ORIGINAL ARTICLE

The Effect of Low-Grade Intraventricular Hemorrhage on the Neurodevelopment of Very Low Birth Weight Infants

How to Cite This Article: Yaghini O, Majidinezhad M, Ghehsareh Ardestani A, Riahinezhad M, Maracy MR.The Effect of Low-Grade Intraventricular Hemorrhage on the Neurodevelopment of Very Low Birth Weight Infants. Iran J Child Neurol. summer 2022; 16(3): 57-65

Omid YAGHINI MD[1],
Maede MAJIDINEZHAD MD[2],
Azam GHEHSAREH ARDESTANI MD[1],
Maryam RIAHINEZHAD MD[1],
Mohammad REZA MARACY MD[3,4]

1. Child Growth and Development Research Center, Research Institute for Primordial Prevention of non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran
2. University of Social Welfare and Rehabilitation Sciences, Tehran, Iran.
3. Environment Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran.
4. Department of Epidemiology and Biostatistics, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran

Corresponding Author
Majidi Nezhad M. MD
University of Social Welfare and Rehabilitation Sciences,

Abstract

Objective
Intraventricular hemorrhage (IVH) is a significant concern for premature very low birth weight (VLBW) neonates worldwide. Recently, the popular theory of the benign nature of low-grade IVH has been argued with uncertain outcomes. This study aimed to assess the effect of low-grade IVH on the neurodevelopment of VLBW neonates.

Materials & Methods
This six-month follow-up cohort study was conducted on VLBW neonates with and without grade I-II IVH diagnosed through brain ultrasonography. Participants were neurologically examined at birth and within six months. Neurodevelopment was assessed using the Bayley-III questionnaire, which includes evaluating cognition, receptive language, expressive language, fine motor, and gross motor performance.

Results
A total of 100 VLBW neonates were recruited, including 40 cases with grade I-II IVH diagnosed through brain ultrasonography and 60 controls. Cases and controls were similar in terms of gestational age, body birth weight, hospitalization duration, gender distribution, and age at Bayley-III evaluation (P>0.05). The neurological assessments at birth showed no significant difference between the two groups (P=0.20), while controls showed significantly better results at the sixth month of age (P =0.004). Concerning different neurodevelopmental indices, after adjusting for demographic characteristics and respiratory-related variables at the time of Bayley-III evaluation,

Tehran, Iran.
Email: maedemajidinezhad@gmail.com

Received: 22-Nov-2020
Accepted: 19-Jun-2021
published:16- Jul-2022

controls presented a higher performance in cognition and gross motor aspects compared to cases (P= 0.04 and 0.03, respectively).

Conclusion

The low-grade IVH affected the sixth-month neurological examination and gross motor performance of the VLBW newborns. Notably, cognition and gross motor were the two affected subscales in the presence of low-grade IVH, independent of demographic factors.

Keywords: Very low birth weight neonate; Intraventricular hemorrhage; Bayley-III; Premature; neurodevelopment.

DOI: 10.22037/ijcn.v16i3.32958

Introduction

Due to advances in neonatal care and improved performance of the preventive approaches, which can be attributed to the identification of prematurity-related risk factors and the remarkable improvement in the handling of premature infants, there has been a considerable decline in the incidence of intraventricular hemorrhage (IVH) over time. IVH is estimated to occur in 15-45% of very low birth weight (VLBW) neonates (1, 2). The first postnatal day of life is critical for VLBW neonates, considering that up to 50% of IVH onset on this day (3). Also, it is reported that over 90% of the IVHs detect in the first week of life, regardless of the gestational age. Therefore, head ultrasonographic screening has been considered a routine way of IVH determination (4, 5).

Papile et al., in 1978, introduced a four-grade classification for the premature IVH for the first time, which is as follows: grade I, defined as subependymal germinal matrix hemorrhage, grade II, identified as lateral ventricle hemorrhage without ventricular dilatation, grade III, known as dilatation of lateral ventricles due to the hemorrhage, and the worst condition is attributed to grade IV of IVH identified by parenchyma involvement in addition to the lateral ventricles hemorrhage that is recently named as periventricular hemorrhage infarction as well (6, 7).

The long-term neurodevelopmental impairment due to grades III and IV of IVH observed in the sonographic evaluations has been well-established (2, 8), while the effects of grades I and II of IVH were heterogeneous. Despite the general belief in the benign nature of grades I and II of intraventricular hemorrhage, recent studies have demonstrated an increased risk of adverse neurodevelopmental outcomes due to grade II - and even grade I - of IVH, while some other papers disagree (9-11).

As the evidence about the effects of grades I and II of IVH on neurodevelopmental outcomes are still inconclusive, this study aimed to assess the six-month neurodevelopment status of VLBW neonates with low-grade IVH in the Iranian population.

Material & Methods

Study Population

Following a cohort design, 100 VLBW neonates hospitalized at the neonatal intensive care unit (NICU) of Alzahra, Shahid Beheshti, and Emam Hossein Hospitals, affiliated to Isfahan University of Medical Sciences, were recruited from September 2017 to June 2019. The sample size was determined based on previous similar studies (12, 13). All VLBW neonates had less than 34 weeks of gestational age, and grade I-II intraventricular hemorrhage was diagnosed with sonography. Written informed consent was obtained from legal guardians of neonates before entering the study and after a comprehensive introduction to the study protocol.

The cases that met the inclusion criteria were included through simple sampling, while another group of VLBW neonates, which did not have any grade of IVH and had no prematurity-related complication, were considered the control group.

The exclusion criteria were as follow: not being VLBW, suffering from other prematurity complications such as sepsis, necrotizing enterocolitis, or central nervous system (CNS) infection, sonographic findings in favor of grade III-IV IVH, and diagnosis of hydrocephalus or CNS malformations such as prosencephalon.

Measurements: All participants underwent brain sonography within the first 7-14 days of life and in the corrected gestational ages of 36-40 weeks to detect IVH and its severity. All sonographies were performed by a single expert radiologist and a single sonography device to minimize the inter-observer bias.

An expert neurologist responsible for the study examined the neurological status of cases and controls at the time of IVH diagnosis, including head circumference, weight, muscle tone and primitive reflexes, neonate's motor function, DTR, and cranial nerve examination. Next, all participants underwent neurological examination at six months of age, consisting of muscle tone for evaluation of any hypertonia and hypotonia and detecting spasticity in lower and upper extremities and spinal cord, head circumference and weight, muscle function and movement, cranial nerve examination, and cognition and other developmental tests related to six-month-olds. In addition, the Bayley questionnaire was filled for them when they had six months of age by an expert who was blind to the allocation of participants. Noteworthy, this questionnaire is introduced by the ministry of health of Iran.

Questionnaire: Bayley-III questionnaire is a valid and reliable tool for the neurodevelopmental assessment of 15 days to 42-month-old newborns. It intends to evaluate five neurodevelopmental entities of cognition, language (including expressive and receptive aspects, fine motor), and gross motor performance. Each of the items is scored as zero (a negative answer) or one (a positive answer). The Bayley questionnaire includes 326 items, including 91 items for cognition-related, 49 perception-related, 48 language-related, 66 fine-motor performance-related, and 72 gross-motor performance-related questions. The score of each entity is the total sum of scores related to each subscale, and total scores were made by adding each entity's score. The total questionnaire score would be compared to the standard curve and eventually interpreted by the neurologist. Soleimani et al. designed the Persian version of this questionnaire in the Pediatric Neurorehabilitation Research Center, University of Social Welfare and Rehabilitation Sciences, in 2014 and reported that the Cronbach alpha coefficient in the cognitive, language (receptive and expressive), fine, and gross motor subtests was 0.96, 0.95, 0.95, and 0.94, respectively (14, 15).

Statistical analysis: Data analysis was administered using SPSS version 23. Descriptive data are presented in mean, standard deviation, counts, and percentages. Inter-group comparisons were performed using the chi-square test. The ANOVA was used for evaluating more than two groups. Linear regression was used to control any potential confounding variable. Statistical significance was considered when the p-value<0.05.

Ethical Considerations: the study protocol was subjected to scrutiny by the Ethics Committee of the Isfahan University of Medical Sciences. Written informed consent was obtained from neonate's legal guardians before entering the study and after a comprehensive introduction to the study protocol.

Results

In the current study, 100 VLBW neonates, including 43 girls and 57 boys, were assessed. The mean gestational age, birth weight, NICU admission duration, and age at the final evaluation were, respectively, 30.71±2.17 weeks, 1398.78±383.66 g, 27.30±15 days, and 6.39±1.06 months. In the case group, a total of 40 newborns had a diagnosis of grade I-II IVH, with a mean age of 6.43±1.25 months, while the mean age of newborns in the control group was 6.37±0.95 months. As shown in Table 1, there was no significant difference between the two groups concerning gestational age, body birth weight, NICU admission duration, gender distribution, and corrected age.

Afterward, we assessed respiratory-related variables, including ventilator requirement, surfactant requirement, and the diagnosis of bronchopulmonary dysplasia (BPD). There was no significant difference between the two groups (P-value>0.05) (Table 2). A comparison of neurological physical examination at birth revealed no significant differences between the two groups (P-value=0.20), while the number of the six months old infants with an abnormal neurological examination was remarkably higher among infants with IVH compared to the healthy controls (P-value=0.004) (Table 3).

The result of detailed neurological assessments through the Bayley version III questionnaire is provided in Table 4. Only gross motor performance was significantly different between the two groups (P-value=0.04).

As shown in Table 4, the univariate analysis of variance, after adjusting for age, gender, gestational age, birth weight, duration of NICU admission, BPD diagnosis, surfactant use, and ventilator requirement, showed that two neurodevelopmental entities (i.e., cognition (P=0.04) and gross motor (p=0.03)) were significantly different between the two groups.

The linear regression showed a significant association between IVH and gross motor function (P = 0.04), while no significant association was found between IVH and cognition. (data not shown)

Table 1. Demographic characteristics of cases and controls

Variable		Case (n=40)	Control (n=60)	P-value
Gestational age (weeks)		30.57±2.36	30.81±2.04	0.59
Body birth weight (g)		1392.75±343.38	1402.88±411.56	0.89
Duration of NICU admission (days)		28.71±15.45	26.32±14.73	0.44
Age at Bayley assessment (months)		6.43±1.25	6.37±0.95	0.80
Gender (Count, percentage)	Male	21 (52.5%)	36 (60%)	0.45
	Female	19 (47.5%)	24 (40%)	

[a]Data was obtained using Independent T-test.
[b]Data was obtained using the Chi-Square test.

Table 2. Comparison of respiratory-related factors between cases and controls

Variable	Case (n=40)	Control (n=60)	P
Ventilator requirement (Yes/No)	15 (39.5%)/23 (60.5%)	13 (21.7%)/47 (87.3%)	0.057
Surfactant use (Yes/No)	38 (100%)/0 (0%)	55 (91.7%)/5 (8.3%)	0.06
Bronchopulmonary dysplasia (Yes/No)	3 (8.1%)/34 (91.9%)	2 (3.3%)/58 (96.7%)	0.30

[a]The obtained using Chi-square test.

Table 3. Comparison of neurological physical examination status between cases and controls at birth and six months old

	At birth	Six months old
Case group (normal/abnormal)	30 (96.8%)/1 (3.2%)	15 (40.5%)/22 (59.5%)
Control group (normal/abnormal)	50 (100%)/0 (0%)	35 (71.4%)/14 (28.6%)
P-value	0.20	0.004

Table 4. Comparison of Bayley assessments between the healthy neonates and cases with intraventricular hemorrhage at six months of age

	Case (n=40)	Control (n=60)	P-value
Cognition	92.62±17.13	97.16±16.27	0.18
Communication	95.35±16.68	98.62±10.54	0.75
Receptive language (subscale)	8.65±2.52	8.70±2.83	0.92
Expressive language (subscale)	8.68±2.70	10.87±1.43	0.44
Motor	98.05±19.08	92.43±20.91	0.17
Fine motor(subscale)	9.50±3.53	9.26±3.51	0.74
Gross motor (subscale)	9.77±3.87	8.10±4.18	0.04

Table 5. Univariate analysis of variances between cases and controls by controlling the confounding variables

	Case (n=40)	Control (n=60)	P-value
Cognition	92.56±17.35	98.98±14.312	0.04
language	98.58±10.67	99.77±10.75	0.85
Receptive language	8.66±2.55	8.77±2.73	0.97
Expressive language	10.87±1.45	11.24±1.95	0.43
Motor	98.07±19.33	94.64±19.23	0.70
Fine motor	9.43±3.55	9.64±3.09	0.64
Gross motor	9.84±3.90	8.44±4.09	0.03

Discussion

In the current study, we compared the trend of neurodevelopment among healthy VLBW neonates and those diagnosed with grades I and II of IVH. The two assessed groups were similar in terms of demographic characteristics and respiratory-related complications; therefore, the probable factors affecting the neurodevelopmental trend of the newborns were similar. According to neurological examinations at sixth-month of age, a statistically significant higher rate of abnormality was evident for newborns with a history of low-grade IVH, while the cases and controls were similar at birth. In the same vein, Stewart et al., in an old study, showed that the chance of adverse outcomes in premature cases without IVH or with low grades of IVH was 3%, while it was up to 38% among those with more advanced IVH (16). A newer study revealed that the rate of major handicaps among newborns with IVH was 15%, in contrast to only 3% in those without IVH (17). The abovementioned studies did not differentiate between newborns without IVH and those with a mild grade, notably grades 1 and 2, of IVH, while we included cases with low-grade IVH.

Further neurodevelopmental evaluations, based on the Bayley scale, revealed remarkable superiority of the healthy controls only in gross motor performance but not in other aspects. In addition, the univariate analysis of variances, adjusted for demographic factors, showed that cognition and gross motor were associated with low-grade IVH in the sixth month of the age. Corroborated with our results, poor motor neurodevelopment has been represented by Pfahl et al. who followed newborns with grades I and II intraventricular hemorrhages for 18-24 months. They reported that birth weight and gestational age were the independent factors for the incidence of IVH (1). Another study by Patra et al., which followed 104 cases with low-grade IVH and 602 healthy newborns from 1992 to 2000, noted remarkable inferiority of patients with low-grade IVH compared to healthy premature ones in both mental and psychomotor developmental indices at 20 months of corrected age (13). Consistent with the mentioned studies, Klebermass-Schrehof et al. demonstrated the correlation of low-grade IVH with impaired mental and psychomotor developmental indices using the Bayley questionnaire. They reported more severe outcomes among premature newborns (less than 28 weeks of gestational age). They also pointed out that cerebral palsy and visual impairment indicators were dramatically affected by the gestational age (12). In contrast to the above findings, Payne et al. conducted a long-term follow-up cohort study on 270 infants with low-grade IVH and did not observed a significant effect for intraventricular hemorrhage on the worsening of neurodevelopmental performance of neonates with the gestational age of fewer than 27 weeks (11). Although we did not assess the role of gestational age and body birth weight on the neurodevelopmental performance of the IVH newborns, it seems that the inclusion criteria defined by Payne et al. (11), such as gestational age and birth weight, have affected the outcomes (i.e., no significant neurodevelopmental difference), while others noted the role of low-grade IVH on both mental and psychomotor performance of the preterm newborns (18, 19)

It should be noted that IVH occurrence in the earlier gestational ages, when the glial cells are being formed and developed, can affect the mental and psychomotor performance in a more steeply negative pattern (3).

Considering the remarkable higher rate of impaired neurological physical examinations and also findings of our study in terms of significant gross motor and cognition impairments among cases at six-month-old, we propose the role of early referral and neurologic physical examination in detecting neurodevelopmental abnormalities and providing timely specific interventions to minimize the subsequent complications. In our study, the fine motor aspect of the two groups was similar. Also, the difference between the two groups concerning motor performance (scale number) was not significant, which can be attributed to the concurrent consideration of both fine and gross motor neuron assessments.

Despite the value of sonographic study for the diagnosis of IVH, magnetic resonance imaging (MRI) is a more valuable modality for following patients with IVH at the time of discharge (8). Contrary to this study and most of the other studies in the literature, a recent study by Reubsaet et al. that used MRI for the IVH assessment demonstrated no association between low-grade IVH and neurodevelopmental performance (20). The development of cortex and myelination may be influenced by the deterioration of IVH, even with low-grade ones. Although sonography can provide an acceptable view of white matter, MRI examinations not only can depict the more unobstructed views of white matter injury but also can be used for long-term follow-up counseling; therefore, MRI findings may have considerable predictive value for the prognosis of motor and mental developmental performances (21). We recommend further studies on this population using MRI as a modality for assessing both the presence of IVH and following up on the patients' cerebral status.

This study demonstrated that low-grade IVH affected the sixth-month neurological examination and gross motor neuron performance of the VLBW newborns. Notably, low-grade IVH only affected cognition and gross motor. Further evaluations with longer follow-ups are strongly recommended.

Acknowledgment

We should thank the pediatric neurology department for their support and patients and their families for their patience. This study is done in Imam Hussein hospital, Isfahan University of Medical Sciences. IR.MUI.MED.REC.1397.323

Author's contribution

OY, MM and MRM contributed to the study concept, statistical analysis, drafting, and editing of the manuscript. OY, MM and AGA contributed to the study design, data collection, and editing of the manuscript. MM and MR contributed to conducting the study and editing the manuscript.

Conflict of interest

None

References

1. Pfahl S, Hoehn T, Lohmeier K, Richter-Werkle R, Babor F, Schramm D, et al. Long-term neurodevelopmental outcome following low grade intraventricular hemorrhage in premature infants. Early human development. 2018;117:62-7.
2. Calisici E, Eras Z, Oncel MY, Oguz SS, Gokce İK, Dilmen U. Neurodevelopmental outcomes of premature infants with severe intraventricular hemorrhage. The Journal of Maternal-Fetal & Neonatal Medicine. 2015;28(17):2115-20.
3. Ballabh P. Intraventricular hemorrhage in premature infants: mechanism of disease. Pediatric research. 2010;67(1):1.
4. Miller SP, Ferriero DM, Leonard C, Piecuch R, Glidden DV, Partridge JC, et al. Early brain injury in premature newborns detected with magnetic resonance imaging is associated with adverse early neurodevelopmental outcome. The Journal of pediatrics. 2005;147(5):609-16.
5. Leviton A, Kuban K, Paneth N. Intraventricular haemorrhage grading scheme: time to abandon? Acta Pædiatrica. 2007;96(9):1254-6.
6. Papile L-A, 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. The Journal of pediatrics. 1978;92(4):529-34.
7. Deng W, Pleasure J, Pleasure D. Progress in periventricular leukomalacia. Archives of neurology. 2008;65(10):1291-5.
8. Inder TE. Neurodevelopmental impact of low-grade intraventricular hemorrhage in very preterm infants. The Journal of pediatrics. 2006;149(2):152-4.
9. Bolisetty S, Dhawan A, Abdel-Latif M, Bajuk B, Stack J, Lui K. Intraventricular hemorrhage and neurodevelopmental outcomes in extreme preterm infants. Pediatrics. 2014;133(1):55-62.
10. Radic JA, Vincer M, McNeely PD. Outcomes of intraventricular hemorrhage and posthemorrhagic hydrocephalus in a population-based cohort of very preterm infants born to residents of Nova Scotia from 1993 to 2010. Journal of Neurosurgery: Pediatrics. 2015;15(6):580-8.
11. Payne AH, Hintz SR, Hibbs AM, Walsh MC, Vohr BR, Bann CM, et al. Neurodevelopmental outcomes of extremely low-gestational-age neonates with low-grade periventricular-intraventricular hemorrhage. JAMA pediatrics. 2013;167(5):451-9.
12. Soleimani F, Azari N, Kraskian Mojembari A, Vameghi R, Sajedi F. Developing of the Persian version of Bayley scales of infant and toddlers development screening test and determine its validity and reliability. Journal of Rehabilitation. 2014;14(6):18-29.
13. Azari N, Soleimani F, Vameghi R, SAJEDI F, Shahshahani S, Karimi H, et al. A psychometric study of the Bayley scales of infant and toddler development in Persian language children. Iranian journal of child neurology. 2017;11(1):50.
14. Stewart A, Thorburn R, Hope P, Goldsmith M, Lipscomb A, Reynolds E. Ultrasound appearance of the brain in very preterm infants and neurodevelopmental outcome at 18 months of age. Archives of Disease in Childhood.

1983;58(8):598-604.
15. Jakobi P, Weissman A, Zimmer EZ, Blazer S. Survival and long-term morbidity in preterm infants with and without a clinical diagnosis of periventricular, intraventricular hemorrhage. European Journal of Obstetrics & Gynecology and Reproductive Biology. 1992;46(2-3):73-7.
16. Vavasseur C, Slevin M, Donoghue V, Murphy J. Effect of low grade intraventricular hemorrhage on developmental outcome of preterm infants. The Journal of pediatrics. 2007;151(2):e6.
17. 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. Child's nervous system. 2012;28(12):2085-92.
18. 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. The Journal of pediatrics. 2006;149(2):169-73.
19. Sherlock RL, Anderson PJ, Doyle LW, Group VICS. Neurodevelopmental sequelae of intraventricular haemorrhage at 8 years of age in a regional cohort of ELBW/very preterm infants. Early human development. 2005;81(11):909-16.
20. Reubsaet P, Brouwer AJ, van Haastert IC, Brouwer MJ, Koopman C, Groenendaal F, et al. The impact of low-grade germinal matrix-intraventricular hemorrhage on neurodevelopmental outcome of very preterm infants. Neonatology. 2017;112(3):203-10.
21. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. New England Journal of Medicine. 2006;355(7):685-94.