MATERIALS AND METHODS

Population
A total of 168 premature neonates whose birth weight ≤1500 g or gestational age ≤34 weeks were examined by cranial ultrasound (CUS) for detection of GM-IVH among the babies admitted between January 2011 and December 2012 in our medical center neonatal intensive care unit. The babies were divided into two groups: GM-IVH and non-IVH. Clinical presentations, precipitating factors of the patients and maternal factors were analyzed.

Results: In univariate analysis, gestational age, birth weight, delivery method, presence of premature rupture of membrane (PROM) and level of sodium and glucose were statistically meaningful factors ($p<0.05$). But only two factors, gestational age and presence of patent ductus arteriosus (PDA) were statistically meaningful in multivariate logistic regression ($p<0.05$). Delivery method [normal vaginal delivery (NVD) to Cesarean section] was borderline significant ($p=0.10$).

Conclusion: Presence of PDA and gestational age were the important risk factors associated with development of GM-IVH.

Key Words: Germinal matrix-intraventricular hemorrhage · Gestational age · Ductus arteriosus, patent.
Detection of IVH and grading system

CUS was performed for all neonates in this study in the first week of life for detection of IVH and its grading were done. If a neonate had GM-IVH, then serial CUS would be done weekly. If not, follow up CUS was taken after 2 weeks. All subjects were divided into two groups—GM-IVH group and Non-IVH groups according to presence of GM-IVH. GM-IVH group was subdivided by grading system proposed by Papile et al.17 (Table 1). Grade I and II group were considered as mild GM-IVH group, Grade III and IV group were as severe GM-IVH group.

Statistical analysis

Statistical analysis was performed by using SPSS version 21.0 (SPSS, Chicago, IL, USA). To compare the continuous variables, the Student's t-test was used. Pearson's chi-square test was used for categorical variables. Logistic regression analysis was used to find the independent association between development of GM-IVH and explanatory variables. Variables that were p≤0.20 as determined by univariate analysis were entered into multivariate logistic regression. The odds ratios (ORs) with a 95% confidence intervals (CIs) were calculated. p value was calculated by logistic regression. IVH and explanatory variables. Variables that were statistically meaningful factors (p<0.05). To operate multivariate analysis, gestational age, birth weight, delivery method, presence of PROM, PDA, RDS, anemia and level of sodium and glucose were selected. All these results were demonstrated on Table 2.

RESULTS

General characteristics

Total 168 patients were included. 93 patients (55.36%) were male.

Table 1. Papile's classification of preterm intraventricular hemorrhage16

| Grade | Description |
|-------|-------------|
| I     | Restricted to subependymal region/germinal matrix which is seen in the cisterna ambiens |
| II    | Extension into normal sized ventricles and typically filling less than 50% of the volume of the ventricle |
| III   | Extension into dilated ventricles |
| IV    | Intraventricular hemorrhage with parenchymal extension |

Table 2. Comparison of neonatal and maternal characteristics between two groups

| Variables                        | Total (n=168) | IVH (n=31) | Non-IVH (n=137) | p value |
|----------------------------------|---------------|------------|-----------------|--------|
| Sex (M : F)                      | 93 : 75       | 18 : 13    | 75 : 62         | 0.737  |
| Multigravida                     | 44            | 8          | 36              | 0.957  |
| Maternal age (year)              | 32.6±3.93     | 31.87±3.41 | 32.80±4.03      | 0.237  |
| Gestational age (weeks)          | 221.66±19.91  | 199.32±22.77| 226.72±15.27    | 0.000  |
| Weight (g)                       | 1668.93±540.83| 1222.58±516.27| 1769.93±494.66 | 0.000  |
| Delivery method (normal delivery vs. caesarean section) | 35 : 133 | 12 : 19 | 23 : 114 | 0.009  |
| Preeclampsia                     | 31            | 6          | 25              | 0.886  |
| PROM                             | 44            | 13         | 31              | 0.030  |
| PDA                              | 34            | 13         | 21              | 0.001  |
| RDS                              | 95            | 22         | 73              | 0.077  |
| Anemia                           | 67            | 16         | 51              | 0.143  |
| Sodium (mEq/L)                   | 140.71±3.92   | 138.03±5.83| 141.32±3.06     | 0.000  |
| Glucose (mg/dL)                  | 69.78±4.86    | 99.90±54.53| 62.96±39.51     | 0.000  |

Data presented as number or mean±standard deviation. *p value was calculated by logistic regression. IVH : intraventricular hemorrhage, PROM : premature rupture of membrane, PDA : patent ductus arteriosus, RDS : respiratory distress syndrome

Univariate analysis

In univariate analysis, gestational age, birth weight, delivery method, presence of PROM and level of sodium and glucose were statistically meaningful factors (p<0.05). To operate multivariate analysis, gestational age, birth weight, delivery method, presence of PROM, PDA, RDS, anemia and level of sodium and glucose were selected. All these results were demonstrated on Table 2.

Multivariate analysis

Only two factors—gestational age and presence of PDA were statistically meaningful in multivariate logistic regression (p<0.05). Delivery method (NVD to Caesarean section) was borderline significant (p<0.10). All these results were demonstrated in Table 3.

Comparison of mild and severe IVH group

Unpaired t-test was done between two groups by variables. Mild group was 24 cases, severe groups was 7 cases. Meaningful difference in gestational age between two groups was revealed (p<0.05). No other variable was statistically meaningful factor.

DISCUSSION

GM-IVH is rare in full-term babies11, but more common in preterm babies and it leaves significant sequelae such as cerebral
palsy and mental retardation. Therefore, it is very important to find the risk factors associated with development of GM-IVH and prepare for them. Many risk factors for the development of GM-IVH have been reported. These contain gender, lack of antenatal steroids, low Apgar score, PROM, intrauterine infection, vaginal delivery, in vitro fertilization, mechanical ventilation, a large PDA, RDS and transfusion of blood products.

However, in our study, there was no significant difference in gender, birth weight, delivery method, preeclampsia, PROM, anemia. The only two factors, gestational age and presence of PDA, were statistically meaningful risk factors for development of GM-IVH. This result could be understood easily because gestational age reflects fetal maturity more accurately than birth weight. As several reports, and our results has shown, it is certain that younger gestational age is related with higher risk for severe GM-IVH. It can be described in terms of the anatomy and pathophysiology of it. It occurs in germinal matrix, an intensively vascularized glioblast tissue. If children were born before the 32 weeks of gestation, the subependymal region is equipped with a tight net of capillaries that are mainly supplied by the Hubein’s artery. After the 32 weeks into pregnancy, the germinal matrix involutes and the vessels will be differentiated. Preterm infants are quite helpless concerning cerebrovascular injury due to a unique constellation of pathophysiological factors. Preterm newborns have difficulty maintaining an adequate cerebral perfusion pressure. Maintain cerebral perfusion pressure is more difficult due to normally reduced hypotension and low cardiac output for the newborns to adjust extraterine life, especially in the first day of life. In addition, intrinsic cerebral vasoreactivity and autoregulatory mechanisms are poorly developed in the immature brain. As decreasing gestational age, the autoregulation pressure range is narrower and lower.

Normal vaginal delivery was borderline significant risk factor (p<0.1). Although there is a objection, some retrospective studies reported that Cesarean delivery does not improve neonatal survival of very low birth weight infants but decreases GM-IVH occurrence. In addition, following hypoperfusion-reperfusion hypothesis seemed to support this. The germinal matrix is a transient neural cell proliferative zone with poor developed vasculature and located on the head of caudate nucleus. This involutes gradually in third trimester. Fragile vessels and the lack of cerebrovascular resistance make GM-IVH. The resistance to ischemic injury is weaker and autoregulation range of blood pressure is lower as decreasing gestational age. Certain situation like presence of PDA or normal vaginal delivery could result in hypoperfusion-reperfusion state. Several possible factors are suggested cardiorespiratory system (hypotension, PDA, hypoperfusion-reperfusion pattern, hypercarpnia, hypoglycemia, hypernatremia), hematologic (anemia, thrombocytopenia), immunologic response, impaired cerebral reactivity, immature anatomy, even though they are not proven yet.

Another reason why the hemorrhage occurs in this region, beside the massive vascularization, is the fact that the area around the caudate nucleus represents a border zone between ventriculopetal and fugal blood supply. Furthermore, the endothelium of the vessels located in the brain of premature newborns is more sensitive to hypoxemia. Hydrostatic and osmotic changes lead more often to the ruptures of the vessels.

An important pathophysiological parameter is the missing or disrupted autoregulation mechanism of premature newborns. This means that the cerebral blood flow is directly influenced by changes of the systemic blood pressure. Hence hypertension, as well as hypotension, will lead directly to changes in the cerebral blood flow. Other triggers that can cause an ICH are rupture of the alveolar, RDS, pneumothorax and artificial ventilation of the newborn. Endotracheal intubation with positive pressure ventilation increases central venous pressure, which can lead to episodic poor cerebral perfusion. But, in the present study, high risk pregnancy situations such as preeclampsia, PROM and RDS were not related to the development of GM-IVH.

There are several limitations in our study. First, the population of our study was small in number. So we couldn’t sort all the cases by gestational age and estimate odds ratio by decreasing gestational age. Second is a retrospective study from a single institution, although this also might be an advantage due to consistency of practice and expertise. Last, this study did not evaluate the neurodevelopmental outcome of patients.

**CONCLUSION**

Despite of several limitations, our study revealed that presence of PDA and gestational age were the important risk factors associated with development of GM-IVH. How the severity of disease relates to gestational age will be necessary to study with larger population in multicenter.

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