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

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KEYWORDS

• Intraventricular hemorrhage • Preterm • Prevention
• Indomethacin • Ibuprofen • Phenobarbital

Preterm birth can result in significant developmental disability, and many studies have identified intraventricular hemorrhage (IVH) as a major cause of adverse outcome for very low birthweight (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 hemorrhage with parenchymal venous infarction and are associated with high degrees of morbidity and mortality.

Nationally, 20% to 25% of all VLBW infants suffer IVH. Among neonates of less than 1500 g birthweight, 10% to 15% suffer the more severe grades of hemorrhage, and more than three quarters of these develop mental retardation or cerebral palsy (CP). Based on data from the United States Census Bureau, the National Institute of Child Health and Human Development Neonatal Network, and the Centers for Disease

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Control, there are more than 3600 new cases of mental retardation attributable to IVH in the United States each year, and the lifetime care costs for these children exceed $3.6 billion.

Preterm birth represents a unique environment for the developing brain, and many important environmental factors, including inflammation, hypotension, and hypoxemia, that contribute to IVH are identified. To address the enormous societal and financial burden of IVH, 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 past 10 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. To further lower the incidence of IVH and thus neurodevelopmental handicap in the preterm population, prevention strategies must target environmental and genetic factors.

INTRAVENTRICULAR HEMORRHAGE 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,[1,2] recent data suggest that medical risk factors may be equally important predictors of neurologic outcome.[3–9] Chief among these is Gr 3–4 IVH.[7]

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 article, IVH is 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.[10–12]

In the newborn period, 5% to 10% of preterm infants who have Gr 3–4 IVH suffer seizures and as many as 50% experience posthemorrhagic hydrocephalus. Finally, mortality is higher in infants who have Gr 3–4 IVH than in gestational age–matched subjects who do not have Gr 3–4 IVH.[12]

Although prematurely born children who have Gr 3–4 IVH are at high risk for CP and mental retardation,[2,13–20] children who have Gr 1–2 IVH also are at risk for developmental disability. One half to three quarters of infants who have Gr 3–4 IVH develop disabling CP in childhood, and in the large and well characterized cohort of Pinto-Martin and colleagues, Gr 3–4 IVH was associated with CP with an odds ratio (OR) of 15.4 (95% CI, 7.6–31.1).[17] Furthermore, 45% to 86% of preterm children who have Gr 3–4 IVH are reported to suffer major cognitive handicaps; approximately 75% of them are 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.[16,20]

PATHOPHYSIOLOGY: INTRAVENTRICULAR HEMORRHAGE IS A COMPLEX DISORDER

Risk Factor Studies

Studies addressing the etiology of Gr 3–4 IVH have identified many 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 (ie, 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.[12,21–27]

Role of Cerebral Blood Flow and the Germinal Matrix Microvasculature

IVH generally has 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. After 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.[28–30] COX-2 expression is induced by hypoxia; hypotension; growth factors, such as epidermal growth factor receptor and transforming growth factor-beta; and inflammatory modulators, including interleukin (IL)-6, IL-1β, tumor necrosis factor α (TNF-α), and nuclear factor κB.[31–42] The resultant prostanoids promote the production and release of vascular endothelial growth factor (VEGF), a potent angiogenic factor.[35,43]

Those same triggers that 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. In vitro, endothelial cells and astrocytes release the pro-inflammatory cytokines, IL-1β 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.[44–47]

The preterm brain is more susceptible to ROS than the adult brain because of the immaturity of those enzyme systems designed to detoxify them. In addition to their release by activated microglia, ROS also are generated after the activation of the COX-2 system.[48] Because of their multifaceted effects on the developing vasculature, ROS are believed to play a significant role in periventricular parenchymal infarction.[49]

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 also might be candidate genes for IVH (**Table 1**).[50–53] Likewise, mutations in collagen IVA1 result in IVH in neonatal mice and porencephaly in human infants, and adults who have intracerebral hemorrhage have a high incidence of the apolipoprotein E4 or E2 allele.[54–58]

Polymorphisms in the proinflammatory cytokine IL-6 also are proposed as possible genetic modifiers of the risk for IVH, although the results are somewhat contradictory.[59,60] Position 174 can be a G or a C, and IL-6 production is believed greater in neonates who have a CC genotype.[60] Harding and colleagues[60] demonstrated that preterm infants ($\leq$32 weeks' gestation) who had the CC genotype at amino acid 174 had a statistically significant increase in the rate of IVH, white matter disease,

Table 1
Candidate genes for intraventricular hemorrhage

Gene	Allele	Effect
Inflammation		
IL-6	174 G or C, 572 G or C	CC has increased IL-6 production, question of increased risk for IVH, white matter disease, and CP
TNF-α		Possible candidate gene for IVH
Hemostasis		
Factor V Leiden		Increased thrombosis, increased risk for perinatal stroke, possible candidate gene for IVH
Prothrombin	G20210A	Increased thrombosis, increased risk for perinatal stroke, possible candidate gene for IVH
Apolipoprotein E4 or E2		Increased incidence in adults who have 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

and disability compared with neonates who had the GC or GG genotype. CP also was seen at twice the rate in infants who had the CC genotype compared with 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 development quotient at 2 years and the British Ability Scales II (BAS) and Movement Assessment Battery for Children at age 5.5 years was not statistically different between the two groups. In contrast, using a considerably larger sample size, Gopel and colleagues[59] noted no effects of the CC genotype on cerebral injury, including IVH, periventricular leukomalacia (PVL), or the need for placement of a ventriculoperitoneal shunt.

A polymorphism at position 572 in the IL-6 gene also has been studied.[61] 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 $\leq$32 weeks' gestation) who had the C allele showed decreased performance on the Griffiths developmental quotient at 2 years and the general cognitive ability portion of the BAS at 5.5 years; they did not have an increased rate of IVH or PVL. The rate of the C allele is very low, however; 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 who have IVH may suffer mutations of TNF-α and IL-6. In addition, thrombin can induce ROS in microglia. Studies of preterm infant have shown that neonates at risk for CP are more likely than their peers to have evidence of activation of systemic inflammatory factors and elevated levels of coagulation factors.[32,62–64]

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 INTRAVENTRICULAR HEMORRHAGE IS INDEPENDENT OF GESTATIONAL AGE

To prevent injury, knowledge of the risk period is critical for success. IVH is encountered most commonly 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 INTRAVENTRICULAR HEMORRHAGE

Screening for Intraventricular Hemorrhage in Very Low Birthweight Preterm Neonates

Management of IVH typically is 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: neuroimaging of the neonate'' suggests that screening ultrasonography should be performed on all preterm neonates of less than 30 weeks' gestation at two time points.[16] The first ultrasound is recommended between 7 and 14 days of age to detect signs of IVH, and the second ultrasound is recommended at 36 and 40 weeks' postmenstrual age to look for CNS lesions, such as periventricular leukomalacia and ventriculomegaly, which 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 2 to 3 years of age in VLBW preterm infants.

Radiologic Assessment of Risk for Intraventricular Hemorrhage

If preventing injury is hoped for in a patient population, markers of impending injury must be sought. In particular, therefore, diffusion-weighted imaging studies in the acute perinatal period are shown predictive of cystic PVL. To the best of the authors' knowledge, however, no antenatal or postnatal MRI findings have been reported that are predictive of IVH.

Short-Term Sequelae of Intraventricular Hemorrhage

Posthemorrhagic hydrocephalus (PHH) and PVL are two significant sequelae of IVH. Patients who have 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 because of the compliance of neonatal brain.[65] The majority of cases of PHH are communicating, as shown in **Fig. 1**, and are believed secondary to the impaired cerebrospinal fluid (CSF) reabsorption, which accompanies the chemical arachnoiditis commonly found after blood is introduced into the CSF. Neonates also can exhibit a noncommunicating 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.[12,66,67]

Further, although Whitelaw[12] has recommended ventricular puncture with removal of between 10 and 20 mL/kg of CSF for cases of rapid ventricular enlargement and increased intracranial pressure, others have explored temporizing measures, such

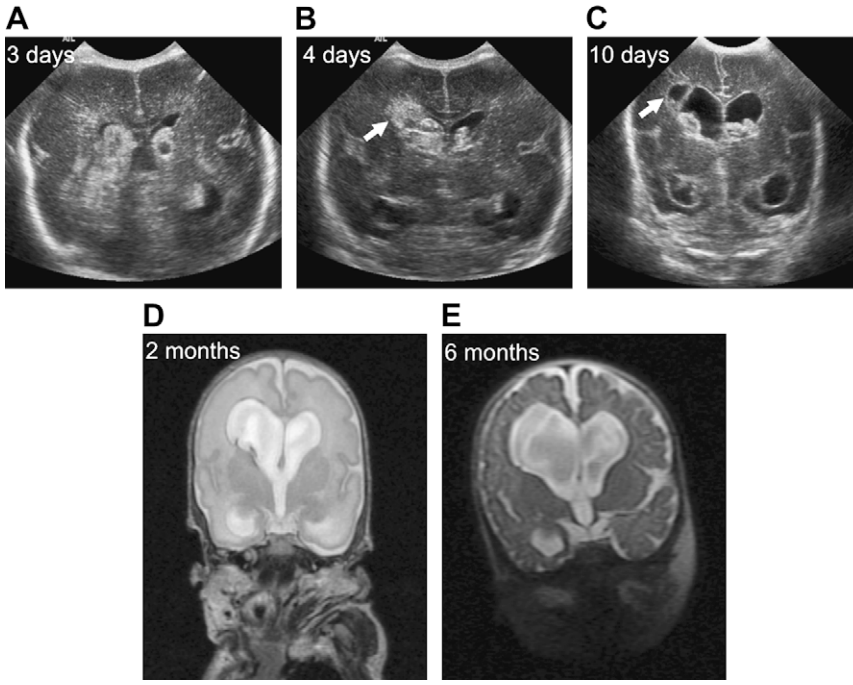

Fig. 1. Serial cranial ultrasounds and MRI studies from a preterm male infant born at 24 weeks of gestation. The initial diagnosis of grade 3 IVH at age 3 days (*A*) was followed by parenchymal involvement of hemorrhage, or grade 4 IVH, on postnatal day 4 (*arrow*) (*B*). A cranial ultrasound performed on day 10 because of increasing occipitofrontal head circumference and full fontanelle revealed bilateral ventriculomegay, residual intraventricular blood and a developing porencephaly (*arrow*) (*C*). MRI study at 2 months demonstrated ventriculomegaly (*D*). Because of excessive increase in head circumference and increasing spasticity, the patient underwent third ventriculostomy after MRI scan at age 6 months (*E*).

as subgaleal shunt placement 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 who had subgaleal shunt placement and 62% of patients who had RES required subsequent permanent shunt placement.[68] Infection rates were similar in the two populations. Future randomized trials are required to confirm this information and determine the appropriate time and manner of intervention.

IVH also can result in white matter abnormalities, including PVL. PVL, shown in **Fig. 2**, is classically defined as multiple cystic foci in the periventricular cerebral white matter,[69] which on histology demonstrate coagulation necrosis and loss of cellular architecture.[70] 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 also have progressed to porencephaly (Greek for "hole in the brain"),[71] 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

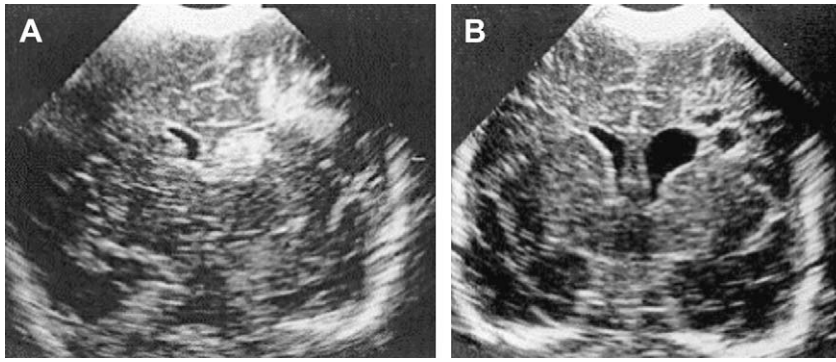

Fig. 2. Serial cranial ultrasounds of a 30-week preterm male infant who had grade 3 IVH and hemorrhagic PVL at age 10 days (*A*). Repeat ultrasound 3 weeks later demonstrated unilateral ventriculomegaly and periventricular cystic cavities consistent with PVL (*B*).

cognitive impairment,[72,73] and many investigators believe that the white matter injury that accompanies IVH represents the major cause of the neurodevelopmental impairments suffered by these neonates.

Finally, a grade 4 IVH also may result in porencephaly independent of PVL or PHH.[74] These hemispheric cavitary lesions generally are 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 birthweight infants are surviving, and it has become increasingly clear that certain newborns seem to do better than their similarly premature counterparts. Differences even are noted in 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.[75] It is uncertain what accounts for this difference, but there is speculatation on environmental, genetic, and pharmacologic effects. 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 also has become apparent that some children respond better to treatment than others. As a result, an understanding of the role that gender and genetics play in 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 for 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 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 INTRAVENTRICULAR HEMORRHAGE

The well-known sequelae of IVH have prompted the development of pharmacologic prevention strategies for this injury to developing brain for almost 4 decades (**Table 2**). These interventions have included phenobarbital, pavulon, vitamin E, ethamsylate, indomethacin, ibuprofen, and recombinant activated factor VIIa. Because the preclinical and clinical trials for pavulon, vitamin E, and ethamsylate took place many years ago and these agents currently are not in wide use, these studies are reviewed only briefly in this article. Mechanisms of action and study results for the other four agents are discussed.

Phenobarbital

Phenobarbital is believed to stabilize blood pressure and potentially offer protection from free radicals. Because variations in blood pressure, subsequent changes in cerebral blood flow, and oxygen free radical damage during reperfusion are believed to contribute to IVH, phenobarbital was proposed as a possible prevention strategy. Whitelaw and Odd[76] reviewed the literature regarding phenobarbital in the prevention of IVH. Overall, eight of the ten trials reviewed showed no statistically significant difference in risk for IVH in phenobarbital- versus control-treated patients. One trial showed an increased risk for 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.[77] These factors would have increased the risk for IVH in this patient group, independent of treatment with phenobarbital. One study showed a decreased risk for IVH in the phenobarbital-treated group, but patients in this study were not checked for IVH before instituting treatment.[78] Rates of severe IVH, studied in all 10 trials, and ventricular dilation or hydrocephalus, studied in four 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.

Table 2
Postnatal prevention strategies for intraventricular hemorrhage

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[a]	Promote clot formation

[a] Rescue therapy to prevent extension of IVH.

Indomethacin

Indomethacin is used in preterm neonates 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 believed to prevent IVH 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.[29,79,80] Indomethacin also is shown to promote microvessel maturation of the germinal matrix in beagle pups[81] and in a pig model to inhibit the alterations in blood-brain barrier permeability that result from ischemia.[29] Consistent with this experimental data, infants treated with indomethacin have been shown to have a decrease in the incidence and severity of IVH.[82,83]

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 E2,[84] whereas others have proposed that this agent may confer neuroprotection by preventing the up-regulation of genes linked to oxidative stress[85] and down-regulating those inflammatory factors, such as IL-6 and TNF-α, which inhibit neurogenesis.[86] In addition, the COX-2 gene has two polymorphic variants, a G or a C at position 765.[84] Patients who have the C allele have reduced COX-2 activity and thus may exhibit different responses to indomethacin than those who have the alternative allele.

Neurodevelopmental outcome has been reported for three of the indomethacin trials. Age at subject assessment and cognitive measures used differed considerably among the studies, and the meta-analysis of Fowlie and Davis[87] concluded that treatment with indomethacin did not affect rates of severe developmental delay or neurosensory impairment. Several investigators have questioned why, if indomethacin decreases the incidence and lowers the severity of IVH, it does not seem to globally improve outcome.[82–84] Harding and colleagues[84] have reported that prematurely born subjects with the COX-2 C765 allele had decreased cognitive performance at age 2 and 5.5 years when compared with their G allele peers.

Furthermore, Ment and colleagues[88] analyzed their indomethacin data on the basis of gender. The rate of IVH was found 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 also was significantly reduced in males treated with indomethacin. In addition, boys treated with indomethacin performed significantly better on the Peabody Picture Vocabulary Test—Revised at 3, 4.5, 6, and 8 years' corrected age when compared with 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 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.[89] Aranda and Thomas[90] reviewed the use of ibuprofen in neonates and found that although ibuprofen has a similar effect to indomethacin on closure of patent ductus arteriosus, it was ineffective with respect to IVH prevention.

Activated Factor VII

Recombinant activated factor VII (rFVIIa) originally was developed in preclinical trials as a hemostatic agent for use in patients who have hemophilia.[91,92] rFVIIa is believed to act in the clotting cascade through tissue factor–dependent and –independent mechanisms.[93] Tissue factor normally is exposed only 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 rFVIIa is used, the plasma concentration is approximately 10 times that seen with endogenous factor VIIa. As a result of this increased concentration, rFVIIa 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 that prevent fibrinolysis and prevent dissolution of this clot are activated. Factor VII was proved safe and effective in treating the hemophiliac patient population and since then, its off-label use has widened to include nonhemophiliac patients who have uncontrolled bleeding resulting from oral anticoagulation, trauma, thrombocytopenia, platelet dysfunction, and liver dysfunction.[94] Placebo-controlled, randomized clinical trials looking at safety and efficacy, however, 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) who had 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.[95] Factor VII was demonstrated to decrease PT more than fresh frozen plasma, but the investigators 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 suggest 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. Although there have not been other randomized clinical trials of factor VII in the neonatal population, two case series, one involving nine patients less than 4 months of age[96] and one nine patients that included 6 preterm infants,[97] have further suggested that factor VII may be safe and effective as a rescue therapy to control bleeding the in the newborn population after conventional treatments are exhausted.

Because 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.[98] Because factor VII is believed to require exposed tissue factor or activated platelets in order for it to promote coagulation, it is believed that the prothrombotic 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.[98] Although results with factor VII in nonhemophiliac 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 VLBW infants without altering rates of severe IVH, death, or neurologic abnormality.[12] Similarly, vitamin E, an antioxidant, also has been shown to decrease the rate of IVH although the effect on high grade IVH was not specifically examined and overall mortality was unaffected.[99] Finally, pavulon (pancuronium) also has 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 preterm neonates.[100]

SUMMARY

IVH remains a common problem of VLBW preterm neonates and may be associated with significant neurodevelopmental disability. Prevention strategies must address 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, although an important first strategy, risks missing treatments that potentially could benefit subgroups of this population. The authors suggest that when studies are performed 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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