Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2022**; 49(5): 101
https://doi.org/10.31083/j.ceog4905101

Original Research

Perinatal Risk Factors for the Development of Neonatal Intraventricular Hemorrhage in Preterm Infants

Yuriko Iwahata[1], Junichi Hasegawa[1,*], Chika Homma[1], Hideyuki Iwahata[1], Natsumi Furuya[1], Haruhiro Kondo[1], Nao Suzuki[1]

[1]Department of Obstetrics and Gynecology, St. Marianna University School of Medicine, 216-8511 Kawasaki, Japan
*Correspondence: hasejun@marianna-u.ac.jp (Junichi Hasegawa)
Academic Editors: Michael H. Dahan and Jacques Balayla
Submitted: 21 January 2022 Revised: 27 February 2022 Accepted: 8 March 2022 Published: 26 April 2022

Abstract

Background: To evaluate the impact perinatal factors closely related to the development of neonatal intraventricular hemorrhage (IVH) in preterm infants. **Methods**: A retrospective case-control study was performed on premature infants born in our perinatal center in 2014–2018. Neonates with IVH were age-matched with normal controls (1:5). Perinatal factors were compared between cases and controls. **Results**: Fourteen cases and 70 controls had a median of 26.5 (range 22–29) weeks gestational age. Significant difference was observed regarding the incidence of clinical chorioamnionitis (43% and 14%, $p = 0.023$) and the use of magnesium sulfate ($MgSO_4$) (14% and 51%, $p = 0.017$). Adjusted odds ratios (95% confidence interval) were 8.3 (1.8–38) in clinical chorioamnionitis and 0.15 (0.03–0.76) in magnesium sulfate. **Conclusions**: Relevant perinatal factor of IVH in premature infants born before 30 weeks of gestation was strongly associated with clinical chorioamnionitis. Furthermore, $MgSO_4$ exposure suggested a neuroprotective effect against IVH.

Keywords: intraventricular hemorrhage; magnesium sulfate; perinatal care; risk factor

1. Introduction

Intraventricular hemorrhage (IVH) is a common complication seen in very low-birthweight neonates. Despite significant improvements in perinatal care, preterm birth still occurs, and the rate of major neurodevelopmental impairment in survivors has not diminished [1]. IVH is the most serious complication as it leads to short- and long-term morbidities, including cerebral palsy and hydrocephalus, especially in neonates with birth weight <1500 g and gestational age <32 weeks [2].

Factors such as intrauterine infection, prolonged labor, premature rupture of membrane, respiratory distress, hypoxia-related injury, ischemia, fluctuation of blood pressure, pneumothorax, and hypovolemia increase the possibility of IVH [3–5]. Despite major efforts made to elucidate the pathogenesis and prevent IVH in the last few decades, the prevention of IVH remains an unsolved problem. Many confounding factors are related to the occurrence of IVH. In particular, premature infants with IVH have many confounders that are strongly associated with early gestational age and hypoxia at delivery.

Therefore, in the present study, we assessed perinatal factors closely related to the development of neonatal IVH in preterm infants after excluding gestational age as a confounder.

2. Materials and Methods

A retrospective, matched case-control study was performed to investigate perinatal risk factors related to the development of IVH in preterm infants. Patients were premature infants born in our perinatal center in 2014–2018. We included cases with neonates who developed IVH, and selected control cases which have the matched gestational age neonates with the cases with IVH. The ratio is 1 (case) to 5 (control). Patients with congenital malformations were excluded from the present study.

The IVH diagnosis was based on ultrasonography performed until the 10th postnatal day by a neonatologist. Grade I is hemorrhage restricted to the germinal matrix. Grade II is intraventricular hemorrhage without ventricular dilatation. Grade III is intraventricular hemorrhage with ventricular dilatation. Grade IV is parenchymal hemorrhage [6].

We also analyzed our perinatal risk factors associated with the onset of IVH. These perinatal risk factors included the following: maternal and neonatal characteristics (maternal age, parity, IVF (*In vitro* Fertilization) pregnancy, multiple gestation, cesarean delivery, gestational age, birth weight, male sex, Apgar score, and umbilical artery pH); complications during pregnancy (prematurity, premature rupture of membrane, preeclampsia, chorioamnionitis, fetal growth restriction, gestational diabetes mellitus, abnormal cardiotocography (CTG)); and medications administered during pregnancy (ritodrine hydrochloride, magnesium sulfate, ampicillin sodium, betamethasone). Magnesium sulfate was commonly administered as a tocolytic agent for the prevention of preeclampsia in our hospital.

Chorioamnionitis is an acute inflammation of the membranes and chorion of the placenta, typically due to

ascending polymicrobial bacterial infection in the setting of membrane rupture. Clinical chorioamnionitis was considered when characteristic clinical signs were present in the mother, which include fever, uterine fundal tenderness, maternal tachycardia (>100/min), fetal tachycardia (>160/min), and purulent or foul-smelling amniotic fluid [7]. On the other hand, histopathologic chorioamnionitis was considered when there was microscopic evidence of infection or inflammation on examination of the placenta or chorioamniotic specimens. Placentas were fixed in formalin for at least 24 hours. Based on the location of leukocytes, a grading system was used as follows [8]: Stage 1 if leukocytes were seen at the subchorion; Stage 2 if the leukocytes were present in the chorionic membrane; and Stage 3 if leukocytes were present beyond the chorionic and amniotic membranes. In the present study, histopathologic chorioamnionitis was considered in cases classified as Stage 2 or 3.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Science software program (Windows version 24.0 J; Chicago, IL, USA). Continuous variables were reported as mean with 95% confidence interval and were compared using the Mann-Whitney U-test. Categorical variables were reported as frequencies and were compared using Fisher's exact test. The multivariable analysis was based on logistic regression analysis. Significant risk factors included clinical chorioamnionitis and $MgSO_4$ determined using univariate analysis were used in the multivariable analysis. p-values of <0.05 were considered statistically significant.

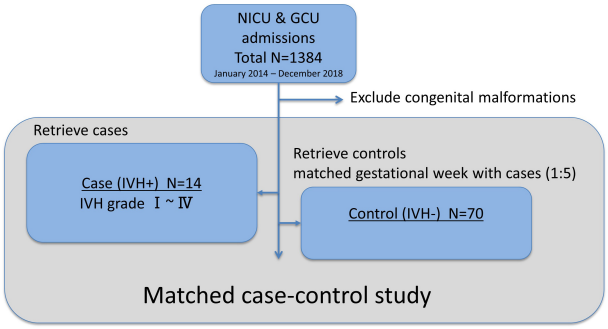

Fig. 1. Study flow diagram.

3. Results

The study flow diagram is demonstrated in Fig. 1. In total, 1384 infants were admitted to the NICU (Neonatal intensive care unit) and GCU (Growing care unit) of St. Marianna University Hospital between January 2014 and December 2018. We excluded patients with congenital malformations for both groups. Fourteen cases (1.0% of admission) who developed IVH grades I to IV were recruited. Thus, 70 controls (1:5) were matched for gestational age to each case.

Baseline characteristics of the subjects are shown in Table 1. Mean gestational age was around 26 weeks for both groups. There was no significant difference observed on the mean birth weight (979 g and 895 g), Apgar score at 1 minute (4.1 and 4.4), and Apgar score at 5 minutes (6.7 and 6.8) for the cases and control groups, respectively.

The observed frequency of perinatal risk factors related to IVH is shown in Table 2. In premature infants, significant risk factor of IVH was clinical chorioamnionitis, which occurred in 43% of cases vs. 14% of controls (p = 0.021). Other factors such as prematurity, premature rupture of membrane, preeclampsia, fetal growth restriction, and gestational diabetes mellitus, histological chorioamnionitis were not significantly different between the two groups. In terms of antenatal drug administration contributing to the risk of IVH, the administration of magnesium sulfate was significantly lower in the case group than in the control group (14% vs. 51%; $p = 0.017$). Administration of other medications, such as ritodrine hydrochloride, steroids, and antibiotics, was not significantly different between the two groups.

The results of multivariate logistic regression analysis are shown in Table 3. Perinatal risk factors that significantly contributed to the development of IVH were the clinical chorioamnionitis (OR 8.3, 95% CI 1.8–38) and the administration of magnesium sulfate was associated with reduction of developing IVH (OR 0.15, 95% CI 0.03–0.76). Of the 14 cases, 3 had no developmental or neurological abnormalities by the age of 2 years, whereas 2 were administered magnesium sulfate.

4. Discussion

In the present study, after controlling for variables such as gestational age, we observed that clinical chorioamnionitis and that lack of antenatal administration of magnesium sulfate was significantly associated with developing IVH. In the published paper, clinical chorioamnionitis was reported as a major risk factor for developing IVH [9].

The association between clinical chorioamnionitis and IVH is biologically and clinically plausible. In general, IVH occurs within 3 days of life and affects infants with fluctuations in blood pressure and respiratory distress. It is frequently associated with extreme prematurity and/or severe perinatal infections [10,11]. Therefore, clinical circumstances during delivery and the first days of life are critical for the development of IVH. Our results suggest that chorioamnionitis is a strong independent contributing factor for IVH. Our date showed clinical chorioamnionitis was a risk factors for developing IVH but not histopathological chorioamnionitis. From this data, a hypothesis came up that clinical chorioamnionitis happens at the end of histopathological chorioamnionitis. In other words, when inflamma-

Table 1. Clinical characteristics of mothers and infants.

Characteristics	Cases N = 14	Controls N = 70	*p*-value
Maternal age	31.3 (28.5–34.1)	32.8 (31.3–34.4)	0.31
Parity	0 (0–3)	0 (0–3)	0.95
IVF pregnancy	1 (7%)	10 (14%)	0.39
Twin pregnancy	3 (21%)	9 (13%)	0.49
Cesarean Delivery	9 (64%)	50 (71%)	0.62
Gestational age (wks)	25.9 (24.3–27.6)	26.4 (25.9–26.9)	0.57
Birth weight (g)	979 (728–1231)	859 (790–929)	0.34
Male gender	6 (43%)	38 (54%)	0.45
Apgar score 1 min.	4.1 (2.4–5.7)	4.4 (4.0–4.9)	0.57
Apgar score 5 min.	6.7 (5.2–8.0)	6.8 (6.3–7.3)	0.74
Umbilical Artery pH	7.30 (7.24–7.31)	7.46 (7.22–7.31)	0.45

Data are presented as mean (95% confidence interval) or number (%).

Table 2. Frequency of complications and medications during pregnancy.

Complications	Cases N = 14	Controls N = 70	*p*-value
Preterm	6 (43%)	23 (33%)	1.000
Premature Rupture of Membrane			
Preeclampsia	5 (38%)	14 (20%)	0.291
Clinical chorioamnionitis	**6 (43%)**	**10 (14%)**	**0.021**
Histological chorioamnionitis			
Stage >II	6 (43%)	18 (26%)	0.209
Stage >III	4 (29%)	6 (9%)	0.057
Fetal growth restriction	2 (14%)	12 (17%)	1.000
Gestational Diabetes Mellitus	0 (0%)	8 (11%)	0.341
Abnormal CTG	7 (50%)	32 (45%)	0.832
Ritodrine hydrochloride	11 (79%)	42 (60%)	0.236
$MgSO_4$	**2 (14%)**	**36 (51%)**	**0.017**
Ampicillin sodium	7 (50%)	38 (54%)	0.778
Betamethasone	11 (79%)	57 (81%)	0.725

Data are presented as number (%). Bold represent significant *p*-values.

Table 3. Results of multivariate logistic regression analysis.

Factors	Adjusted Odd ratio (95% confidence interval)
Clinical chorioamnionitis	8.3 (1.8–38.0)
$MgSO_4$	0.15 (0.03–0.76)

tion becomes severe, chorioamnionitis might come to have clinical symptoms such as fever, uterine tenderness, elevation of white blood cells. However further study of placental pathology in chorioamnionitis is needed. In addition, we evaluated funisitis but no funisitis was found.

In our hospital, magnesium sulfate was used not only for the prevention of eclampsia but also as a tocolytic agent in the threatened premature delivery in obstetric practice. Our study showed the antenatal administration of magnesium sulfate was contributed to reduction of IVH. Although there is controversy regarding its impact on neonatal outcomes, several studies have tested the hypothesis that antenatal exposure to magnesium sulfate is neuroprotective for low-birthweight infants [12,13].

In the published reports, magnesium sulfate has been known for the effect to reduce 'cerebral palsy' [14,15]. However, our study revealed that magnesium sulfate is also effective for reducing 'fetal intraventricular hemorrhage'.

Our data revealed that of the 14 cases, 3 had no developmental or neurological abnormalities by the age of 2 years, whereas 2 were administered antenatal magnesium sulfate. Our findings support the theory that antenatal magnesium sulfate significantly reduces the percentage of IVH. These results point to the importance of antenatal care, particularly in preventing IVH. However, the role of tocolytic magnesium sulfate in the development of IVH requires further clarification.

The limitations of this study are as follows: First, this was a retrospective case-control study. Therefore, exis-

tence of selection bias should be considered. Second, we did not investigate the relationship between prevention of IVH and the timing and dosage of magnesium sulfate, because we use magnesium sulfate for the purpose of not only prevention of eclampsia but also tocolytic agent. Thus, we cannot determine the dose and the timing. Third, the number of the cases (N = 14) might be too small to determine the statistical difference so larger cases will be needed.

5. Conclusions

IVH in premature infants born below 30 weeks of gestation was a strong independent factor associated with clinical chorioamnionitis. Furthermore, the antenatal administration of $MgSO_4$ was contributed to reduction of IVH, thereby suggesting that the administration of $MgSO_4$ has a neuroprotective effect against IVH. This supports the importance of appropriate antenatal care in preventing IVH in at-risk neonates.

Author Contributions

YI and JH conceived the study, drafted the initial protocol, analyzed the data, and manuscript writing. CH, HI, NF and HK coordinated the study, developed the database, and analyzed the data. NS guarantors for the study. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments, or comparable ethical standards. The study protocol was approved by the Institutional Review Board of the St. Marianna University School of Medicine (No. 4962, Sep. 17th, 2020). Written informed consent was not obtained from patients. However, patients were provided the announcement of the present study in the notice of our hospital. Although the analysis was retrospective, data collected were kept confidential. All patient information was anonymized and de-identified before analysis.

Acknowledgment

We would like to express our gratitude to all those who helped us during the writing of this manuscript. Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Rysavy MA, Li L, Bell EF, Das A, Hintz SR, Stoll BJ, *et al*. Between-Hospital Variation in Treatment and Outcomes in Extremely Preterm Infants. New England Journal of Medicine. 2015; 372: 1801–1811.

[2] Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR, *et al*. Trends in neonatal morbidity and mortality for very low birthweight infants. American Journal of Obstetrics and Gynecology. 2007; 196: 147.e1–147.e8.

[3] Jantzen C, Lodha A, Lucia M, Lee SK, Ye XY, Sankaran K. Effects of nosocomial infection trends on neonatal outcomes in preterm infants <33 weeks of gestational age in Canadian NICUs. Zhongguo Dang Dai Er Ke Za Zhi. 2015, 17:1019–1027.

[4] Christian EA, Jin DL, Attenello F, Wen T, Cen S, Mack WJ, *et al*. Trends in hospitalization of preterm infants with intraventricular hemorrhage and hydrocephalus in the United States, 2000–2010. Journal of Neurosurgery: Pediatrics. 2016; 17: 260–269.

[5] Al-Mouqdad MM, Abdelrahim A, Abdalgader AT, Alyaseen N, Khalil TM, Taha MY, *et al*. Risk factors for intraventricular hemorrhage in premature infants in the central region of Saudi Arabia. International Journal of Pediatrics and Adolescent Medicine. 2019; 8: 76–81.

[6] 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. The Journal of Pediatrics. 1978; 92: 529–534.

[7] Gibbs RS, Duff P. Progress in pathogenesis and management of clinical intraamniotic infection. American Journal of Obstetrics and Gynecology. 1991; 164: 1317–1326.

[8] Redline RW, Faye-Petersen O, Heller D, Qureshi F, Savell V, Vogler C. Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. Pediatric and Developmental Pathology. 2003; 6: 435–448.

[9] Villamor-Martinez E, Fumagalli M, Mohammed Rahim O, Passera S, Cavallaro G, Degraeuwe P, *et al*. Chorioamnionitis Is a Risk Factor for Intraventricular Hemorrhage in Preterm Infants: A Systematic Review and Meta-Analysis. Frontiers in Physiology. 2018, 9: 1253–1253.

[10] Mohamed MA, Aly H. Transport of premature infants is associated with increased risk for intraventricular haemorrhage. Archives of Disease in Childhood. Fetal and Neonatal Edition. 2010; 95: F403–F407.

[11] Inder TE, Perlman JM, Volpe JJ. Preterm Intraventricular Hemorrhage/Posthemorrhagic Hydrocephalus. Volpe's Neurology of the Newborn. 2018; 115: 637–698.e21.

[12] Zeng X, Xue Y, Tian Q, Sun R, An R. Effects and Safety of Magnesium Sulfate on Neuroprotection: a Meta-analysis Based on PRISMA Guidelines. Medicine. 2016; 95: e2451.

[13] Petrova A, Mehta R. Magnesium sulfate tocolysis and intraventricular hemorrhage in very preterm infants. Indian Journal of Pediatrics. 2012; 79: 43–47.

[14] Paulsen ME, Dietz RM. Magnesium sulfate prevents cerebral palsy in premature infants. The Journal of Pediatrics. 2018; 194: 265–268.

[15] Rouse DJ, Gibbins KJ. Magnesium sulfate for cerebral palsy prevention. Seminars in Perinatology. 2013; 37: 414–416.