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The Diagnosis, Management and Postnatal Prevention of Intraventricular Hemorrhage in the Preterm Neonate

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SYNOPSIS

Intraventricular hemorrhage occurs in 20 – 25% of very low birth weight preterm neonates and may be associated with significant short- and long-term sequelae. In the newborn period, infants with IVH are at risk for both post-hemorrhagic hydrocephalus and periventricular leukomalacia, while as many as 75% of those with parenchymal involvement of hemorrhage suffer significant neurodevelopmental disability at follow-up.

Because of the persistent prevalence of IVH and the significant medical and societal impact of this disease, numerous postnatal pharmacologic prevention strategies have been explored. These must address both the environmental and genetic causes of this injury to developing brain, and randomized clinical prevention trials should provide long-term neurodevelopmental follow-up to assess the impact of preterm birth, injury and pharmacologic intervention on developing brain.

Keywords

intraventricular hemorrhage; preterm; prevention; indomethacin; ibuprofen; phenobarbital

Introduction

Preterm birth can result in significant developmental disability, and numerous studies have identified intraventricular hemorrhage (IVH) as a major cause of adverse outcome for very low birth weight (VLBW) preterm neonates. IVH, or hemorrhage into the germinal matrix tissues of the developing brain, has been attributed to changes in cerebral blood flow to the immature germinal matrix microvasculature and secondary periventricular venous infarction. The more severe grades of IVH are characterized by the acute distension of the cerebral ventricular system with blood and intraventricular hemorrhage with parenchymal venous infarction and are associated with high degrees of morbidity and mortality.

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Nationally, 20 - 25% of all VLBW infants suffer IVH. Importantly, 10 – 15% of neonates of < 1500 g birth weight suffer the more severe grades of hemorrhage, and over three-quarters of these develop mental retardation and/or cerebral palsy. Based on data from the U.S. Census Bureau, the NICHD Neonatal Network and the Centers for Disease Control, there are over 3600 new cases of mental retardation attributable to IVH in the United States each year, and the lifetime care costs for these children exceeds 3.6 billion dollars.

Preterm birth represents a unique environment for the developing brain, and many important environmental factors including inflammation, hypotension, and hypoxemia that contribute to IVH have been identified. To address the enormous societal and financial burden of IVH, both pharmacologic and care-oriented prevention strategies have been implemented. These studies have led to significant reductions in the incidence of IVH by changing practices in newborn resuscitation and perinatal care.

Nonetheless, the incidence of Grades (Gr) 3 – 4 IVH has not changed over the last ten years, and the role of genetics factors in the pathophysiology of IVH is just beginning to be explored. These data suggest that, for VLBW infants, IVH is a complex disorder. In order to further lower the incidence of IVH and thus neurodevelopmental handicap in the preterm population, prevention strategies must target both environmental and genetic factors.

IVH is an important predictor of adverse neurodevelopmental outcome

Although several early studies reported that cognitive outcome may be directly related to gestational age at birth^{55,95}, recent data suggest that medical risk factors may be equally important predictors of neurologic outcome.^{6,37,45,61,65,87,91} Chief among these is Gr 3 - 4 IVH.⁶⁵

IVH occurs in infants of 32 weeks' gestation or less, and the overall incidence of IVH is inversely related to gestational age. For the purposes of this chapter, IVH will be described by the following classification: Grade 1 – germinal matrix hemorrhage; Grade 2 – intraventricular blood without distension of the ventricular system; Grade 3 – blood filling and distending the ventricular system; and Grade 4 – parenchymal involvement of hemorrhage, also known as periventricular venous infarction.^{68,93,96}

In the newborn period, 5 - 10% of preterm infants with Gr 3 – 4 IVH suffer seizures and as many as 50% experience posthemorrhagic hydrocephalus. Finally, mortality is higher in infants with Gr 3 – 4 IVH than in GA-matched subjects without Gr 3 – 4 IVH.⁹⁶

While prematurely born children with Gr 3 - 4 IVH are at high risk for cerebral palsy and mental retardation,^{8,21,46,57,71,85,89,90,95} children with Gr 1 – 2 IVH are also at risk for developmental disability. One half to three quarters of infants with Gr 3 – 4 IVH develop disabling CP in childhood, and in the large and well characterized cohort of Pinto-Martin, Gr 3 – 4 IVH was associated with CP with an odds ratio (OR) of 15.4 (95% CI 7.6 – 31.1).⁷¹ Furthermore, 45 – 86% of preterm children with Gr 3 – 4 IVH have been reported to suffer major cognitive handicaps, approximately 75% of them are either in special education classrooms or receive extensive special education services in school, and a recent review found that the presence of Gr 3 – 4 IVH is significantly associated with mental retardation at 2 to 9 years, with OR values ranging from 9.97 to 19.0.^{57,90}

Pathophysiology: IVH is a complex disorder

Risk factor studies

Studies addressing the etiology of Gr 3 – 4 IVH have identified numerous environmental and medical risk factors including low gestational age, absence of antenatal steroid exposure,

antenatal maternal hemorrhage, maternal chorioamnionitis/infection/inflammation, maternal fertility treatment, outborn status (i.e., neonatal transport), early sepsis, hypotension requiring therapeutic intervention, hypoxemia, hypercapnia, pneumothorax, pulmonary hemorrhage, respiratory distress syndrome, severity of illness score, seizures, small for gestational age status, treatment for acidosis, and treatment with pressors.^{5,36,43,44,53,66,83,96}

Role of cerebral blood flow and the germinal matrix microvasculature

Intraventricular hemorrhage has generally been attributed to alterations in cerebral blood flow to the immature germinal matrix microvasculature. During the risk period for IVH, this region is richly supplied with microvessels lacking basement membrane deposition, tight junctions, and glial endfoot investiture, all components of a competent blood brain barrier. In response to hypotension, hypoxemia, hypercapnia, or acidosis, cerebral blood flow rises, hemorrhage begins within the germinal matrix and blood may rupture into the ventricular system. Following ventricular distension by an acute hemorrhagic event, blood flow falls. Venous stasis occurs within the periventricular white matter, and parenchymal venous infarction may follow.

Significant modulators of cerebral blood flow in the developing brain include the cyclooxygenase 2 (COX-2) system and prostaglandins (PGs).^{50,51,60} COX-2 expression is induced by hypoxia, hypotension, growth factors such as epidermal growth factor receptor, transforming growth factor β (TGF β), and inflammatory modulators including IL-6, IL-1 β , TNF- α , and NF κ B.^{1,19,41,42,48,67,69,75,76,80,82,86} The resultant prostanoids promote the production and release of vascular endothelial growth factor (VEGF), a potent angiogenic factor.^{48,81}

Those same triggers which initiate hemorrhage into the germinal matrix set in motion a cascade leading to the disruption of tight junctions, increased blood brain barrier permeability, and microglial activation within the developing periventricular white matter. These events are mediated by cytokines, VEGF, and nitric oxide (NO). In vitro, both endothelial cells and astrocytes release the pro-inflammatory cytokines IL-1 β and TNF- α , and both of these promote transmigration of leukocytes across the endothelium and developing blood brain barrier. Furthermore, hypoxia alone has been shown to alter the blood brain barrier proteins ZO-1, occludin, and ZO-2. Finally, reactive microglia release reactive oxygen species (ROS), which in turn not only contribute to endothelial damage, but also alter hemostasis and increase anaerobic metabolism.^{13,17,72,74}

The preterm brain is more susceptible to ROS than adult brain because of the immaturity of those enzyme systems designed to detoxify them. In addition to their release by activated microglia, ROS are also generated following the activation of the COX-2 system.³ Because of their multifaceted effects on the developing vasculature, ROS are believed to play a significant role in periventricular parenchymal infarction.²⁵

Genetic factors may play a role

The relatively recent description of the thrombophilias associated with the Factor V Leiden and prothrombin G20210A mutations and the implication of both in perinatal stroke suggest these might also be candidate genes for IVH.^{22,28,30,70} Likewise, mutations in collagen IVA1 result in IVH in neonatal mice and porencephaly in human infants, and adults with intracerebral hemorrhage have a high incidence of the apolipoprotein E4 or E2 allele.^{2,4,31,32,100}

Polymorphisms in the proinflammatory cytokine IL-6 have also been proposed as possible genetic modifiers of the risk for IVH, although the results have been somewhat contradictory.^{29,39} Position 174 can be either a G or a C, and IL-6 production is thought to be greater in neonates with a CC genotype.³⁹ Harding, et al., demonstrated that preterm infants (≤ 32 weeks'

gestation) with the CC genotype at amino acid 174 had a statistically significant increase in the rate of IVH, white matter disease, and disability, compared to neonates with the GC or GG genotype.³⁹ Cerebral palsy was also seen at twice the rate in infants with the CC genotype compared to GC or GG genotype, but this did not reach statistical significance. Despite the increase in IVH and white matter disease, long term developmental outcome as measured by the Griffiths mental development scales at two years and the BAS-II and movement ABC scales at age 5.5 years was not statistically different between the two groups. In contrast, employing a considerably larger sample size, Gopel noted no effects of the CC genotype on cerebral injury including IVH, PVL, or the need for placement of a ventriculo-peritoneal shunt.²⁹

A polymorphism at position 572 in the IL-6 gene has also been studied.³⁸ Similar to the 174 position, the 572 position can be a G or more rarely a C, and the C allele is associated with higher levels of IL-6. Preterm neonates (born at ≤ 32 weeks' gestation) with the C allele showed decreased performance on the Griffiths Developmental quotient at two years and the general cognitive ability portion of the BAS at 5.5 years; interestingly, they did not have an increased rate of IVH or PVL. However, the rate of the C allele is very low, thus the number of patients included in this study was small, and results must be interpreted with caution.

Finally, recent studies suggest that the interaction of thrombophilia mutations, inflammatory factors, and ROS may contribute to IVH. Infants with IVH may suffer mutations of TNF- α and IL-6. In addition, thrombin can induce ROS in microglia. Preterm infant studies have shown that neonates at risk for CP are more likely than their peers to have both evidence for activation of systemic inflammatory factors and elevated levels of coagulation factors.^{16,19,20,52}

In summary, available epidemiologic, laboratory and clinical studies suggest that multiple environmental and genetic factors may affect the risk for IVH independently or interactively via at least five different and yet overlapping pathways: angiogenesis and vascular pathology, control of cerebral blood flow in the developing brain, inflammation/infection, oxidative pathways, and coagulation and thrombophilia mutations. Therapies to prevention IVH must address the complexity of this disease.

The risk period for IVH is independent of gestational age

If one is to prevent injury, knowledge of the risk period is critical for success. IVH is most commonly encountered within the first 24 hours after birth, and hemorrhages can progress over 48 hours or more. By the end of the first postnatal week, 90% of the hemorrhages can be detected at their full extent, and this risk period for IVH is independent of gestational age.

Management of IVH

Screening for IVH in VLBW preterm neonates

Management of IVH is typically confined to screening for sequelae of IVH and managing systemic issues of the neonate, such as blood pressure and respiratory status, which might influence progression of IVH. The American Academy of Neurology Practice Parameter for "Neuroimaging of the Neonate" suggests that screening ultrasonography should be performed on all preterm neonates of <30 weeks gestation at two time points.⁵⁷ The first ultrasound is recommended between 7 - 14 days of age in order to detect signs of IVH, and the second ultrasound is recommended at 36 - 40 weeks postmenstrual age in order to look for CNS lesions such as periventricular leukomalacia and ventriculomegaly, which will affect long term outcome. MRI is better than ultrasound at detecting white matter abnormalities, hemorrhagic lesions, and cysts, and emerging data are providing preliminary evidence for the importance of this imaging modality at term equivalent as a predictor of outcome at two to three years of age in VLBW preterm infants.

Radiologic assessment of risk for IVH

If one hopes to prevent injury in a patient population, markers of impending injury must be sought. It is of particular note, therefore, that diffusion-weighted imaging studies in the acute perinatal period have been shown to be predictive of cystic PVL. To the best of our knowledge, however, no ante- or postnatal MRI findings have been reported which are predictive of IVH.

Short-term sequelae of IVH

Posthemorrhagic hydrocephalus (PHH) and periventricular leukomalacia (PVL) are two significant sequelae of IVH. Patients with PHH usually present with rapidly increasing head circumferences, enlarging ventricles on radiologic examination and signs of increased intracranial pressure, but the signs and symptoms of hydrocephalus may not be evident for several weeks post-hemorrhage due to the compliance of neonatal brain.⁹² The majority of cases of PHH are communicating, as shown in Figure 1, and are believed to be secondary to the impaired CSF reabsorption which accompanies the chemical arachnoiditis commonly found after blood is introduced into the CSF. Neonates can also exhibit a non-communicating hydrocephalus secondary to the acute obstruction of the foramen of Monro or the aqueduct by clot, or to subependymal scarring. Randomized controlled trials performed to evaluate several potential treatments to prevent or reduce the extent of PHH include intraventricular streptokinase, repeated lumbar or ventricular punctures, and DRIFT (drainage, irrigation, and fibrinolytic therapy), but these interventions have proved ineffective.^{96,97,99}

Further, while Whitelaw has recommended ventricular puncture with removal of between 10 and 20 ml/kg of CSF for cases with rapid ventricular enlargement and increased ICP⁹⁶, others have explored temporizing measures such as subgaleal shunt placement (SGS) or ventricular reservoir placement for intermittent tapping (RES) with the hope of avoiding permanent VP shunt placement. A small retrospective review of these interventions in IVH patients recently determined that 91% of patients with SGS and 62% of patients with RES required subsequent permanent shunt placement.⁹⁴ Infection rates were similar between the two populations. Future randomized trials are required to confirm this information and determine the appropriate time and manner of intervention.

IVH can also result in white matter abnormalities, including periventricular leukomalacia (PVL). PVL, shown in Figure 2, is classically defined as multiple cystic foci in the periventricular cerebral white matter⁹, which on histology demonstrate coagulation necrosis and loss of cellular architecture.²³ When PVL follows IVH, it has been attributed to the sometimes profound and long-lasting decreases in cerebral blood flow that accompany the introduction of blood into the CSF. Some of these cases of PVL after IVH have also progressed to porencephaly (Greek for “hole in the brain”)³⁴, so it is important to distinguish enlarged ventricles caused by white matter destruction from those under increased pressure as in PHH.

Depending on the severity and location of the PVL lesions, the clinical presentation of affected children may range from spastic diplegia to decreased visual fields and cognitive impairment^{10,33}, and many investigators believe that the white matter injury which accompanies IVH represents the major cause of the neurodevelopmental impairments suffered by these neonates.

Finally, a grade 4 IVH may also result in porencephaly independent of PVL and/or PHH.⁵⁶ These hemispheric cavitory lesions are generally freely communicating with the ventricular system, although rarely a porencephaly may present as a fluid-filled cyst that obstructs the ventricular system and may present with symptoms of increased intracranial pressure.

Rationale for prevention strategies

As support in the neonatal period has improved, more low birth weight infants are surviving, and it has become increasingly clear that certain newborns seem to do better than their similarly premature counterparts. Differences have even been noted between rates of IVH at different neonatal intensive care units with those treating higher patient volumes and with a higher neonatologist-to-housestaff ratio having lower rates of IVH.⁸⁴ It is uncertain what accounts for this difference, but one could speculate upon environmental, genetic, and pharmacologic effects. Both environmental and pharmacologic strategies to prevent IVH have increasingly been tried with varying degrees of success, although it is not the mandate of this review to discuss environmental manipulations or antenatal pharmacologic agents for the prevention of IVH.

Furthermore, as pharmacologic treatments have emerged, it has also become apparent that some children respond better to treatment than others. As a result, an understanding of the role that both gender and genetics play in both the natural course of IVH and in response to IVH prevention strategies is critical, as it will enable better allocation of resources to those infants at greatest risk of IVH and those most likely to benefit from the intervention.

Finally, newborn follow-up is critical to the successful evaluation of any proposed intervention. Therapeutic strategies designed to modulate cerebral blood flow to the preterm brain may alter perfusion to other developing organs and result in adverse renal and/or gastrointestinal sequelae. Similarly, agents believed to modulate blood pressure may impair neurogenesis and thus cognition in the developing nervous system.

Postnatal pharmacologic preventions strategies for IVH

The well known sequelae of IVH have prompted the development of pharmacologic prevention strategies for this injury to developing brain for almost four decades (Table 1). These interventions have included phenobarbital, pavulon, vitamin E, ethamsylate, indomethacin, ibuprofen, and recombinant activated factor VIIa. Since the preclinical and clinical trials for pavulon, vitamin E, and ethamsylate took place many years ago and these agents are not currently in wide use, these studies will be only briefly reviewed at this time. Mechanisms of action and study results for the other four agents are discussed below.

Phenobarbital—Phenobarbital is thought to stabilize blood pressure and potentially offer protection from free radicals. Since variations in blood pressure, subsequent changes in cerebral blood flow, and oxygen free radical damage during reperfusion are thought to contribute to IVH, phenobarbital was proposed as a possible prevention strategy. Whitelaw and Odd reviewed the literature regarding phenobarbital in the prevention of IVH.⁹⁸ Overall, eight of the ten trials reviewed showed no statistically significant difference in risk of IVH between phenobarbital and control treated patients. One trial showed an increased risk of IVH in the phenobarbital treated group, but in this study, the phenobarbital group was younger in age and smaller in size than the control group.⁴⁷ These factors would have increased the risk of IVH in this patient group, independent of treatment with phenobarbital. One study showed a decreased risk of IVH in the phenobarbital treated group, but patients in this study were not checked for IVH before instituting treatment.²⁴ Rates of severe IVH, studied in all 10 trials, and ventricular dilation and/or hydrocephalus, studied in 4 trials, also did not differ significantly between phenobarbital and control-treated infants. Whitelaw and Odd concluded that in the ten trials examined, patients treated with phenobarbital did not have a significant decrease in IVH or severity of IVH, but they did have an increased risk for requiring mechanical ventilation.

Indomethacin—Indomethacin is used in preterm neonates both to close patent ductus arteriosus and for prevention of IVH. Indomethacin acts via nonspecific inhibition of the constitutive and inducible isoforms of cyclooxygenase, COX-1, and COX-2 respectively, which subsequently decreases prostaglandin synthesis. Indomethacin is thought to prevent IVH both through effects on blood flow and on basement membrane maturation. Insults such as hypertension, asphyxia, or hypercapnia typically lead to hyperemia in experimental animals, but intravenous delivery of indomethacin blunts this response and improves cerebral autoregulation.^{51,73,88} Indomethacin has also been shown to promote microvessel maturation of the germinal matrix in beagle pups⁵⁹, and in a pig model to inhibit the alterations in blood brain barrier permeability which result from ischemia.⁵¹ Consistent with this experimental data, infants treated with indomethacin have been shown to have a decrease in both the incidence and severity of IVH.^{58,79}

Despite the obvious effect in preventing IVH, the long term cognitive benefit of indomethacin treatment has been more controversial, and recent scientific work has attempted to understand the effect of indomethacin on developing brain. Some groups have proposed that indomethacin should be neuropathologic because it blocks COX activity with a resulting inhibition in production of the neuroprotective prostaglandin E2⁴⁰, while others have proposed that this agent may confer neuroprotection by preventing the upregulation of genes linked to oxidative stress⁷⁸ and downregulating those inflammatory factors, such as IL-6 and TNF-alpha, which inhibit neurogenesis.⁶⁴ In addition, the COX2 gene has two polymorphic variants, a G or a C at position 765.⁴⁰ Patients with the C allele have reduced COX2 activity, and may thus exhibit different responses to indomethacin than those with the alternative allele.

Neurodevelopmental outcome has been reported for three of the indomethacin trials. Age at subject assessment and cognitive measures employed differed considerably among the studies, and the meta-analysis of Fowlie and Davis concluded that treatment with indomethacin did not affect rates of severe developmental delay or neurosensory impairment.²⁶ Several authors have questioned why, if indomethacin decreases the incidence and lowers the severity of IVH, it does not appear to globally improve outcome.^{40,58,79} It is interesting to note, therefore, that Harding, et al., have reported that prematurely born subjects with the COX2 C765 allele had decreased cognitive performance at age 2 and 5.5 years when compared to their G allele peers.⁴⁰

Furthermore, Ment, et al., analyzed their indomethacin data on the basis of gender.⁶² The rate of IVH was found to be significantly decreased with indomethacin treatment in male infants, but there was no corresponding decrease in IVH rate after indomethacin treatment in female neonates. IVH grade was also significantly reduced in males treated with indomethacin. In addition, boys treated with indomethacin performed significantly better on the Peabody Picture Vocabulary Test-R at 3, 4.5, 6, and 8 years' corrected age when compared to placebo treated boys. This increased performance was independent of the decrease in IVH and was not seen in girls. These data suggest that gender may play an important role in both injury to the developing brain and long term cognitive outcome and that gender must be considered when evaluating new treatments.

Ibuprofen—Intravenous ibuprofen was tested in newborns as a result of evidence in newborn animals that it improved cerebral blood flow autoregulation.¹⁴ Aranda and Thomas reviewed the use of ibuprofen in neonates and found that while ibuprofen has a similar effect to indomethacin on closure of patent ductus arteriosus, it was ineffective with respect to IVH prevention.⁷

Activated factor VII—Recombinant activated factor VII (rVIIa) was originally developed in preclinical trials as a hemostatic agent for use in patients with hemophilia.^{12,54} rVIIa is

thought to act in the clotting cascade through both tissue factor dependent and independent mechanisms.⁴⁹ Tissue factor is normally only exposed at sites of endothelial damage. The enzymatic activity of endogenous factor VIIa is weak unless bound to tissue factor. Upon binding to tissue factor, downstream factors in the coagulation cascade are activated leading to conversion of prothrombin to thrombin with subsequent conversion of fibrinogen to fibrin. When rVIIa is used, the plasma concentration is about ten times that seen with endogenous factor VIIa. As a result of this increased concentration, rVIIa is able to bind to activated platelets leading to a “thrombin burst,” a major increase in the amount of thrombin generated, which is independent of tissue factor. This leads to the formation of a thrombin clot, and factors which prevent fibrinolysis are activated as well in order to prevent dissolution of this clot. Factor VII was proven to be safe and effective in treating the hemophiliac patient population, and since then, its “off-label” use has widened to include non-hemophiliac patients with uncontrolled bleeding due to oral anticoagulation, trauma, thrombocytopenia, platelet dysfunction, and liver dysfunction.²⁷ However, placebo controlled randomized clinical trials looking at safety and efficacy are lacking for the off-label use of factor VII. In neonates, Greisen and Andreasen conducted a small study on preterm infants (gestational age less than 33 weeks) with prolonged PT. Ten babies were evaluated for side effects of factor VII administration and to compare different doses of factor VII, and then two babies were randomized to rFVIIa with four randomized to fresh frozen plasma (FFP).³⁵ Factor VII was demonstrated to decrease PT more than FFP, but the authors note that the PT may not be representative of clotting function, as the test they used is particularly sensitive to factor VII concentration in the sample. The results suggested that the half-life of rFVIIa in preterm babies was similar to that of adults, ranging between 2 and 3 hours. The neonates included in this study had no adverse events. While there have not been other randomized clinical trials of factor VII in the neonatal population, two case series, one involving 9 patients less than 4 months of age,¹¹ and one with 9 patients that included 6 preterm infants⁶³, have further suggested that factor VII may be safe and effective as a rescue-therapy to control bleeding in the newborn population after conventional treatments have been exhausted.

Since evidence suggests that Factor VII may be an effective agent in prevention of bleeding in a diverse array of situations, it has also been proposed as a potential treatment for IVH.⁷⁷ Since factor VII is thought to require exposed tissue factor or activated platelets in order for it to promote coagulation, it is thought that the pro-thrombotic effects of factor VII should be restricted to the site of injury, thus contributing to its safety. Administration just after onset of IVH would be expected to promote clotting in the periventricular region without promoting a hypercoagulable state.⁷⁷ While results with factor VII in non-hemophiliac patients are preliminary and further study is necessary, its proposed mechanism of action, positive results in some patient populations with major bleeding, and the observed safety so far in the admittedly small number of neonates in which it has been assessed, suggest that this is an intervention which deserves further study in the setting of IVH.

Other prevention trials—Additional postnatal treatments evaluated have included ethamsylate, vitamin E, and pavulon. Ethamsylate promotes platelet adhesion and increases stability of the capillary basement membrane by causing hyaluronic acid polymerization. In clinical trials, ethamsylate decreased the rates of IVH in very low birth weight infants, without altering rates of severe IVH, death, or neurological abnormality.⁹⁶ Similarly, vitamin E, an anti-oxidant, has also been shown to decrease the rate of IVH although the effect on high grade IVH was not specifically examined and overall mortality was unaffected.¹⁵ Finally, pavulon (pancuronium) has also been tested as an intervention to decrease IVH in mechanically ventilated newborns. By inducing muscular paralysis, pavulon is believed to prevent asynchronous breathing and the alterations in oxygenation and secondary changes in cerebral blood associated with this phenomenon in the preterm neonate.¹⁸

Summary

Intraventricular hemorrhage remains a common problem of VLBW preterm neonates, and may be associated with significant neurodevelopmental disability. Prevention strategies must address both the environmental and genetic causes of this injury to developing brain. The effect of gender on the efficacy of indomethacin treatment and of genetics on the cognitive outcome of preterm neonates argues that as new interventions are developed, their effect on specific subgroups of neonates must be considered in addition to their overall population effect. Studying all preterm neonates as a single group, while an important first strategy, risks missing treatments which could potentially benefit subgroups of this population. We would suggest that when studies are carried out in the future, in addition to evaluating safety and efficacy in the entire study group, researchers should analyze their data with respect to gender and ideally genetic polymorphisms. This strategy for assessing interventions should allow for a more thorough analysis of potential benefits.

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Figure 1.

Serial cranial ultrasounds and MRI studies from a preterm male infant born at 24 weeks of gestation. The initial diagnosis of Grade 3 IVH at age 3 days (panel A) was followed by parenchymal involvement of hemorrhage, or Grade 4 IVH, on postnatal day 4 (arrow, panel B). A cranial ultrasound performed on day 10 because of increasing occipitofrontal head circumference and full fontanelle revealed bilateral ventriculomegaly, residual intraventricular blood and a developing porencephaly (arrow, panel C). MRI study at 2 months demonstrated ventriculomegaly (panel D). Because of excessive increase in head circumference and increasing spasticity, the patient underwent third ventriculostomy following MRI scan at age 6 months (panel E).

Figure 2. Serial cranial ultrasounds of a 30 week preterm male with Grade 3 IVH and hemorrhagic PVL at age 10 days (panel A). Repeat ultrasound 3 weeks later demonstrated unilateral ventriculomegaly and periventricular cystic cavities consistent with PVL (panel B).

Table 1

Postnatal Prevention Strategies for IVH

Pharmacologic agent	Proposed Mechanism
Phenobarbital	Stabilize blood pressure and free radical production
Pavulon	Prevent asynchronous breathing in ventilated newborns with secondary BP stabilization
Ethamsylate	Promote platelet adhesion; increase capillary basement membrane stability
Vitamin E	Free Radical Protection
Indomethacin	Promote microvascular maturation; blunt fluctuations in BP and cerebral blood flow
Ibuprofen	Improve autoregulation of cerebral blood flow
Factor VIIa [*]	Promote clot formation

* Rescue therapy to prevent extension of IVH

Table 2

Candidate Genes for IVH

Gene	Allele	Effect
Inflammation		
IL 6	174 G or C, 572 G or C	CC has increased IL-6 production, question of increased risk of IVH, white matter disease, and cerebral palsy
TNF α		Possible candidate gene for IVH
Hemostasis		
Factor V Leiden		Increased thrombosis, increased risk of perinatal stroke, possible candidate gene for IVH
prothrombin	G20210A	Increased thrombosis, increased risk of perinatal stroke, possible candidate gene for IVH
Apolipoprotein E4 or E2		Increased incidence in adults with intracerebral hemorrhage, candidate gene for IVH
Vascular Stability		
COL4A1		Mutations result in IVH in neonatal mice and porencephaly in human infants, candidate gene for IVH