Review Article
J Korean Neurosurg Soc 66 (3) : 258-262, 2023
https://doi.org/10.3340/jkns.2022.0266
pISSN 2005-3711 eISSN 1598-7876

Pharmacological Management of Germinal Matrix-Intraventricular Hemorrhage

Jaewoo Chung,[1,2] Sang Koo Lee,[1,2] Chun-Sung Cho,[1,2] Young Jin Kim,[1,2] Jung Ho Ko,[1,2] Jung-Ho Yun,[1,2] Jin-Shup So,[2] In-Ho Jung[2]

Department of Neurosurgery,[1] Dankook University College of Medicine, Cheonan, Korea
Department of Neurosurgery,[2] Dankook University Hospital, Cheonan, Korea

Germinal matrix-intraventricular hemorrhage (GM-IVH) is among the devastating neurological complications with mortality and neurodevelopmental disability rates ranging from 14.7% to 44.7% in preterm infants. The medical techniques have improved throughout the years, as the morbidity-free survival rate of very-low-birth-weight infants has increased; however, the neonatal and long-term morbidity rates have not significantly improved. To this date, there is no strong evidence on pharmacological management on GM-IVH, due to the limitation of well-designed randomized controlled studies. However, recombinant human erythropoietin administration in preterm infants seems to be the only effective pharmacological management in limited situations. Hence, further high-quality collaborative research studies are warranted in the future to ensure better outcomes among preterm infants with GM-IVH.

Key Words : Germinal matrix hemorrhage · Cerebral intraventricular hemorrhage · Preterm infant · Erythropoietin.

INTRODUCTION

Germinal matrix-intraventricular hemorrhage (GM-IVH) is among the devastating neurological complications with mortality and neurodevelopmental disability rates ranging from 14.7% to 44.7% in preterm infants[4,12,16,21,23,34]. GM-IVH originates from the hemorrhage of the immature capillary network of the subependymal GM, which disrupts the ependymal lining and burst into the lateral cerebral ventricle[31]. In the United States, the incidence of preterm labor has decreased, but one in 10 babies is still born preterm[22]. The medical techniques have improved throughout the years, as the morbidity-free survival rate of very-low-birth-weight infants has increased; however, the neonatal and long-term morbidity rates have not significantly improved[1,8,15,17]. The knowledge of the nature of preterm infants are limited as the medical conditions vary from each preterm infant in gestational age, weight, and comorbidities, thereby making it hard to conduct a well-designed randomized controlled study. Hence, there are no standardized protocols for the treatment of GM-IVH due to a lack of strong evidence[29]. In this review article, we briefly describe the pharmacological management of GM-IVH based on previous literature.

• Received : December 5, 2022 • Revised : February 3, 2023 • Accepted : February 14, 2023
• Address for reprints : **Jaewoo Chung**
Department of Neurosurgery, Dankook University Hospital, Dankook University College of Medicine, 201 Manghyang-ro, Dongnam-gu, Cheonan 31116, Korea
Tel : +82-41-550-6280, E-mail : j.chung@dankook.ac.kr, ORCID : https://orcid.org/0000-0002-3512-6610

PATHOGENESIS OF GM-IVH

The GM is located in the subependymal of the ventricular walls, which later develops to cerebral neuroblasts and glia[2,24,28]. The vasculature in GM is formed at approximately 7–8 weeks of gestation and persists until the beginning of the third trimester[24,28]. The thickness of the GM decreases after 24 weeks, which is late second trimester period of gestation, and the GM almost disappears by 36–37 weeks[2]. The vasculature of the GM lacks muscle or collagen; therefore, it is vulnerable to hemodynamic or mechanical stress. According to the classification of hemorrhages by Papile et al.[20], grade I is defined as the hemorrhage confined to the GM, grade II as the hemorrhage extending into the lateral ventricles, it grade III as the presence of ventricular dilatation; and grade IV as the presence of parenchymal hemorrhage.

Once GM-IVH occurs in preterm infants, they are at a high risk of developing poor neurodevelopmental outcomes, including cerebral palsy, intellectual deficits, deafness, and blindness[6]. Approximately 10% of preterm infants at <32 weeks' gestational with grade II/III GM-IVH progresses to grade III/IV GM-IVH within 1 week[33]. Moreover, the mortality rate of preterm infants with GM-IVH is >20%; >80% of these infants expire within the first week after birth[11,16,23,25]. Therefore, pharmacological management for GM-IVH in preterm infants is focused on preventing GM-IVH, suppressing the progression of GM-IVH and improving the neurological outcomes after GM-IVH.

PHARMACOLOGICAL MANAGEMENT OF GM-IVH

Pharmacological management for preventing GM-IVH

Phenobarbitone

In theory, reducing hemodynamic stress on the immature vessel network in GM might prevent GM-IVH or at least reduce the possibility of suppressing the increment of the amount of IVH. An early observational study showed that phenobarbitone has possibility of regulation of systemic blood pressure and have protective effect after brain ischemic injury[32]. A 2013 Cochrane review of 12 controlled trials involving 982 preterm infants revealed controversial results on the effect of phenobarbitone on the incidence of GM-IVH[26]. This meta-analysis study showed that the use of phenobarbitone did not have a significant reduction in the risk of IVH, posthemorrhagic ventricular dilatation, neurodevelopmental impairment, or in-hospital death. However, it had increased the risk of the need for mechanical ventilation. In conclusion, based on this strong evidence, postnatal phenobarbital cannot be recommended as a prophylaxis for GM-IVH in preterm infants[26].

Pharmacological management for suppressing the progression of GM-IVH

Ethamsylate (diethylammonium 1,4-dihydroxy-3-benzene sulfonate)

The vessel network of GM in preterm infants lack basement membrane deposition, tight junctions, and glial endfoot investiture, which makes it vulnerable to cerebral blood flow. Therefore, reinforcing basement stability and accelerating hemostasis are expected to suppress the progression of GM-IVH theoretically. Although the exact mechanism is unclear, ethamsylate reduces bleeding time and blood loss from wounds[30]. Therefore, using ethamsylate was suggested in preterm infants with GM-IVH[18]. A Cochrane database systematic review of 1410 preterm infants from seven trials revealed that ethamsylate significantly reduces the risk of grade III and IV GM-IVH among infants at <35 weeks' gestation[14]. However, in a single group of GM-IVH infants at <32 weeks' gestation with, ethamsylate did not show a significant reduction in the progression of GM-IVH[14]. However, from this review, use of ethamsylate in preterm infants did not show a significant difference in neonatal mortality rate or neurodevelopmental outcome at 2 years. The adverse side-effect of ethamsylate is hypotension; however, the systematic review showed that there was no significant difference in the hypotension rate between infants treated with ethamsylate and those receiving a placebo drug. In conclusion, the use of ethamsylate in preterm infants is safe and has protective effects against the progression of GM-IVH in limited situations; however, there is a lack of evidence showing that it improves the mortality rate or neurodevelopmental outcome.

Pharmacological management for improving the neurological outcomes after GM-IVH

Recombinant human erythropoietin (EPO)

Once the occurrence of mortality due to GM-IVH has been controlled in preterm infants, improving or at least preventing the progression of neurodevelopmental impairments is the next step. EPO accelerates red blood cell production owing to its hematopoietic properties; therefore, recombinant human EPO (rhEPO) is used in various types of anemia and in cases requiring reduction in the number of blood transfusions. rhEPO is also known to have a neuroprotective effect. Hence, it is expected to have a major role in GM-IVH. High-dose rhEPO administration in very-preterm infants (<32 weeks) resulted in significantly higher hematocrit level, reticulocyte count, and white blood cell count and lower platelet count without increasing the rates of mortality or short-term major adverse events, including retinopathy, IVH, sepsis, necrotizing enterocolitis and bronchopulmonary dysplasia[9,10]. A Cochrane database systematic review of 34 studies involving 3643 preterm infants revealed that early rhEPO treatment is safe and significantly decreased the rates of IVH, periventricular leukomalacia, and necrotizing enterocolitis[19]. As the long-term neurodevelopmental outcomes of early rhEPO treatment still remain unclear, the authors do not recommend its routine use due to its limited benefits in preterm infants. However, a recent research study showed rhEPO has benefits in improving the mortality rate and neurodevelopmental outcomes, including atrophy and cognition[13,27]. The beneficial neuroprotective effect of the early administration of rhEPO in preterm infants needs more firm evidence, as it is proven to be safe and it seems to be the only promising treatment for improving long-term neurodevelopmental outcomes.

Vitamin E (tocopherol)

Vitamin E is known for its potent antioxidant properties and it is presumed to scavenge free radicals and protect the capillary endothelial cells of the matrix from injury[3]. Brion et al.[5] conducted a pooled analysis of 26 randomized clinical trials, which showed that vitamin E did not significantly reduce the morbidity or mortality rate. Although vitamin E supplement significantly reduced the risk of GM-IVH, it increases the rate of sepsis among preterm infants. The results of the subgroup analyses showed that high-dose intravenous vitamin E supplementation increased the risk of sepsis and while decrease parenchymal cerebral hemorrhage. Moreover, besides the intravenous route of vitamin E supplementation, other modes of supplementation reduced risk of GM-IVH and its progression. Finally, if the serum tocopherol level is >3.5 mg/dL, the risk of sepsis increases while the risk of severe retinopathy decreases. As most included studies were conducted in the 1970s and 1980s, when the mortality rate of preterm infants was high, the result of this analysis should be carefully interpreted[7]. A recent study showed that vitamin E supplementation did not significantly decrease the risk of GM-IVH in preterm infants, which contradicts the results of the previous pooled analysis[3]. In conclusion, no strong evidence supports the routine use of vitamin E in preterm infants to prevent GM-IVH or suppress its progression.

CONCLUSION

To this date, there is no strong evidence on pharmacological management on GM-IVH, due to the limitation of well-designed randomized controlled studies. However, rhEPO admisistration in preterm infants seems to be the only effective pharmacological management in limited situations. Hence, further high-quality collaborative research studies are warranted in the future to ensure better outcomes among preterm infants with GM-IVH.

AUTHORS' DECLARATION

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Informed consent

This type of study does not require informed consent.

Author contributions

Conceptualization : JC; Data curation : JC; Formal analysis : JC; Methodology : JC; Project administration : JC; Writing - original draft : JC; Writing - review & editing : SKL, CSC, YJK, JHK, JHY, JSS, IHJ

 https://doi.org/10.3340/jkns.2022.0266

Data sharing

None

Preprint

None

ORCID

Jaewoo Chung	https://orcid.org/0000-0002-3512-6610
Sang Koo Lee	https://orcid.org/0000-0003-2500-9493
Chun-Sung Cho	https://orcid.org/0000-0001-6077-652X
Young Jin Kim	https://orcid.org/0000-0002-6770-3523
Jung Ho Ko	https://orcid.org/0000-0002-1185-4381
Jung-Ho Yun	https://orcid.org/0000-0003-4091-1346
Jin-Shup So	https://orcid.org/0000-0001-5725-4536
In-Ho Jung	https://orcid.org/0000-0002-4135-5743

References

1. Anderson JG, Baer RJ, Partridge JC, Kuppermann M, Franck LS, Rand L, et al. : Survival and major morbidity of extremely preterm infants: a population-based study. **Pediatrics 138 :** e20154434, 2016
2. Ballabh P : Pathogenesis and prevention of intraventricular hemorrhage. **Clin Perinatol 41 :** 47-67, 2014
3. Barekatain B, Saraeian S, Farghadani M, Armanian AM, Shahsanaee A, Rouhani E, et al. : Effect of vitamin E in prevention of intraventricular hemorrhage in preterm neonates. **Int J Prev Med 9 :** 97, 2018
4. Bolisetty S, Dhawan A, Abdel-Latif M, Bajuk B, Stack J, Lui K, et al. : Intraventricular hemorrhage and neurodevelopmental outcomes in extreme preterm infants. **Pediatrics 133 :** 55-62, 2014
5. Brion LP, Bell EF, Raghuveer TS : Vitamin E supplementation for prevention of morbidity and mortality in preterm infants. **Cochrane Database Syst Rev (4) :** CD003665, 2003
6. Davis AS, Hintz SR, Goldstein RF, Ambalavanan N, Bann CM, Stoll BJ, et al. : Outcomes of extremely preterm infants following severe intracranial hemorrhage. **J Perinatol 34 :** 203-208, 2014
7. Egesa WI, Odoch S, Odong RJ, Nakalema G, Asiimwe D, Ekuk E, et al. : Germinal matrix-intraventricular hemorrhage: a tale of preterm infants. **Int J Pediatr 2021 :** 6622598, 2021
8. 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. **Am J Obstet Gynecol 196 :** 147.e1-e8, 2007
9. Fauchère JC, Dame C, Vonthein R, Koller B, Arri S, Wolf M, et al. : An approach to using recombinant erythropoietin for neuroprotection in very preterm infants. **Pediatrics 122 :** 375-382, 2008
10. Fauchère JC, Koller BM, Tschopp A, Dame C, Ruegger C, Bucher HU, et al. : Safety of early high-dose recombinant erythropoietin for neuroprotection in very preterm infants. **J Pediatr 167 :** 52-57.e1-e3, 2015
11. Gilard V, Chadie A, Ferracci FX, Brasseur-Daudruy M, Proust F, Marret S, et al. : Post hemorrhagic hydrocephalus and neurodevelopmental outcomes in a context of neonatal intraventricular hemorrhage: an institutional experience in 122 preterm children. **BMC pediatr 18 :** 288, 2018
12. Heuchan AM, Evans N, Henderson Smart DJ, Simpson JM : Perinatal risk factors for major intraventricular haemorrhage in the Australian and New Zealand Neonatal Network, 1995-97. **Arch Dis Child Fetal Neonatal Ed 86 :** F86-F90, 2002
13. Hierro-Bujalance C, Infante-Garcia C, Sanchez-Sotano D, Del Marco A, Casado-Revuelta A, Mengual-Gonzalez CM, et al. : Erythropoietin improves atrophy, bleeding and cognition in the newborn intraventricular hemorrhage. **Front Cell Dev Biol 8 :** 571258, 2020
14. Hunt R, Hey E : Ethamsylate for the prevention of morbidity and mortality in preterm or very low birth weight infants. **Cochrane Database Syst Rev (1) :** CD004343, 2010
15. Inoue H, Ochiai M, Yasuoka K, Tanaka K, Kurata H, Fujiyoshi J, et al. : Early mortality and morbidity in infants with birth weight of 500 grams or less in Japan. **J Pediatr 190 :** 112-117.e3, 2017
16. Kadri H, Mawla AA, Kazah J : The incidence, timing, and predisposing factors of germinal matrix and intraventricular hemorrhage (GMH/IVH) in preterm neonates. **Childs Nerv Syst 22 :** 1086-1090, 2006
17. Larroque B, Bréart G, Kaminski M, Dehan M, André M, Burguet A, et al. : Survival of very preterm infants: epipage, a population based cohort study. **Arch Dis Child Fetal Neonatal Ed 89 :** F139-F144, 2004
18. McCrea HJ, Ment LR : The diagnosis, management, and postnatal prevention of intraventricular hemorrhage in the preterm neonate. **Clin Perinatol 35 :** 777-792, vii, 2008
19. Ohlsson A, Aher SM : Early erythropoiesis-stimulating agents in preterm or low birth weight infants. **Cochrane Database Syst Rev 11 :** CD004863, 2017
20. 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. **J Pediatr 92 :** 529-534, 1978
21. Pieper CH, Smith J, Maree D, Pohl FC : Is nCPAP of value in extreme preterms with no access to neonatal intensive care? **J Trop Pediatr 49 :** 148-152, 2003
22. Purisch SE, Gyamfi-Bannerman C : Epidemiology of preterm birth. **Semin Perinatol 41 :** 387-391, 2017
23. Ramenghi LA, Fumagalli M, Groppo M, Consonni D, Gatti L, Bertazzi PA, et al. : Germinal matrix hemorrhage: intraventricular hemorrhage in very-low-birth-weight infants: the independent role of inherited thrombophilia. **Stroke 42 :** 1889-1893, 2011
24. Raybaud C, Ahmad T, Rastegar N, Shroff M, Al Nassar M : The premature brain: developmental and lesional anatomy. **Neuroradiology 55 Suppl 2 :** 23-40, 2013
25. Schindler T, Koller-Smith L, Lui K, Bajuk B, Bolisetty S; New South Wales and Australian Capital Territory Neonatal Intensive Care Units' Data Collection : Causes of death in very preterm infants cared for in neonatal intensive care units: a population-based retrospective cohort study.

BMC Pediatr 17 : 59, 2017
26. Smit E, Odd D, Whitelaw A : Postnatal phenobarbital for the prevention of intraventricular haemorrhage in preterm infants. **Cochrane Database Syst Rev 2013 :** CD001691, 2013
27. Song J, Wang Y, Xu F, Sun H, Zhang X, Xia L, et al. : Erythropoietin improves poor outcomes in preterm infants with intraventricular hemorrhage. **CNS Drugs 35 :** 681-690, 2021
28. Takashima S, Tanaka K : Microangiography and vascular permeability of the subependymal matrix in the premature infant. **Can J Neurol Sci 5 :** 45-50, 1978
29. Valdez Sandoval P, Hernández Rosales P, Quiñones Hernández DG, Chavana Naranjo EA, García Navarro V : Intraventricular hemorrhage and posthemorrhagic hydrocephalus in preterm infants: diagnosis, classification, and treatment options. **Childs Nerv Syst 35 :** 917-927, 2019
30. Vinazzer H : Clinical and experimental studies on the action of ethamsylate on haemostasis and on platelet functions. **Thrombosis research 19 :** 783-791, 1980
31. Volpe JJ : Impaired neurodevelopmental outcome after mild germinal matrix-intraventricular hemorrhage. **Pediatrics 136 :** 1185-1187, 2015
32. Wimberley PD, Lou HC, Pedersen H, Hejl M, Lassen NA, Friis-Hansen B : Hypertensive peaks in the pathogenesis of intraventricular hemorrhage in the newborn. Abolition by phenobarbitone sedation. **Acta Paediatr Scand 71 :** 537-542, 1982
33. Wu T, Wang Y, Xiong T, Huang S, Tian T, Tang J, et al. : Risk factors for the deterioration of periventricular-intraventricular hemorrhage in preterm infants. **Sci Rep 10 :** 13609, 2020
34. Yeo KT, Thomas R, Chow SS, Bolisetty S, Haslam R, Tarnow-Mordi W, et al. : Improving incidence trends of severe intraventricular haemorrhages in preterm infants <32 weeks gestation: a cohort study. **Arch Dis Child Fetal Neonatal Ed 105 :** 145-150, 2020

 https://doi.org/10.3340/jkns.2022.0266