

Risk Factors of Germinal Matrix Intraventricular Hemorrhage in Premature Infants

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Abstract

Objective: To determine whether some clinical parameters can be used to predict the hemorrhage and whether the relationship between these clinical variables and the grades of hemorrhage is linear.

Methods: A total of 230 premature infants, born at a gestational age less than 34 weeks were retrospectively reviewed. Germinal matrix-intraventricular hemorrhage (GM-IVH), the grade of the hemorrhage, and clinical data were assessed with a checklist. Variables were analyzed by using Mann Whitney U and Fisher's exact tests and then multiple logistic regression analysis was used to evaluate the independent risk factors.

Findings: Resuscitation, gestational age, hypotension, multiple birth, and birth weight were found to be independent risk factors. We determined non-linear relationship between the grades of hemorrhage and the clinical parameters. But when we classified hemorrhages as grade 1, grade 2-3 and grade 4, the relationships were found linear.

Conclusion: Premature infants who had resuscitation, low gestational age, hypotension, multiple birth, and low birth weight are more likely to have GM-IVH. The relationship between the clinical variables and the grades of GM-IVH does not seem to be linear.

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Key Words: Ultrasonography; Risk Factors; Premature Infants; Hemorrhage; Germinal Matrix

Introduction

The incidence of germinal matrix-intraventricular hemorrhage (GM-IVH) has decreased steadily but it is still an important problem because it has a major impact on the neurodevelopmental outcome of premature infants^[1].

Identification of potential risk factors may aid to predict in which patients hemorrhage is most likely to occur, may contribute to early diagnosis, and may help to take suitable measures to prevent injury and consequently neurological sequelae. Several studies have reported the relationship between GM-IVH and perinatal risk factors but to

our knowledge, correlation between the grades of hemorrhage has not been reported. We therefore aim to retrospectively evaluate whether clinical parameters can be used to help predict the GM-IVH hemorrhage and to describe the relationship between the clinical variables and the grades of hemorrhage.

Subjects and Methods

Subjects

Cranial ultrasonographies and medical records of

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the premature infants born at a gestational age (GA) of less than 34 weeks, who were admitted to our neonatal intensive care unit between October 2009 and November 2011, were retrospectively evaluated. The exclusion criteria were known or suspected congenital and chromosomal anomalies, metabolic disorders, central nervous system infections and an unknown GA and/or perinatal data. Ethics committee approval for this study was obtained.

Risk Factors

The following perinatal clinical data were retrospectively collected by an senior neonatologist:

- Gender (male/female)
- GA at birth (weeks)
- Birth weight (grams)
- Multiple birth (singleton/twin/triplet)
- Mode of delivery (vaginal or cesarean section)
- Antenatal corticosteroid treatment for prevention of respiratory distress syndrome (two doses with an interval of 24 hours given at least 48 hours before birth)
- Maternal diabetes mellitus (gestational and pregestational diabetes mellitus)
- Preeclampsia
- Premature rupture of the membranes (PROM)
- Cardiopulmonary resuscitation (intubation in delivery room and need for mechanical ventilation)
- Sepsis (early onset neonatal infectious disease defined as a positive blood culture)
- Hypotension (first days, requiring inotropic treatment)

Cranial Ultrasonography

Cranial US were performed using the portable machine (Mindray, Shenzhen, China) with a transducer frequency of 6.5 MHz to 8.5 MHz. Ultrasonography was performed at bedside by a radiologist (Y.P.) and first scan was obtained within 7 days following birth. A minimum of two cranial US was performed during the first week of life and examinations were repeated weekly or more frequently as clinically indicated for the first month. Standardized images including anterior fontanel, posterior fontanel and mastoid fontanel views, were taken.

Cranial ultrasonography images were retrospectively re-evaluated by three of the authors (Y.P., A.P, N.E.) who were blinded to the infants' clinical data and outcome. The existence of GM-IVH and grade of the hemorrhage were recorded from the images. GM-IVH was diagnosed and classified according to previously published criteria^[2]. We called grade 0, when there was no hemorrhage; grade 1, when echogenicity was confined to the germinal matrix; grade 2, when there was intraventricular hemorrhage without ventricular distension; grade 3, when there was intraventricular hemorrhage with ventricular distension; grade 4 or PVHI, when there was periventricular, unilateral or bilateral asymmetric echogenicity accompanying IVH. Patients who had bilateral symmetric echogenicities that were compatible with PVL alone were excluded from the study.

Statistical Analysis

Data analyses were performed by using statistical software (SPSS 15.0 for windows; SPSS inc.,

Table 1: Demographic characteristics of the patients associated with germinal matrix-intraventricular hemorrhage

Characteristic	No (0)	Grade 1	Grade 2	Grade 3	Grade 4	P. value*	P. value‡	
Gender, n	Male	90	10	8	7	14	0.5	0.3
	Female	66	15	2	7	11		
Gestational age weeks (SD)	29.5 (2.9)	29.1 (2.6)	25.8 (1.7)	27.7 (2.5)	26.6 (2.8)	<0.001	NL	
Birth weight (gr) mean (SD)	1364 (489)	1300 (394)	1364 (489)	1125 (394)	924 (274)	<0.001	NL	
Multiple births, n	23	9	1	3	8	0.02	NL	
Mode of delivery, n	Vaginal	51	9	5	5	11	0.3	0.7
	C/S	105	16	5	9	14		

*Fisher's Exact test for hemorrhage positive or negative and ‡Chi-square for grade 1-4 hemorrhage.

SD: standard deviation; NL: significant but there is not a linear relationship in terms of the grades of hemorrhage; CS: Caesarean section

Table 2: Maternal risk factors associated with germinal matrix-intraventricular hemorrhage

Risk factors	No (0)	Grade 1	Grade 2	Grade 3	Grade 4	P. value*	P. value‡
Antenatal corticosteroid treatment, n	47	4	1	1	6	0.02	0.1
Maternal diabetes mellitus, n	19	1	2	1	2	0.5	0.5
Preeclampsia, n	27	6	1	4	3	0.8	0.6
PROM, n	31	3	2	5	5	1.0	0.5

*Fisher's Exact test for haemorrhage positive or negative and ‡Chi-square for grade 1-4 haemorrhage.
PROM: Premature rupture of the membranes

Chicago, IL, USA). A power analysis was performed to determine whether sample size of each group was adequate to do statistical analysis. The clinical parameters were compared between infants with and without GM-IVH using a Fisher's exact test for categorical variables (hemorrhage positive or negative) and Mann Whitney U test for numerical variables (grade 1-4 hemorrhage). A difference with $P < 0.05$ was considered significant. The clinical parameters at which univariate analyses were significant were entered into logistic regression analysis to identify independent risk factors. Gestational age and birth weight were entered into logistic regression analysis separately in order to account for the strong influence of preterm delivery on the occurrence of low birth weight.

Findings

Demographic Characteristics Related to GM-IVH

Between October 2009 and September 2011, 287 premature infants (<34 weeks) were eligible for the study. Seventy patients were excluded for the following reasons: unknown gestational age or perinatal clinical data (n=25), known or suspected congenital and chromosomal anomalies (n=15), metabolic disorders (n=7), central nervous system infections (n=5), bilateral symmetric echo-

genicities compatible with PVL alone (n=5).

Demographic characteristics associated with GM-IVH are shown in Table 1. Univariate analyses showed that gender and mode of delivery were not associated with presence of the hemorrhage. There was also no significant association in terms of the grades of hemorrhage.

A strong association was found between presence of hemorrhage and low gestational age. There was no linear relationship between the clinical parameter (low gestational age) and the grades of hemorrhage. But when we analyzed grade 2 and grade 3 as one group the relationship was found to be linear. Similar statistical findings were found while analyzing birth weight.

All of the multiple births were twins in our study. Hemorrhage was more common in twins, but this association was only of marginal statistical significance ($P = .044$)

Maternal Risk Factors Related to GM-IVH

The relation between hemorrhage and maternal risk factors are shown in Table 2. Germinal matrix-intraventricular hemorrhage was lower in infants whose mothers took a full course of antenatal corticosteroids. Hemorrhage was also lower in infants of mothers with pregestational or gestational DM than without DM but there was no statistical significance. Preeclampsia and PROM were not found to be related to hemorrhage in our study.

Table 3: Neonatal risk factors associated with germinal matrix-intraventricular hemorrhage

Risk factors	No (0)	Grade 1	Grade 2	Grade 3	Grade 4	P. value*	P. value‡
Cardiopulmonary resuscitation in the delivery room, n	17	10	3	6	16	<0.001	NL
Sepsis, n	14	4	1	1	5	0.2	0.5
Hypotension, n	2	2	1	4	8	<0.001	NL

*Fisher's Exact test for haemorrhage positive or negative and ‡Chi-square for grade 1-4 haemorrhage.
NL: Significant but there is not a linear relationship in terms of the grades of hemorrhage

Table 4: Results of Multiple Logistic Regression Analysis to predict GM-IVH in preterm infants born at <34 weeks*

Risk factors	Regression Coefficient (B)	Standard deviation	Odds ratio	95% CI	P. value
Resuscitation	1.47	0.39	4.33	2.02-9.29	<0.001
Gestational age‡	-0.26	0.06	0.77	0.68-88	<0.001
Multiple birth‡	0.80	0.39	2.23	1.03-4.95	0.04
Hypotension	2.18	0.86	8.81	1.62-47.81	0.01
Multiple birth	0.83	0.40	2.30	1.05-5.04	0.04
Constant	5.90	1.95			0.002

*Only variables of significant value from the univariate analysis were entered into the multiple logistic regression analysis.

‡A separate analysis of differences in birth weight was carried out in the premature infants in order to account for the strong influence of preterm delivery on the occurrence of low birth weight. CI: confidence for interval,

Neonatal Risk Factors Related to GM-IVH

The relation between hemorrhage and neonatal risk factors are shown in Table 3. Among all the risk factors, cardiopulmonary resuscitation in the delivery room was found to be the most significant factor. Sepsis showed no statistical significance. Hypotension was significantly associated with germinal matrix-intraventricular hemorrhage.

All variables that showed significant difference in the univariate analysis were used in a stepwise forward logistic regression analysis to determine true association between positive risk factors and hemorrhage (Table 4). Gestational age and birth weight were entered into logistic regression analysis separately to account for the strong influence of low gestational age on the occurrence of low birth weight. Resuscitation, gestational age, hypotension, multiple birth, and birth weight were found to be independent risk factors.

Discussion

We demonstrated that some clinical parameters can be used as a predictor of GM-IVH in premature infants. Cardiopulmonary resuscitation in the delivery room, low gestational age, low birth weight, hypotension and multiple births, are more likely to be associated with GM-IVH. We also found nonlinear relationship between the clinical parameters and the grades of GM-IVH that have not been reported before. But when we classified hemorrhages as grade 1, grade 2-3 and grade 4, the relationships were found linear.

Male gender was reported as an independent

risk factor for intraventricular hemorrhage by some investigators and it was found to be related to poor neurological outcome^[3-6]. The results of our study and those of the study of Locatelli et al^[7] suggest otherwise. The percent of hemorrhage among the grades were similar between male and female premature infants in our study. Kent et al^[6] suggest that gender differences for mortality and long-term neurological outcome lose significance at 27 weeks gestation. In our study, preterm infants with grade 1 and 3 hemorrhages had mean gestational age older than 27 weeks. Mean gestational age of the infants with grade 2 and 4 hemorrhages were 25.8 and 26.6, respectively.

Low gestational age and low birth weight are well known risk factors for germinal matrix-intraventricular hemorrhage, as already reported by others in larger series^[8-11]. We found both of them as an independent risk factor, that is, one of them could help to predict hemorrhage. There were statistically no difference between grade 0 and 1, grade 0 and 3, grade 1 and 3, grade 2 and 3. The relationship was non-linear. Grade 1 hemorrhage may be seen in term and normal birth weight premature infants and it generally does not have poor neurological outcome. Grade 2 and 3 hemorrhages have usually similar neurological outcome, but of all grades, grade 4 has the poorest outcome^[12].

Multiple births are also known as a risk factor for GM-IVH^[13]. It has a strong influence on the occurrence of low gestational age and birth weight. Vermeulen et al^[10] found no significant influence of multiple births on the development hemorrhage in their large series but we found it as an independent risk factor in the multiple logistic regression analyses. Previous results may be due to study time (1990-1996). Multiple births are

now more common, likely as a result of IVF but mode of conception has no influence on the incidence of neonatal morbidity or mortality^[14,15].

A cesarean section might protect against the development of GM-IVH and periventricular leucomalacia. It might be true, especially for chorioamnionitis^[16]. Looney et al^[17] suggested that intracranial hemorrhage following vaginal delivery was more common than cesarean section. Vermeulen et al^[10] found that cesarean section was nearly protective for abnormalities on ultrasonography. Some studies did not reveal any relationship between mode of delivery and GM-IVH^[7,8]. We concluded that the protective role of cesarean section is speculative and actually we did not find any significant difference in our study.

The protective effect of antenatal steroid therapy has been reported in earlier studies^[8,10]. The protective mechanism of it may be due to an increase in neonatal blood pressure which prevents blood pressure fluctuations or may result from enhanced maturation of the cardiopulmonary system and germinal matrix of the premature infant^[10]. Antenatal steroid therapy was not found to be significantly protective by some authors^[4,7,11]. This may be related to incomplete course of antenatal steroid therapy before birth. In our study only full dose of corticosteroid therapy considered positive for antenatal steroid therapy.

Maternal diabetes mellitus was not found to be related with RDS or other major complications of prematurity with modern management and adequate prenatal care by Bental et al^[13]. Furthermore, in our study, it seemed to have some preventive effect on GM-IVH development. This finding is different from other studies and we think that it might be due to either preventative measures taken against respiratory distress syndrome or predisposition to thrombosis rather than hemorrhage. But this warrants further investigations with more patients and long term follow up.

Although preeclampsia was found to be a risk factor for periventricular leukomalacia by some authors^[18], it was not reported to be related to intraventricular hemorrhage^[7,11]. Preeclampsia in this age group (<34 weeks) may be protective because of treatment regimens as magnesium sulfate, antenatal steroids and elective cesarean section^[18].

Premature rupture of the membranes (PROM) is the leading identifiable cause of prematurity and is also responsible for the neonatal problems resulting from prematurity^[19]. We did not find significant relationship between PROM and GM-IVH, as already reported by Vural et al^[8]. Locatelli et al^[7] observed no significant relationship between PROM and antenatal variables, associated with severe neurodevelopmental outcome among neonates born at less than 32 weeks. Potential prolonged exposure to inflammation/infection could be harmful to the developing fetus. But antibiotics are now widely used and they were reported to have a protective effect on the neonatal morbidity in women with PROM at a gestation of 34 weeks or less^[20].

Cardiopulmonary resuscitation in the delivery room was the strongest factor in the prediction of hemorrhage in our study. Both the time at which ventilation was initiated and the duration of ventilation are important determinants of severe IVH. Risk for severe IVH in premature infants who never had intubation in delivery room or during the first 3 days of life was reported to be minimum^[21]. Premature infants necessitating mechanical ventilation were found to have an increased risk of GM-IVH in many studies^[8,10,18]. This may reflect the severity of the illness or be associated with fluctuations of blood pressure in premature infant, which is thought to be the main cause of GM-IVH^[10,22].

Sepsis is identified as a potential risk factor for the development of IVH in premature infants in some studies by only univariate analysis^[4,8,10]. Vermeulen et al^[10] found it as a significant factor in logistic regression analysis. It has been suggested that GM-IVH may be due to damaging of the fetal blood-brain barrier by cytokines^[10,22]. It is important to note that our findings were different from those of other studies. We did not find significant relationship between sepsis and GM-IVH. It may be due to early onset of antibiotic therapy.

Hypotension can lead to a decrease in cerebral blood flow which may cause injury of the germinal matrix capillaries by reperfusion^[8]. It has been reported as a significant factor for predicting GM-IVH by univariate analysis^[4,8]. In our study hypotension was more commonly seen in grade 4 hemorrhage and we found it as an independent risk factor.

As a retrospective analysis, there are several limitations to our study. This is a retrospective, single center study. We tried to include all premature infants with GM-IVH, but perhaps we still missed some. We did not include the patients who had congenital and chromosomal anomalies or metabolic disorders. As some patients did not have long follow-up because of death or transferring to another hospital, we could not exactly know whether they had congenital and chromosomal anomalies or metabolic disorders. We only reviewed determined risk factors. We tried to choose risk factors that can be obtained at first day for early prediction of GM-IVH. But we might have missed some relevant associations and risk factors. Ultimately, we hope to be able to determine whether these significant factors are associated with late neurodevelopmental problems in further studies.

Conclusion

GM-IVH is well recognized if it is thought of early. This study revealed that premature infants who had cardiopulmonary resuscitation in delivery room are more likely to have GM-IVH. Low gestational age, hypotension, multiple birth, and low birth weight are other important risk factors. In addition, the relationship between the clinical variables and the grades of GM-IVH is not linear.

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Authors' Contribution

Y. Pekcevik, E. Arun Ozer, N. Erdogan: Concept / Design
 Y. Pekcevik, A. Pasinli, E. Arun Ozer: Acquisition of Data
 Y. Pekcevik, A. Pasinli, E. Arun Ozer, N. Erdogan: Data Analysis / Interpretation
 Y. Pekcevik, Manuscript Preparation
 Y. Pekcevik, N. Erdogan: Critical Revision of the Manuscript
 All authors approve final version of the paper.

Conflict of Interest: None

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