=56)	91.79±10.93		93.75±14.12		94.04±15.03	
PROM (+) (n=5)	88.00±16.05	0.72	92.20±12.83	0.88	87.40±20.39	0.48
PROM (-) n=54)	91.67±11.07		93.43±14.39		93.87±14.94	
Transport						
(+) (n=13)	82.69±17.03	0.05*	83.69±18.90	0.03*	81.62±23.32	0.04*
(-) (n=46)	93.80±7.97		96.04±11.37		96.63±10.37	
Sepsis (+) (n=25)	86.80±14.78	0.04*	86.88±16.21	0.005*	86.72±20.99	0.1
Sepsis (-) (n=34)	94.71±6.62		98.06±10.36		98.18±6.00	
Convulsion						
(+) (n=2)	60.00±7.07	0.05*	62.00±16.97	0.007*	55.00±12.73	0.007*
(-) (n=57)	92.46±9.92		94.42±12.91		94.97±12.66	
RDS (+) (n=23)	88.48±12.56	0.15	90.09±15.15	0.26	88.22±16.94	0.04*
RDS (-) (n=36)	93.19±10.43		95.39±13.31		96.58±13.48	
IUGR (+) (n=9)	86.67±12.25	0.03*	94.44±15.67	0.22	88.00±15.00	0.06
IUGR (-) (n=50)	92.20±11.21		93.48±14.05		94.28±15.36	
Mechanical ventilation						
(+) (n=28)	88.04±14.10	0.058	88.82±16.87	0.021*	87.93±47.77	0.019
(-) (n=31)	94.35±7.39		97.39±9.81		98.19±10.93	

[a]Mann-Whitney U test; *p<0.05; SD: Standard deviation; ICH: Intracranial hemorrhage; PROM: Premature rupture of membranes; RDS: Respiratory distress syndrome; IUGR: Intrauterine growth restriction.

TABLE 6: Correlation of composite scores of premature patients with Grade I-II ICH by gestational week and birth weight.

		Cognitive compozite score	Language compozite score	Motor compozite score
Gestation week	Correlation coefficient	0.187	0.162	0.300
	p[a]	0.157	0.22	0.021
Birth weight	Correlation coefficient	0.166	0.102	0.293
	p[a]	0.209	0.443	0.024

[a]Spearman correlation analysis; ICH: Intracranial hemorrhage.

guage domain, and RDS in the motor domain. Positive correlation was observed between gestational week and birth weight and Bayley III motor domain scores.

The optimal transport is in utero transport. Irrespective of the conditions, preterms may be at risk of ICH due to such negativities as hypothermia, hypoxia, and hypoglycemia during transport. In the present research, 13 (22%) of the Grade I-II ICH cases and nine (43.5%) of those with advanced bleeding had histories of transport and registered low Bayley III cognition, language, and motor domain scores. A previous study in this field reported ICH as severe morbidity in preterms born at <32 gestational weeks and undergoing transport and the ages of 0-7 days.[17] Mohamed and Aly also showed that transport exacerbated the risk of severe bleeding.[18]

Sepsis increased the risk of ICH development 0.47-fold in the present study. In their study from 1996, Egarter et al. reported that early sepsis increased the risk of ICH 8-fold, while Hansen and Leviton described chorioamnionitis as risk factors in the etiology of ICH.[19,20] Linder et al. reported that early sepsis in preterms from in vitro fertilization pregnancies affected Grade III-IV ICH, and that antenatal steroid low partial carbon dioxide levels lowered the risk.[21] Bayley III cognition and language domain scores were significantly low among preterms with sepsis undergoing Grade I-II ICH in the present study, while the insignificant effect of PROM was attributed to the low case numbers.

Since cerebral blood flow autoregulation is immature in preterm infants, fluctuations in systemic blood pressure may cause ICH, the principal risk factors including hypercarbia, acidosis, asphyxia, and convulsions.[21,22] In the present research, 39% of the Grade I-II ICH cases and 71.4% of the advanced ICH group had received mechanical ventilator support due to RDS and/or respiratory problems. Children in the Grade I-II ICH group were found to experience motor and language domain retardation. Klebermass-Schrehof et al. and Patra et al. reported that pre-school preterms younger than 32 weeks with and without Grade I-II ICH suffered CP and visual retardation.[6,7] A significant association between cases' respiratory problems and development of ICH was emphasized in both studies.

In the etiology of ICH, IUGR increased the risk 0.154-fold. No difference was observed in Bayley III language or motor domains in cases with Grade I-II ICH, although cognition domain scores were significantly lower.

Conditions such as maternal and fetal problems (infections, placental circulatory disorders, vascular problems, congenital anomalies, etc.) that lead to fetal growth retardation, perinatal hypoxia/asphyxia cerebral damage, postnatal RDS, seizures, and ventilator therapy requirements cause retardation in the visual and motor domains.[23] Retardation in the cognition domain was also observed in the present study in children with IUGR in the motor and language domains with respiratory support and/or RDS. Özbek also reported retardation in the cognition domain in the IUGR group with Grade I-II ICH compared to an AGA group.[24]

Our neurodevelopmental evaluation revealed that both low birth weight and a low gestational week increased the degree of bleeding. In the correlation analysis, Bayley scores increased as gestational week and birth weight increased. Statistically significant retardation in the motor domain was observed in <1,500 g Grade I-II cases. When the cases with gestational age below and above 32 weeks were compared, Bayley scores were found to be lower than the others in the group <32 week. However, no statistically significant difference was found. This was attributed to the low number of <32 week cases. Anderson et al. reported positive correlation between birth weight and motor development.[25] Klebermass-Schrehof et al. performed a Bayley III-based neurodevelopmental evaluation of <32 week preterms with Grade I-II ICH and reported low motor and visual scores at two and 3.5 years, with <28 week preterms being particularly affected.[7]

The most commonly seen major neurological sequela is CP. This was identified in 10 of all the cases in the present research, 60% as spastic diparesis and 40% spastic tetraparesis. CP was detected in three (5%) of the Grade I-II ICH cases and in 33% of the advanced grade group. Patra et al. evaluated extremely low birth weight preterms with Grade I-II ICH at 20 months using the Bayley II Scale, and determined a prevalence of neurodevelopmental retardation of 45% and of CP of 8%.[6] The authors reported a prevalence of neurodevelopmental retardation of 15% and of CP of 3% in cases without ICH at a similar gestational week. The prevalence of CP was similar in the present study.

Klebermass-Schrehof et al. observed marked adverse effects in the motor, cognition, and visual domains as the degree of ICH increased, reporting a frequency of CP of 34.8-35% in Grade I-II at <32 gestational weeks and of 90% in Grade IV cases.[7] Those authors drew particular attention to motor domain functions and emphasized that children with and without Grade I-II ICH exhibited similar neurodevelopment in the first years, while a significant difference was observed at 66th-month evaluation. That study also reported that 26%-27% of Grade I-II

ICH patients and 45.5%-90.9% of advanced grade patients exhibited problems in the visual domain. The authors also reported 3.2% abnormality in Grade I-II in terms of hearing problems.[7]

While the most important mechanisms reported in the development of ICH are hypoxia, ischemic injury, free hydroxyl radicals, the Fenton reaction, and vasospasm, direct damage and destruction of the germinal matrix in low-grade ICH prevent neuronal precursors there from migrating to the cortex and forming astrocytes and oligodendroglia. Since oligodendroglia play a role in myelination, this causes underdevelopment of white matter and ultimately motor domain movement problems. Insufficient astrocyte and oligodendroglia migration has been reported to lead to problems in gray matter formation and to cognition, language, and vision domain problems.[26]

Blindness associated with ROP was determined in 1.6% of cases of Grade I-II ICH and 14.3% of cases with Grade III-IV-PVL, and hearing problems in 1.6% cases of Grade I-II ICH. Our rates were lower than in the previous literature. Since neurodevelopment is an active process, findings in the first 2-4 years are not particularly decisive. Since the diagnosis of motor function disorders in particular may extend beyond the age of five years, the frequency may change due to cases diagnosed subsequently.

Vasileiadis et al. compared the cranial MRI findings of preterms with low-grade ICH with those with no ICH and reported a 16% loss of brain tissue volume in those with hemorrhage.[26] The authors recommended that follow-up studies including risk factors be performed. In the present observational study, examination of neurodevelopmental prognosis in Grade I-II ICH revealed that gestational week, birth weight, transport, RDS/ventilator therapy, and seizure adversely affected mean Bayley III scores.

CONCLUSION

In conclusion, the present research showed that the immature cerebral structure of premature infants with Grade I-II ICH was damaged due to hypoxia/asphyxia, circulatory and respiratory failure in the perinatal period, and that bleeding in the clinical manifestation caused significant retardation in the language and cognitive domains, but particularly in the motor domain.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Sultan Kavuncuoğlu, Filiz Bolu;* ***Design:*** *Sultan Kavuncuoğlu, Filiz Bolu;* ***Control/Supervision:*** *Filiz Bolu, Esin Yıldız Akdemir, Sultan Kavuncuoğlu;* ***Data Collection and/or Processing:*** *Filiz Bolu;* ***Analysis and/or Interpretation:*** *Filiz Bolu, Esin Yıldız Akdemir, Sultan Kavuncuoğlu;* ***Literature Review:*** *Filiz Bolu, Esin Yıldız Akdemir;* ***Writing the Article:*** *Filiz Bolu, Esin Yıldız Akdemir, Sultan Kavuncuoğlu;* ***Critical Review:*** *Sultan Kavuncuoğlu;* ***References and Fundings:*** *Filiz Bolu;* ***Materials:*** *Filiz Bolu, Esin Yıldız Akdemir.*

REFERENCES

1. Mancini MC, Barbosa NE, Banwart D, Silveira S, Guerpelli JL, Leone CR. Intraventricular hemorrhage in very low birth weight infants: associated risk factors and outcome in the neonatal period. Rev Hosp Clin Fac Med Sao Paulo. 1999;54(5):151-4. [Crossref] [PubMed]
2. Larroque B, Marret S, Ancel PY, Arnaud C, Marpeau L, Supernant K, et al; EPIPAGE Study Group. White matter damage and intraventricular hemorrhage in very preterm infants: the EPIPAGE study. J Pediatr. 2003;143(4):477-83. [Crossref] [PubMed]
3. Sherlock RL, Anderson PJ, Doyle LW; Victorian Infant Collaborative Study Group. Neurodevelopmental sequelae of intraventricular haemorrhage at 8 years of age in a regional cohort of ELBW/very preterm infants. Early Hum Dev. 2005;81(11):909-16. [Crossref] [PubMed]
4. Fernández-Carrocera LA, González-Mora E. Trastornos del neurodesarrollo en ni-os con antecedente de hemorragia subependimaria/intraventricular a los tres a-os de edad [Neurodevelopmental disorders in children with an antecedent of subependymal/intraventricular hemorrhage at 3 years of age]. Gac Med Mex. 2004;140(4):367-73. Spanish. [PubMed]
5. Szymonowicz W, Yu VY, Bajuk B, Astbury J. Neurodevelopmental outcome of periventricular haemorrhage and leukomalacia in infants 1250 g or less at birth. Early Hum Dev. 1986;14(1):1-7. [Crossref] [PubMed]
6. Patra K, Wilson-Costello D, Taylor HG, Mercuri-Minich N, Hack M. Grades I-II intraventricular hemorrhage in extremely low birth weight infants: effects on neurodevelopment. J Pediatr. 2006;149(2):169-73. [Crossref] [PubMed]
7. Klebermass-Schrehof K, Czaba C, Olischar M, Fuiko R, Waldhoer T, Rona Z, et al. Impact of low-grade intraventricular hemorrhage on long-term neurodevelopmental outcome in preterm infants. Childs Nerv Syst. 2012;28(12):2085-92. [Crossref] [PubMed]
8. Bayley N. Bayley Scales of Infant and Oddler Development. 3rd ed. San Antonio (TX): Harcourt Assessment; 2006. [Crossref]
9. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. J Pediatr. 1991;119(3):417-23. [Crossref] [PubMed]
10. Ovali F. Intrauterine growth curves for Turkish infants born between 25 and 42 weeks of gestation. J Trop Pediatr. 2003;49(6):381-3. [Crossref] [PubMed]
11. Belady PH, Farkouh LJ, Gibbs RS. Intra-amniotic infection and premature rupture of the membranes. Clin Perinatol. 1997;24(1):43-57. [Crossref] [PubMed]
12. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, et al; National Institute of Child Health and Human Development Neonatal Research Network. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA. 2004;292(19):2357-65. [Crossref] [PubMed]
13. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978;92(4):529-34. [Crossref] [PubMed]
14. de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. Behav Brain Res. 1992;49(1):1-6. [Crossref] [PubMed]
15. Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2006;117(2):572-6. Erratum in: Pediatrics. 2006;118(3):1324. [Crossref] [PubMed]
16. Russman BS. Cerebral palsy: definition, manifestations and etiology. Turk J Phys Med Rehab. 2002;48(2):4-6. [Link]
17. Kavuncuoğlu S, Bayram N, Öztürk E, Aldemir E, Özbek S. Neonatal transportun preterm bebeklerin morbidite ve mortalitesine etkileri [The effect on mortality and morbidity of neonatal transport in preterm babies]. IKSST Derg. 2014;6(1):23-9. [Crossref]
18. Mohamed MA, Aly H. Transport of premature infants is associated with increased risk for intraventricular haemorrhage. Arch Dis Child Fetal Neonatal Ed. 2010;95(6):F403-7. [Crossref] [PubMed]
19. Egarter C, Leitich H, Karas H, Wieser F, Husslein P, Kaider A, et al. Antibiotic treatment in preterm premature rupture of membranes and neonatal morbidity: a metaanalysis. Am J Obstet Gynecol. 1996;174(2):589-97. [Crossref] [PubMed]
20. Hansen A, Leviton A. Labor and delivery characteristics and risks of cranial ultrasonographic abnormalities among very-low-birth-weight infants. The Developmental Epidemiology Network Investigators. Am J Obstet Gynecol. 1999181(4):997-1006. [Crossref] [PubMed]
21. Linder N, Haskin O, Levit O, Klinger G, Prince T, Naor N, et al. Risk factors for intraventricular hemorrhage in very low birth weight premature infants: a retrospective case-control study. Pediatrics. 2003;111(5 Pt 1):e590-5. [Crossref] [PubMed]
22. Noori S, Seri I. Hemodynamic antecedents of peri/intraventricular hemorrhage in very preterm neonates. Semin Fetal Neonatal Med. 2015;20(4):232-7. [Crossref] [PubMed]
23. Kessenich M. Developmental outcomes of premature, low birth weight, and medically fragile infants. NBIN. 2003;3(3):80-7. [Crossref]
24. Özbek İ. Prematüre ve intraventriküler hemoraji/periventriküler lökomalazili bebeklerde prognozu etkileyen faktörlerin araştırılması [Tıpta uzmanlık tezi]. Adana: Çukurova Üniversitesi; 2006. Erişim linki: [Link]
25. Anderson PJ, De Luca CR, Hutchinson E, Roberts G, Doyle LW; Victorian Infant Collaborative Group. Underestimation of developmental delay by the new Bayley-III Scale. Arch Pediatr Adolesc Med. 2010;164(4):352-6. [Crossref] [PubMed]
26. Vasileiadis GT, Gelman N, Han VK, Williams LA, Mann R, Bureau Y, et al. Uncomplicated intraventricular hemorrhage is followed by reduced cortical volume at near-term age. Pediatrics. 2004;114(3):e367-72. [Crossref] [PubMed]