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SEVERITY AND OUTCOMES OF INTRACRANIAL HAEMORRHAGES IN VERY LOW BIRTH WEIGHT INFANTS

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Abstract

Objectives: To investigate the incidence and severity of intracranial haemorrhages in very low birth weight infants and evaluate associated neurodevelopmental outcomes at 2 years of postconceptual corrected age.

Methods: The subjects of present study were preterm neonates with very low birth weight who were treated at two units of neonatal intensive care in 2012. All infants had serial cranial ultrasound scans. Neurologic development was assessed at the age of 2 using Bayley scale of infant development.

Results: During study period 100 very low birth weight infants were available, who underwent cranial ultrasound exams. Intracranial haemorrhage was diagnosed in seventeen patients with following frequencies: 10% III grade intraventricular haemorrhage, 9% haemorrhagic parenchymal infarction (7 of which also had III grade intraventricular haemorrhage, and one with I grade intraventricular haemorrhage), 2% II grade interventricular haemorrhage and 4% I grade intraventricular haemorrhage. From 17 patients with intracranial haemorrhages, 7 (41%) died during neonatal period. Posthaemorrhagic ventriculomegaly and/or porencephalic cysts were found in 3 survived patients with intracranial haemorrgahic lesions (10 from 17). In 5 patients were noted some cystic changes in ventricular system with a tendency for further disappearance. Correlation between interventricular haemorrhage / haemorrhagic parenchymal infarction, absence of antenatal prophylaxis with steroids and need for intubation at birth was found. Neurological development at 2 years of age was evaluated in 9 preterm infants from 10 survived patients. Infantile cerebral palsy was found in 2 patients with II grade intraventricular haemorrhage and 2 with III grade intraventricular haemorrhage and haemorrhagic parenchymal infarction from those 9 preterm infants. Motor problems not connected with infantile cerebral palsy were found in 1 patient with III grade intraventricular haemorrhage. Normal development was noticed in 3 patients with I grade intraventricular haemorrhage and one with small haemorrhagic parenchymal infarction.

Conclusions: The incidence of III grade intraventricular haemorrhage and haemorrhagic parenchymal infarction is higher than I and II grade intraventricular haemorrhages. Such finding doesn't match with the majority of publications in western countries. Some preventable risk factors for intraventricular haemorrhage / haemorrhagic parenchymal infarction development were found during this study. The mortality is high in III grade intraventricular haemorrhage and haemorrhagic parenchymal infarction groups. Permanent cerebral lesions with later development of neurologic abnormalities are found in survived patients.

Keywords: *prematurity, cranial ultrasound, intraventricular haemorrhage, haemorrhagic parenchymal infarction, infantile cerebral palsy.*

Introduction

The survival incidence of prematures and neonates with complications is increasing during perinatal period with the improvement of medical technologies. However, the incidence of brain dysfunction in survived infants is still on the rise [*Kiely J, Susser M, 1992; Guyer B et al., 1998; Volpe J, 1998; Martin J et al., 2005*]. Intracranial haemorrhage (ICH) is one of the most serious neurological complications in very low birth weight infants during the neonatal period [*Volpe J, 2008; Marba S et al., 2011*]. The magnitude of the ICH problem is relatively connected to high and not changing incidence of premature birth. Intraventicular haemorrhage is the most common type of

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ICH in this category of newborns [*Liu J et al., 2010*]. It is important to detect this pathology as early as possible because it is connected with the high incidence of mortality and can lead to disturbances in the neuropsychomotor development of those newborns [*Baumert M et al., 2008*]. The most common localization of intraventricular haemorrhage in preterm infants is the germinal matrix, which is located in the periventricular subependymal region and is irrigated by fragile and immature vasculature. Germinal matrix is an important proliferation source of neuronal precursors before their final migration to cerebral cortex [*Volpe J, 1989*]. There are a variety of methods used to detect the neonatal cranial lesions, such as computed tomography, magnetic resonance tomography and neurosonography. With the development of neonatal cranial ultrasound (CUS) technology, CUS has become the main method of identification of IVH in newborns. Ultrasound has many advantages such as convenience, the dynamic observation and the absence of radiation. It has a high sensitivity during the diagnosis of intraventricular and intraparenchimal haemorrhages [*Szymonowicz W et al., 1984; Blankenberg F et al., 2000; LeFlore J et al., 2003; Anca I, 2011; Tam E et al., 2011*]. The incidence of ICH has steadily decreased but it is still the most important problem because it has a major impact on the psychomotor development of premature infants [*Di Salvo D, 2001*]. According to Volpe J (2008), the risk of long-term neurologic disability is about 15% I grade IVH, 25% II grade IVH, 50% III grade IVH and 75% haemorrhagic parenchymal infarction (HPI) associated with III grade IVH.

The aim of this study was to investigate the incidence and severity of ICH in very low birth weight preterm infants, and the evaluation of neurologic outcomes associated with them at 2 years of postconceptual corrected age.

Materials and methods

The subjects of present study were preterm very low birth weight neonates (less than 32 weeks of gestational age and/or less than 1500 grams birth weight). The newborns treated at neonatal intensive care units of 3rd level (NICUs of Research Centre of Maternal and Child Health Protection and the Institute of Reproductive Health, Perinatology, Obstetrics and Gynecology, Yerevan, Armenia) from February to December, 2012. The parents of the infants had given both written and verbal consent and were acquainted with the booklet describing the study.

The cranial ultrasound scans were carried out at the cot of each infant during neonatal period following the protocol. The first exam was done immediately after birth, the second one was done at 2-3 weeks after birth, the third one - before discharging home or to another unit (usually 34-37 weeks postconceptual age) and the fourth – at equivalent age. Additional scans were performed if the infant's clinical state deterioincidenced or specific neurological symptoms. Neurosonography was done using portable scanner Zonare (z.one ultra-Convertible Ultrasound System; Zonare Medical Systems Inc, Mountain View, California, USA) with microconvex C9-4t sensor transducer of 7.5 and 8 *MHz* frequency. AlI infants were scanned by a single operator including normal cerebral anatomy or presence of ICH (I, II, III grade IVH, and/or haemorrhagic parenchymal infarction (HPI) [*Volpe J, 2008*]. The protocol included at least five coronal slices, one midsagittal and two left and right parasagittal views according to Meijler G (2012). All images were stored in a digital format for later study.

The results associated with neurologic development were evaluated by the pediatrician using Bayley scale of infant development (BSID-III) [*Bayley N, 2006*]. All exams were recorded in digital format video. BSID-III is an individually administered instrument that assesses motor (fine and gross), language (receptive and expressive), cognitive, social-emotional and adaptive behavioral [*Black M, Matula K, 1999*] development of infants and children. This measure consists of a series of games and tasks and lasts about 45 - 60 minutes to administer [*Lawrence G et al., 2010*]. Raw scores of successfully completed items are converted to scale scores and to composite scores. These scores are used to determine the child's performance compared with norms taken from typically developing children of their age (in months) [*Torras-Mañà M et al., 2014*]. Statistical analysis was performed with IBM SPSS Statistics 20. The incidence of pathological findings was studied. The associations between findings during neuro-

sonography and clinical and perinatal data were assessed using Fisher's exact test (2-sided) for categorical variables and Mann-Whitney test for quantitative variables. P <0.05 indicated a significant difference.

Results

During study period 100 very low birth weight infants were admitted. These infants underwent serial CUS exams. Seventeen infants from 100 investigated had ICH during neurosonography (Table 1). Ten patients (59%) had III grade IVH, five of which also had cerebellar haemorrhage. Nine infants (53%) had HPI, seven of which with III grade IVH (41%), and one with I grade IVH. II grade intraventricular haemorrhage was found in 2 patients (12%), one of which later had cystic periventricular leucomalacia. I grade intraventicular haemorrhage was diagnosed in four infants (24%).

During neonatal period 7 (41%) patients from 17 with haemorrhagic parenchymal infarction died, 5 (71%) of which had III grade intraventricular haemorrhage plus haemorrhagic parenchymal infarction, 1 had III grade intraventricular haemorrhage and 1 had haemorrhagic parenchymal infarction. The incidence of severe intraventricular haemorrhage and haemorrhagic parenchymal infarction together was 12% and mortality incidence in patients with III grade intraventricular haemorrhage and/or haemorrhagic parenchymal infarction was 60%. Posthaemorrhagic ventriculomegaly was found in 3 survived patients (10 out of 17) after III grade intraventricular haemorrhage and/or porencephalic cysts in brain parenchyma after HPI. One had mild ventriculomegaly after III grade IVH. Some cystic changes were noted in lateral ventricles after I grade IVH or II grade IVH with disappearance in later scans in 5 patients. One patient with small HPI had normal scan at equivalent age. Some typical examples of early and late CUS scans and results after ICH are shown in Figure 1.

All possible demographic, anamnestic and clinical data for finding risk factors for intraventricular haemorrhage and haemorrhagic parenchymal infarction were found. The results are shown in Table 2. The absence of antenatal prophylaxis with steroids was the risk factor for intracranial haemorrhage, which was significantly associated with II and III grades of intraventricular haemorrhage

Table 1.

Incidence and severity of intracranial haemorrhage in study group

Type of haemorrhage		Total number of findings, n (%)
Intraventricular haemorrhage	I grade	4 (24%)
	II grade	2 (12%)
	III grade	10 (59%)
Haemorrhagic parenchymal infarction		9 (53%)
III grade intraventricular haemorrhage + haemorrhagic parenchymal infarction		7 (41%)

Notes: coded by the highest grade of haemorrhage*

Table 2.

Risk factors for interventricular haemorrhage and haemorrhagic parenchymal infarction development

Groups \ Risk factors	No antenatal steroids, n (%)	Intubation at birth, n (%)	p
IVH grade II-III (n=13)	11 (84.5)	2 (15.5)	0.037
no IVH (n=87)	46 (53)	1(1)	0.044
HPI (n=7)	7 (100)	-	-
no HPI (n=93)	50 (54)	-	0.019

(84% vs 53%, p=0.037) and haemorrhagic parenchymal infarction (100% vs 54%, p=0.019). The intubation at birth also was associated with II and III grades of intraventricular haemorrhage (15.5% vs 1%, p=0.044).

From survived 10 ex-premature infants 7 were examined using BSID-III test, 2 were consulted by phone-call. Parents refused to participate and did not give any information about child development in another case. From those infants, 2 with III grade interventricular haemorrhage and haemorrhagic parenchymal infarction have some motor problems (diagnosed as ICP), but could walk with orthesis. One infant had III grade IVH motor problems not connected to infantile cerebral palsy (ICP) (some neurological abnormality in tone and reflexes, clumsiness fine and gross motor problems), 2 children with II grade IVH (one also had cystic periventricular leucomalacia) had ICP (spastic hemiplegia), 3 patients with I grade IVH and one with small haemorrhagic parenchymal infarction had normal psychomotor development.

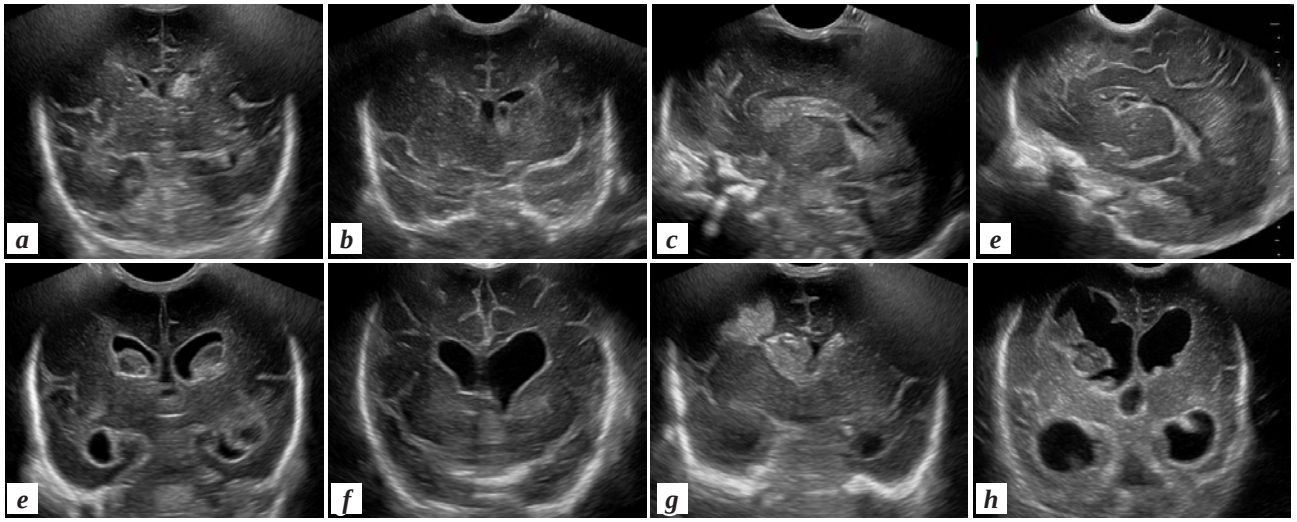

Figure 1. *Neurosonographic changes and outcomes after intracranial haemorrhage.*
***a**. shows I grade intraventricular haemorrhage (day 4)*
***b**. shows the same patient on18th day after birth with later cystic transformation who had a normal developmental outcome.*
***c-d**. show II grade intraventricular haemorrhage after birth with later development of cyst in lateral ventricle on 26th day of life. This patient survived but has cerebral palsy.*
***e-f**. are examples of III grade intraventricular haemorrhage on 14th day with posthaemorragic ventriculomegaly on 44th day. The child developed non- cerebral palsy motor problems.*
***g-h**. are examples of III grade intraventricular haemorrhage and haemorrhagic parenchymal infarction (found on 3rd day after birth) with later posthaemorrhagic ventriculomegaly and porencephalic cyst development on 23rd day. The child survived, but has cerebral palsy.*

All cases with intracranial haemorrhage with their cranial ultrasound (CUS) technology findings, demographic data and outcomes are shown in Table 3 and 4. Table 4 shows that the patients with ICP and 1 patient with small HPI but normal motor development also had developmental problems in adaptive behavioral domain.

Conclusions

In the studied cohort of very low birth weight of premature newborns total incidence of ICH was 17%, which is less than presented in the modern western literature [*Volpe J, 2008*]. Severe forms of intracranial lesions (III grade IVH, HPI) were seen more frequently than mild forms of I grade IVH and II grade IVH and it is not correlated with gestation age and birth weight. Small lesions, which later ruptured into ventricular cavity or parenchyma and became II or III grade IVH, were found in 3 infants at first few days of life. Two patients had I or II grade haemorrhage in one side and II or III grade in the other side. The patient was included in a group of more severe form in such cases.

The incidence of I grade IVH in very low birth weight preterm infants of Armenian population included in our study was 24% from all cases of ICH, II grade – 12%, III grade– 59%, HPI – 53% and the incidence of HPI+ III grade IVH was 41%, while in published data by J. Volpe (2008) it is 40% I grade, 25% II grade, 20% III grade and 15% HPI+ III grade IVH. The incidence of severe haemorrhage was higher than mild one in patients included in our study, which was a distinctive feature while comparing with the results of majority of publications inch western countries. [*Horbar J et al., 2002; Larroque B et al., 2003; Hamrick S et al., 2004; Wilson-Costello D et al., 2005; Volpe J, 2008*]

One of the research objectives was the attempt to find risk factors explaining the results. Expressed association between IVH/HPI, absence of antenatal prophylaxis with steroids and need for intubation at birth, which in most cases are preventable factors, was found during our study.

Preterm infants are at increasing risk of infantile cerebral palsy with abnormality of motor, adaptive and intellectual abilities [*Vohr B et al., 2000; Hack M et al., 2002; Casey P et al., 2006; Jaakkola J et al., 2006*]. In addition, cognitive def-

TABLE 3.

Early outcomes of the patients with intracranial haemorrhages

Patient	ICH type	Gestation (weeks)	Weight (g)	Sex	Mode of Delivery	Use of steroids	Days of IMV	Mortality	CUS findings at the last scan
1	IVH grade I/II/c-PVL	29	1340	M	Vaginal	Yes	4	Survived	Cyst in ventricular system and brain parenchyma
2	IVH grade I/HPI	27	1150	M	Vaginal	No	5	Not survived	–
3	IVH grade I	29	1550	F	Vaginal	Yes	0	Survived	Small cyst in germinal matrix
4	IVH grade I	30	1480	M	Vaginal	No	0	Survived	Small cyst in germinal matrix
5	IVH grade I	32	1010	M	C-Section	Yes	0	Survived	Small cyst in germinal matrix
6	IVH grade II/III/HPI	31	1250	M	C-Section	No	8	Not survived	–
7	IVH grade II	27	970	M	Vaginal	Yes	0	Survived	Cyst in ventricular system
8	IVH grade III/HPI/Cerebellar haemorrhage	25	830	F	Vaginal	No	6	Not survived	–
9	IVH grade III/HPI	26	930	F	C-Section	No	3	Not survived	–
10	IVH grade III/HPI/Cerebellar haemorrhage	29	1200	M	C-Section	No	5	Not survived	–
11	IVH grade III/HPI/Cerebellar haemorrhage	32	1250	M	C-Section	No	2	Not survived	–
12	IVH grade III	25	550	M	Vaginal	No	6	Not survived	–
13	IVH grade III/Cerebellar haemorrhage	31	1650	F	Vaginal	No	0	Survived	Mild ventriculomegaly
14	IVH grade III/HPI/Cerebellar haemorrhage	31	1500	F	C-Section	No	13	Survived	PHVM, porencephalic cyst
15	IVH grade III/HPI	32	1770	F	C-Section	No	0	Survived	
16	IVH grade III	27	1050	M	C-Section	No	16	Survived	PHVM
17	HPI like lesion	28	1150	M	C-Section	Yes	0	Survived	No any pathological transformation

***Abbreviations: IVH** – interventricular haemorrhage; **HPI** – haemorrhagic parenchymal infarction; **c-PVL** – cystic periventricular leucomalacia; **CUS** - cranial ultrasound; **PHVM** – posthaemorrhagic ventriculomegaly; **IMV** – intermittent mechanical ventilation; **C-Section** caesarean section.*

TABLE 4.

Developmental outcomes of survived patients with intracranial haemorrhages at the age of 23-26 month

Patient	ICH grade	BSID (months)	Developmental outcome	GM	FM	MC	C	CC	RC	EC	Com.C	SE	GAC	CON	SO	PR
1	IVH grade I/II/c-PVL	25	ICP	8	8	88	8	90	10	8	94	80	71*	76*	77*	68*
3	IVH grade I	24	ND	9	12	103	10	100	10	13	109	100	108	109	108	99
4	IVH grade I	24	ND	10	12	107	11	105	10	11	103	105	118	109	118	114
5	IVH grade I	26	ND	8	12	100	10	100	10	9	86	90	112	103	116	107
7	IVH grade II	24	ICP	1*	10	73*	11	105	7	5*	77*	85	65*	65*	77*	76*
13	IVH grade III/Cerebellar haemorrhage	-	No Data	-	-	-	-	-	-	-	-	-	-	-	-	-
14	IVH grade III/HPI/ Cerebellar haemorrhage	-	Not examined, has ICP**	-	-	-	-	-	-	-	-	-	-	-	-	-
15	IVH grade III/HPI	-	Not examined, has ICP**	-	-	-	-	-	-	-	-	-	-	-	-	-
16	IVH grade III	23	Non-ICP motor problems	5*	6*	73*	11	105	12	13	115	85	107	117	93	105
17	HPI like lesion	25	ND	10	13	110	11	105	11	9	100	85	69*	79*	59*	80*

***Notes**: *– score is in abnormal range (for scaled score normal range is from 7 to 13, for composite score - from 85 to 115. Scores below these ranges indicate developmental delay).*

***– diagnosed by neurologists*

***Abbreviations: ICP** - cerebral palsy; **ND** - normal development; **GM** - gross motor scale score; **FM** - fine motor scale score; **MC** - motor composite score; **C** - cognitive scale score; **CC** - cognitive composite score; **RC** - receptive communication scale score; **EC** - expressive communication scale score; **Com.C** - communication composite score; **SE** - social-emotional composite score; **GAC** - general adaptive composite; **CON** - conceptual adaptive domain; **SO** - social adaptive domain; **PR** - practical adaptive domain.*

icits, behavioral and emotional problems are also more prevalent in this population of newborns, which can cause difficulties in academic deficiencies [*Hack M et al., 2004; Dahl L et al., 2006; Reijneveld S et al., 2006*].

All patients with I grade IVH have normal development in this cohort of newborns. ICP was found in infants with II grade IVH (one also had cystic periventricular leucomalacia, a major risk factor for ICP development) who had problems in adaptive-behavioral development and HPI also highly correlated with motor problems. Many newborns with III grade intraventricular haemorrhage died during neonatal period. This data are a little bit different from western literature data [*Volpe J, 2008*]. It can be explained by a small number of patients included in study. However, the presented results of own studies may provide important information for neonatologists and neurologists consulting parents of newborns with ICH

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