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Pathogenesis and Prevention of Intraventricular Hemorrhage in Preterm Infants

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Intraventricular hemorrhage (IVH) is a serious concern for preterm infants and can predispose such infants to brain injury and poor neurodevelopmental outcomes. IVH is particularly common in preterm infants. Although advances in obstetric management and neonatal care have led to a lower mortality rate for preterm infants with IVH, the IVH-related morbidity rate in this population remains high. Therefore, the present review investigated the pathophysiology of IVH and the evidence related to interventions for prevention. The analysis of the pathophysiology of IVH was conducted with a focus on the factors associated with cerebral hemodynamics, vulnerabilities in the structure of cerebral vessels, and host or genetic predisposing factors. The findings presented in the literature indicate that fluctuations in cerebral blood flow, the presence of hemodynamic significant patent ductus arteriosus, arterial carbon dioxide tension, and impaired cerebral venous drainage; a vulnerable or fragile capillary network; and a genetic variant associated with a mechanism underlying IVH development may lead to preterm infants developing IVH. Therefore, strategies focused on antenatal management, such as routine corticosteroid administration and magnesium sulfate use; perinatal management, such as maternal transfer to a specialized center; and postnatal management, including pharmacological agent administration and circulatory management involving prevention of extreme blood pressure, hemodynamic significant patent ductus arteriosus management, and optimization of cardiac function, can lower the likelihood of IVH development in preterm infants. Incorporating neuroprotective care bundles into routine care for such infants may also reduce the likelihood of IVH development. The findings regarding the pathogenesis of IVH further indicate that cerebrovascular status and systemic hemodynamic changes must be analyzed and monitored in preterm infants and that individualized management strategies must be developed with consideration of the risk factors for and physiological status of each preterm infant.

Key Words : Hemrrhage, cerebral intraventricular · Preterm infants · Pathogenesis · Prevention.

INTRODUCTION

Intraventricular hemorrhage (IVH) is a major concern for preterm infants and is a predisposing factor for brain injury and poor neurodevelopmental outcomes. Improvements in perinatal and neonatal care have increased the survival rate of preterm infants, particularly those born at the gestational age of less than 25 weeks[113]. However, the incidence of IVH in such infants remains approximately 25–30%[18,24]. These findings indicate that determining optimal management

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strategies for IVH can be challenging for neonatologists. Therefore, obtaining a comprehensive understanding of the pathophysiology of IVH and evidence-based interventions for prevention may enable the development of individualised care for this vulnerable population. The present review investigated the underlying pathogenesis of IVH with support from available evidence on the topic and discussed potential IVH prevention strategies that can be employed during prenatal, perinatal, and early postnatal periods.

PATHOGENESIS

The pathophysiology of IVH in preterm infants is multifactorial and complex. The present review investigated the pathogenesis of IVH focusing on factors associated with cerebral haemodynamics, vulnerabilities in the structure of cerebral vessels, and host or genetic predisposing factors. Fig. 1 presents an overview of the pathogenesis of IVH.

ALTERED CEREBRAL HAEMODYNAMICS

Cerebral blood flow fluctuation

Cerebrovascular autoregulation (CAR) plays an essential role in the maintenance of stable and adequate cerebral flow in the states of hypotension and hypoperfusion or hypertension. Lou et al.[65] examined impaired CAR (measured through 133 Xe clearance) in preterm infants with respiratory distress syndrome (RDS) alone and those with concurrent RDS and asphyxia. Another study used continuous-wave Doppler ultrasound to determine whether preterm infants experience considerable changes in cerebral blood flow (CBF) relative to changes in their mean arterial blood pressure (MABP)[83]. A growing body of evidence has supported the association among cerebral perfusion, CAR capacity, and severe IVH; this association was determined through near-infrared spectroscopy in sick infants[59,60]. Preterm infants have impaired CAR in the first few days after birth[59,116,123]. A study used near-infrared spectroscopy to demonstrate that very low birth weight neonates exhibit a considerable concordant change in both their cerebral intravascular oxygen levels and MABP that is consistent with impaired CAR[112]. Soul et al.[101] reported a high prevalence of cerebral pressure passivity in very low birth weight infants (96.7%; 87 of 90 infants), with the prevalence being higher in hypotensive infants. By contrast, several studies have reported CBF to have no association with MABP in preterm infants receiving high-frequency oscillatory ventilation support or before or after treatment for hypotension, which may indicate that preterm infants have intact CAR[63,78,120]. However, CAR is a dynamic and evolving process. Erratic haemodynamic changes occurring in pressure-passive cerebral circulation may precede IVH in preterm infants[59]. Thewissen et al.[107] reported that hypotensive preterm infants experienced significantly longer

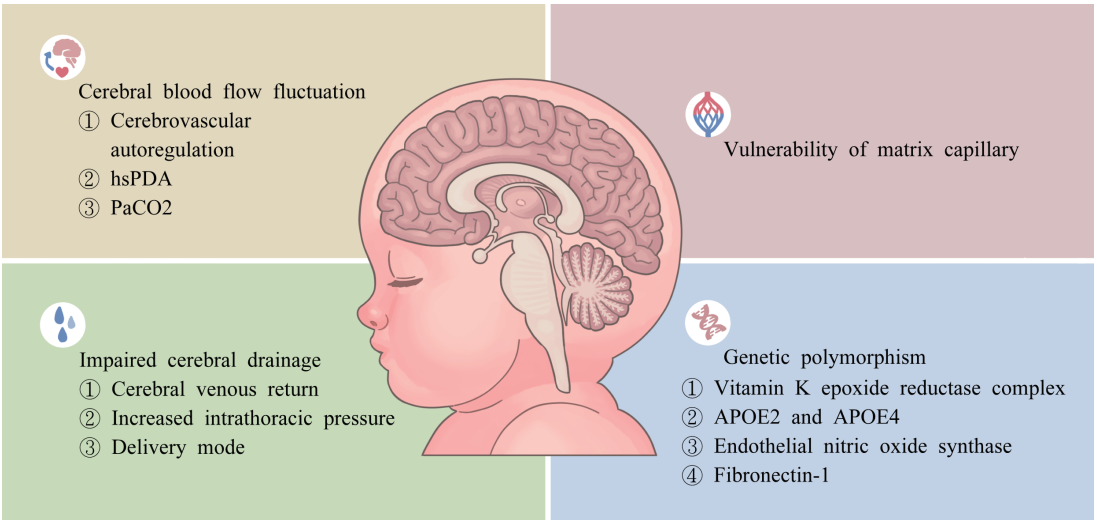

Fig. 1. Overview of the pathogenesis of IVH. IVH : intraventricular hemorrhage, hsPDA : hemodynamic significant patent ductus arteriosus, $PaCO_2$: arterial carbon dioxide tension, APOE : apolipoprotein E.

periods of cerebral hypoxia and impaired CAR and that these characteristics were associated with early IVH or death. Critically ill preterm infants with pressure-passive circulation were reported to have a higher rate of IVH occurrence than do neonates with effective autoregulation[112]. This indicates that blood pressure extremes are more harmful to vulnerable preterm infants. Vesoulis et al.[117] indicated that extreme MABP measurements (i.e., <23 and >46 mmHg) in preterm infants born at a gestational age of <30 weeks were associated with a significantly higher incidence of severe IVH.

The presence of hemodynamic significant patent ductus arteriosus (hsPDA) has been demonstrated to increase the risk of severe IVH in preterm infants[32,89]. However, findings regarding the effect of hsPDA on cerebral oxygenation and CBF have differed[28,115]. Chock et al.[17] discovered preterm infants without hsPDA to have nonsignificantly lower cerebral pressure-passive index scores than did those with hsPDA. In addition, the presence of hsPDA was reported to partly contribute to changes in CBF[77]. The association between hsPDA and IVH may be the result of complex interaction among hemodynamic instability, coagulation, and hsPDA management[13]. Although the detailed mechanism underlying this association is not well elucidated, the sustained patency of ductus arteriosus in combination with cardiac function immaturity was identified to potentially contribute to the occurrence of IVH[79]. Martini et al.[67] discovered that hsPDA was associated with an increase in cerebrovascular reactivity during the transition period. In preterm infants with hsPDA, a positive association was noted between changes in CBF and the severity of cardiac dysfunction, and the incidence of IVH was reported to be higher in such infants[48].

Arterial carbon dioxide tension ($PaCO_2$) affects vasoreactivity and regulates CBF. Hypocarbia has been determined to be associated with higher risks of lung injury and IVH[31,33]. Permissive hypercarbia may be induced to protect the lungs and is commonly used in the care of preterm infants. However, excessively elevated $PaCO_2$ can led to a 2-fold higher risk of IVH when $PaCO_2$ becomes greater than 60 mmHg[33] and can lead to a 5-fold higher risk of IVH when $PaCO_2$ becomes greater than 75 mmHg[49]. A retrospective study reported that fluctuations in $PaCO_2$ may be a more prominent predisposing factor for severe IVH than the presence of hypercarbia alone is[3]. The positive correlation between the transcutaneous CO_2 level and cerebral blood volume in premature infants indicates that such infants experience strong CO_2 cerebrovascular reactivity[4]. Other factors, including a lower gestational age[92,118], having undergone dopamine treatment[67], prolonged hyperglycaemia[6], and lower initial haematocrit[51], have been reported to be independently associated with CBF fluctuations and a significant high risk of IVH in preterm infants.

Impaired cerebral venous drainage

The internal cerebral vein is generally used to evaluate the status of cerebral venous drainage. High-grade fluctuation in the internal cerebral vein was reported to be associated with IVH[46], and an increase in the preload, the diastolic pressure of the right ventricle, or intrathoracic pressure was determined to impede central venous return and increase in cerebral venous pressure[88]. Lower superior vena cava flow is caused by considerable shunting of hsPDA[10] and impaired myocardial function[56] and is associated with an increased risk of IVH[57].

High positive pressure ventilation settings can increase intrathoracic pressure and reduce central venous return. In addition, persistent higher mean airway pressure from high-frequency oscillatory ventilation was reported to increase the likelihood of developing IVH[76]. However, a meta-analysis of 17 randomised controlled trials indicated that the rates of infants receiving high-frequency oscillatory ventilation developing IVH did not significantly differ from those of infants receiving conventional ventilation[20]. Furthermore, infants receiving synchronised and volume-targeted ventilation were demonstrated to have a lower risk of severe IVH than did those receiving original pressure-limited ventilation because synchronised and volume-targeted ventilation involves the use of a lower intrathoracic pressure[55]. Pneumothorax in neonates with a gestational age of <28 weeks was reported to be a risk factor for IVH. This may be because increased intrathoracic pressure in combination with a lack of CAR can lead to impaired cerebral venous return[87].

Prolonged labour and excessive stretch force applied by hands or instruments can damage the cerebral venous system and result in intracranial haemorrhage in term neonates[12,84]. Prolonged labour was reported to be a risk factor for IVH[62]. Although several studies have indicated that IVH rates in children delivered using different modes do not differ[93,122], others have reported a positive correlation between vaginal delivery and IVH[21,45], particularly for neonates born at a gestational age of <26 weeks[44].

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VULNERABILITY OF MATRIX CAPILLARY

The capillaries of the germinal matrix have unique vascular infrastructure and a high metabolic demand for rapid angiogenesis. The features of a fragile capillary network include a paucity of pericytes, immature basement membranes, and poor support from muscles or collagen[30,124]. Primitive sinusoid capillaries generally remain undifferentiated in the germinal zone until term[91]. The subependymal matrix is a border zone located between the cerebral small arteries and deep cerebral vein. This location renders this matrix susceptible to hemodynamic instability and focal hypoxic changes[30].

GENETIC PREDISPOSING FACTORS

Due to the advances in genomics, a growing body of evidence believed genetic variants to be involved in various mechanisms underlying IVH development. Polymorphisms in the gene encoding vitamin K metabolism (vitamin K epoxide reductase complex 1)[96] and transportation (*APOE2* and *APOE4*)[29] have been demonstrated to influence the risk of IVH in preterm infants. Szpecht et al.[105] reported that endothelial nitric oxide synthase and fibronectin-1 polymorphism genes[103] are respectively associated with a 3.4- and 7-fold higher risk of IVH in preterm infants. However, because the results of genetic studies on IVH have been conflicting, additional studies are required to verify the role of genetic factors in the aetiology and pathogenesis of IVH[104,108].

PREVENTION

Antenatal factors

Antenatal corticosteroid was demonstrated to reduce the severity of RDS and long-term morbidity[68]. Ment et al.[70] conducted a randomised controlled trial and discovered that preterm infants who received antenatal steroids had a lower risk of IVH. Administering a course of corticosteroids to women prior to their anticipated preterm births reduced the occurrence of IVH of all grades and particularly reduced the occurrence of severe IVH in preterm infants born at the gestational age of 22–29 weeks[121]. Antenatal steroids were indicated to have the highest efficacy in reducing the likelihood of IVH development when administered 24 hours to 7 days before birth[36]. Antenatal steroids were also demonstrated to reduce the risk of IVH indirectly by improving RDS and shortening the required duration of mechanical ventilation[42]. Although the mechanism underlying this effect remains unclear, it is likely related to the suppression of cerebral angiogenesis[119].

Tocolytics are widely used to reduce the likelihood of extreme preterm birth. However, findings regarding their effect on long-term neurodevelopmental outcomes in preterm infants have been conflicting. Pinto Cardoso et al.[86] conducted a population-based cohort study and discovered that a composite adverse outcome (death/severe IVH) was significantly lower in preterm infants with tocolytic exposure than in those without. Antenatal exposure of magnesium sulfate lowered the risk of severe intraventricular hemorrhage[7,9]. By contrast, a high dose of magnesium sulfate was suggested to increase the risk of IVH[75]. Mittendorf et al.[74] reported that antenatal exposure to magnesium sulfate exerted a paradoxical dose effect on neuroprotection. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine continue to support the short-term (usually less than 48 hours) use of magnesium sulfate in obstetric care for fetal neuroprotection before anticipated early preterm (less than 32 weeks of gestation) delivery[127]. Intravenous administration of magnesium sulfate with one dose of 4–8 g in pregnant women who are at risk of preterm delivery within 7 days might benefit the preterm infants[126].

PERINATAL MANAGEMENT

Delayed cord clamping (DCC) of more than 30 seconds at birth is crucial to ensure that a sufficient amount of blood and stem cells can transfuse from the placenta to the newborn[16,81]. DCC can improve cerebral oxygenation at birth[81] and reduce the incidence of iron deficiency anaemia at infancy[53] in term and late preterm infants. Although a meta-analysis revealed that DCC is not associated with a significant reduction in the incidence of IVH[35], some randomised controlled trials have demonstrated that compared with immediate cord clamping, DCC in extremely preterm infants is associated with a lower risk of severe IVH[43,47]. However, implementing DCC during preterm labour can be challenging because the maternal-neonatal condition is often unstable and resuscitation is often required. Umbilical cord milking (UCM) is an alternative

method that offers advantages over to DCC because it does not necessitate a delay in resuscitation initiation. Compared with immediate cord clamping, UCM can immediately increase pulmonary blood flow to improve oxygenation[52] and reduce the need for blood transfusion[8,52]. Toledo et al.[109] discovered UCM to be associated with a lower IVH rate than that of immediate cord clamping in preterm infants at the gestational age of 27–32 weeks. However, UCM can cause a rapid increase in CBF and thus can significantly increase the risk of severe IVH compared with DCC, particularly in preterm infants born at a gestational age of 28 weeks or less[8,52]. The available evidence indicates that UCM cannot replace DCC as a placenta transfusion strategy in extremely preterm infants. If immediate resuscitation is necessary, it might be an alternative way to DCC that to lift the clamped umbilical cord high to transfuse cord blood into the neonate by gravity.

Numerous scholars have investigated whether caesarean section in preterm deliveries can reduce the rate of IVH development. Rahman et al.[90] and Ljustina et al.[64] have enrolled preterm infants born at the gestational age of 27–34 weeks and reported caesarean section to have no notable effect on IVH reduction. A retrospective study reported no association between the delivery mode and all forms of birth trauma, including IVH, in preterm deliveries[66]. However, other studies have indicated that elective caesarean section exerted a protective effect on IVH in preterm infants[2,42,45]. Hübner et al.[44] reported that preterm infants born at a gestational age of 24–25 weeks benefitted from antenatal steroid treatment in combination with caesarean section. Gamaleldin et al.[38] reported that IVH was less likely to occur if preterm infants born at less than 27 weeks of gestation were delivered by caesarean section. The American College of Obstetricians and Gynecologists suggested caesarean section might be considered and recommended for preterm infants at gestational age of 23–24 weeks and of 25 weeks, respectively[5]. Elective caesarean section might be considered as a strategy to prevent IVH for extremely preterm infants (who had birth weight less than 1000 g or born at less than 27 weeks of gestation) in Taiwan.

POSTNATAL STRATEGY

Pharmacological agents

In addition to closing hsPDA, indomethacin has been suggested to prevent IVH in preterm infants because of its effects on blood vessels. Whether indomethacin or other nonsteroidal anti-inflammatory drugs can reduce the incidence and severity of IVH in preterm infants remains the topic of debate. A multicentre controlled trial demonstrated that low-dose prophylactic indomethacin administered between 6 and 12 hours after birth reduced the incidence or severity of IVH and had no notable adverse effects[71]. Kalani et al.[50] discovered that early ibuprofen administration had a similar IVH-preventive effect. Two recent meta-analyses revealed that indomethacin prophylaxis was associated with a lower rate of severe IVH[1,125]. In contrast, several retrospective studies and clinical trials reported that prophylactic indomethacin not only demonstrated no IVH-preventive effect but also increased the risks of impaired renal function and bleeding tendency[61,72,82]. Indomethacin might appear to be a promising candidate, but proper patient selection is the crux.

Circulatory management

Perinatal transition from foetal to postnatal circulation causes considerable hemodynamic stress on the cardiovascular system. Preterm infants experience more extreme upheaval during the first few days of life than full-term neonates do because of their premature organ function. The disruption of placental circulation forces the malfunctional myocardium of preterm infants to experience an abruptly increased systemic arterial resistance as well as an increased afterload[19,106]. The presence of a left-to-right shunt of patent ductus arteriosus (PDA) can cause the left ventricle to experience volume overload and unstable CBF[17,77]. The incompetence of premature myocardial function can result in impaired cerebral venous drainage[56]. These hemodynamic changes may be worsened by the immature cerebrovascular regulation of preterm infants[59]. Therefore, precise circulatory management aimed at hemodynamic alteration is necessary to prevent IVH.

Prevention blood pressure extremes in preterm infants

Blood pressure being at either extreme in preterm infants can be hazardous and is associated with IVH[117]. Extremely preterm infants have varying rates of hypotension (15–50%)[25]. Although no clear definition for normal blood pressure for preterm infants has been established, many studies and neonatologists have defined hypotension in preterm infants as an MABP value less than gestational age (in weeks)[15,27]. However, blood

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pressure is not a favourable indicator of cerebral or systemic perfusion. Therefore, administration of inotropic drugs or volume expansion for hypotensive preterm infants with clinical signs of favourable perfusion may be unnecessary[26]. Advances in cerebrovascular monitoring have indicated that optimal MABP may be defined as favourable cerebral oxygenation or a minimum cerebrovascular reactivity index value, as determined through near-infrared spectroscopy. Such a definition would prevent the overuse of inotropic drugs and unintentional aggregation of the severity of IVH[22,114]. Several studies indicate that hydrocortisone therapy is increasingly being used for refractory hypotensive preterm infants because such infants are proposed to have an inadequate hypothalamic-pituitary-adrenal axis response to stress during the first week of life[99,110].

Management of hsPDA

Whether conservative monitoring or aggressively treating PDA leads to more favourable results remains the topic of debate. Those who support conservative management on the basis of frequent spontaneous closure occurring[98] lack evidence regarding such management's association with decreased morbidity[73]. However, adverse events were verified to occur both in cases of medical and surgical closure[95]. Nevertheless, early screening and treatment of PDA were reported to be associated with a decrease in mortality and morbidity in preterm infants[54,94]. Most neonatologists decide to treat or not to treat PDA on the basis of clinical signs and sonographic evidence of PDA-related cardiac dysfunction and organ hypoperfusion. Early targeted therapy for PDA in properly selected preterm infants may improve clinical short-term and long-term outcomes[40].

Traditionally, pharmacological closure of hsPDA has been completed using an intravenous cyclooxygenase inhibitor. Such treatment has a closure rate of 70–80%[73]. A study, however, indicated that a high dose of oral ibuprofen may be the most effective alternative to such treatment and have fewer side effects[73]. Intravenous acetaminophen has gradually come to be considered a treatment of choice because its closure rate is similar to that of cyclooxygenase inhibitors and does not affect renal function or increase the risk of necrotising enterocolitis[80]. Surgical ligation and transcatheter closure of PDA can be used as back-up therapy for patients who fail medical treatment and continue to exhibit cardiopulmonary compromise[102].

Optimisation of cardiac function in preterm infants

The cardiac function of preterm infants is not suited to cope with an increased afterload and preload alteration. An animal model revealed the foetal myocardium to have a lower compliance than that of a mature heart[37]. The preterm heart exhibited low ventricle-arterial coupling during the early days of life. In addition, hsPDA was demonstrated to contribute to overload in the immature left ventricle and consistently lower contractility[11]. Cardiac dysfunction and uncoupling under conditions of an increased afterload have been reported to impede cerebral venous return and contribute to IVH in preterm infants[56,57]. The stress-velocity relationship was reported to be an effective indicator of cardiac function and is calculated from end-systolic wall stress (an index of left ventricle afterload) and the left ventricle rate-corrected mean velocity of circumferential fibre shortening (an index of left ventricle contractility). Serial echocardiographic assessment of the stress-velocity relationship can be employed to determine whether contractility has been improved by the administration of inotropic drugs and maintain the afterload at an acceptable level by using vasodilators[111].

Neonatal bundle of care for the prevention of IVH

Optimising management in the immediate post-delivery period—the first 72 hours of life—to reduce the incidence of IVH has been extensively investigated in the literature[14,100]. Widely accepted practices related to such management include (1) maintaining a supine midline with a neutral head position[58]; (2) tilting the incubator to 10° to 30° to avoid the head-down position[58]; (3) ensuring minimal handling, including suction[69]; (4) avoiding rapid flushes and blood withdrawal through intravenous or arterial routes[97]; (5) avoiding routine endotracheal suction[69]; and (6) initiating additional intervention for pain or stress relief in the form of non-nutritive sucking and oral breast milk or sucrose[41]. Several studies have indicated that neonatal neuroprotective care bundles that incorporate these practices can reduce the incidence and severity of IVH; however, studies that have applied such practices have obtained inconsistent results[23,34,39,85]. Therefore, additional studies are required to develop optimal management practices.

CONCLUSION

IVH in infants can contribute to complex and multifactorial interactions. Although advances in obstetric management and neonatal care have led to lower mortality in such infants, the incidence rate of IVH remains unchanged, which is a cause of considerable concern. Therefore, prevention strategies focused on both general care and individualised management must be reviewed.

The routine administration of antenatal corticosteroids, the use of magnesium sulphate, and maternal transfer to a specialised centre can lead to more favourable outcomes, including a lower likelihood of developing IVH, in preterm infants. In addition, incorporating a neuroprotective care bundle into the routine care provided to preterm infants can potentially reduce the rate of IVH development.

The interaction between the cerebrovascular status and systemic hemodynamic changes in preterm infants must be analysed and monitored. Management strategies should be individualised on the basis of specific risk factors for and physiological status of each preterm infant. In addition, the integration of a multifaceted prevention programme could lead to a reduction in the incidence of 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 : PCT; Data curation : PCT; Formal analysis : PCT; Methodology : PCT; Project administration : PCT; Visualization : PCT; Writing - original draft : PCT; Writing - review & editing : PCT

Data sharing

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