Prevention of periventricular haemorrhage

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Abstract

Periventricular haemorrhage is an important cause of adverse neurodevelopmental outcome in prematurely born infants. This review looks at the current practices in place for prevention of PVH and subsequent brain protection. Antenatal corticosteroids undoubtedly reduce the incidence of PVH and indomethacin given postnatally reduces the incidence of this complication but does not appear to improve long-term neurodevelopmental outcome. There is emerging evidence that inhaled nitric oxide may be effective as a neuroprotective agent.

Keywords intracranial haemorrhage; intraventricular haemorrhage; prematurity; preterm infant; preterm labour

Introduction

Periventricular haemorrhage (PVH) is an acquired lesion most commonly seen in the preterm infant. It is a generic term to incorporate germinal matrix-intraventricular haemorrhage (GMH-IVH) and also includes haemorrhagic infarction in the white matter adjacent to the ventricles secondary to the GMH-IVH. In this review we will use the term PVH throughout to refer to any degree of GMH-IVH or venous infarction. PVH may occur with other forms of brain injury such as periventricular leukomalacia and may be complicated by post-haemorrhagic hydrocephalus. All of these conditions have a major impact on the morbidity, mortality and long-term neurodevelopmental outcome of the preterm infant.

Incidence

Germinal matrix-intraventricular haemorrhage is primarily a complication of prematurity. The incidence increases with decreasing gestational age. The incidence of PVH in the 1980s was around 50% but with the introduction of surfactant and antenatal steroids the incidence has decreased. Subsequently, however this decline has not been sustained and the rate has remained constant at around 15–25% in preterm infants, but in babies born extremely prematurely, the incidence is much higher at around 45%.

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Pathogenesis

The pathogenesis of PVH is multi-factorial. The germinal matrix is the source of developing neuronal and glial cells in the immature brain and is situated on the head of the caudate nucleus underneath the ventricular ependyma. It has a high metabolic demand and as such requires a rich vascular supply. This network of vessels has inherent fragility due to a number of different areas of immaturity. Changes in cerebral blood flow that are known to occur in sick preterm infants render the fragile germinal matrix vessels very vulnerable to haemorrhage. Several factors can influence cerebral blood flow as shown in Table 1.

The role of coagulopathy and thrombocytopaenia has been investigated and a number of studies have shown a low platelet count to be positively associated with PVH. Other forms of coagulopathy have been associated with IVH but as these are common in sick preterm infants their precise role is unknown.

Other factors that may be important in the pathogenesis of IVH are cytokines and vascular endothelial growth factor (VEGF). Low thyroid stimulating hormone and thyroxine levels have been found in premature infants that died or had severe IVH although this is not implicated directly in the pathogenesis.

There is a mounting body of evidence to suggest that genetic factors may play a role in the formation of PVH. Most premature infants despite their instability and vulnerability do not develop PVH whilst some relatively well, stable infants may develop severe PVH. A study looking at the incidence of several neonatal morbidities in a population of preterm twins showed a familial susceptibility to PVH.

Diagnosis

Most PVH is detected by routine cranial ultrasound screening. Ultrasonography will pick up 90% of PVH in the first week of life, with the majority in the first 72 h. Half of all PVH is seen on the first day of life and may progress over 24–48 h to a more severe degree of haemorrhage. PVH appearing after the first 2 weeks of life has been described but this tends to be less severe with less risk of serious adverse outcome.

Clinically most PVH have a silent presentation. However, some will present with a catastrophic deterioration in the infants clinical state with cardiovascular compromise, acidosis, anaemia, bulging fontanelle and abnormal movements. The incidence of clinical seizures related to PVH has been reported at 5–15% although subclinical seizures in infants with PVH have been reported to be as high as 75%.

Outcome

The incidence of preterm birth is rising and the advances in perinatal care have meant that more of these babies are surviving along with their complications of prematurity. Gestational age at delivery is directly related to outcome with the lower gestational age babies having more neurodevelopmental problems. One of the main antecedents of poor outcome is severe PVH.

Infants with severe PVH have a higher mortality rate than their age-matched controls; infants with severe PVH have been reported to have a mortality between 40 and 86%. The wide variation in these mortality figures may be in part due to health professional and parental views on large IVH.

Clinical risk factors for periventricular haemorrhage

Hypoxia	Pneumothorax
Hypercarbia	Positive pressure ventilation
Acidosis	Hypotension
Ventilator asynchrony	Hypertension
Respiratory distress syndrome	Sepsis
Patent ductus arteriosus	Dehydration
Tracheal suctioning	Extreme prematurity
Rapid bolus of fluid	Less than 1000 g birth weight
Rapid bicarbonate infusion	Hypoxia–ischaemia
Coagulopathy	Thrombocytopaenia

Table 1

In the newborn period approximately 5–15% of infants with severe PVH will have seizures and up to 50% will develop post-haemorrhagic hydrocephalus. Long-term neurological sequelae in infants with a moderate-severe PVH are about 35% and up to 75% in infants with PVH. A recent report suggests that functional outcome may be better than previously thought in infants with unilateral PVH.

Prevention

Intraventricular haemorrhage is a perinatal event. Interventions should therefore be targeted to this time. Intervention can focus on antenatal interventions or can be given after the baby is born.

Antenatal

Preventing preterm labour: intraventricular haemorrhage is almost exclusively a condition of prematurity. The lower the gestation of the infant the higher the incidence and severity of PVH. Therefore, preventing preterm delivery should reduce the incidence of PVH and its complications and adverse long-term outcomes.

Preterm labour occurs in about 10% of all births. Approximately three quarters of these are below 30 weeks gestation when the incidence is higher. Thirty to forty percent of preterm deliveries are elective for either maternal or foetal reasons but the remainder is due to spontaneous preterm labour. Preterm labour has a multi-factorial and complex aetiology. It is known that infection and inflammation play a part as well as cervical dysfunction, multiple pregnancies and possible social, nutritional and environmental factors. Previous preterm delivery is a consistent risk factor for further premature delivery. Many of these factors are difficult to influence i.e. social factors etc but research has been directed at identifying high risk groups for and prevention of preterm labour.

Cervical cerclage: whilst many interventions have been tried over the years only a few have been shown to be of any real benefit in preventing preterm labour. Cervical cerclage is commonly used in women with recurrent second trimester pregnancy loss. It may be done prophylactically in women thought to be at high risk of severe preterm labour or as an emergency in women who have a shortening cervix. Systematic review of randomized trials compared prophylactic cerclage to no cerclage and only showed a small reduction in delivery before 33 weeks (relative risk 0.75, 95% confidence interval 0.58–0.98) but no reduction in pregnancy loss or preterm delivery. It therefore cannot be recommended to reduce the incidence of PVH.

Progesterone: the role of progesterone in maintaining pregnancy has been studied and may suppress uterine smooth muscle activity. A recent Cochrane review has shown that progesterone given to women with previous spontaneous preterm birth, women presenting in threatened preterm labour and those with a shortened cervix on ultrasound have a significantly lower rate of preterm delivery. In women with multiple pregnancy it reduces the use of tocolysis. Meis et al. in 2003 also showed that the infants of women who received progesterone had significantly less IVH than their non-treated counterparts. Further work is needed to confirm these findings.

Infection: vaginal infection is thought to play a role in prevention of preterm birth. Antibiotic treatment of abnormal bacterial flora, or bacterial vaginosis has produced conflicting evidence. Women with previous bacterial vaginosis may benefit from treatment with antibiotics with a reduction in pre-labour rupture of membranes and low birth weight. A recent Cochrane review of screening for bacterial vaginosis, trichomas vaginalis and candidiasis and treatment before 20 weeks gestation showed a significant reduction in the risk of preterm birth (3% versus 5% in the routine antenatal care group) with a relative risk of 0.55 (95% confidence interval 0.41–0.75) and in the risk of low birth weight delivery.

Treatment of preterm labour

A range of tocolytic agents has been used to try to postpone preterm birth.

Indomethacin: prostaglandins play an important role in the onset and maintenance of labour and inhibitory drugs, such as indomethacin have been used and subject to systematic review. Data is extremely limited but indomethacin appears to be an effective tocolytic, but although maternal side effects appear to be limited there is concern that there are serious adverse effects on the foetus, such as premature closure of the ductus arteriosus and deterioration in renal function. Indomethacin has been shown to be effective in preventing PVH when given after birth (see below).

Betamimetics (e.g. terbutaline, salbutamol, ritodrine) appear to be effective at delaying delivery for long enough to allow a full course of antenatal steroids or transfer to a tertiary perinatal centre. Side effects for the mother are common and the drug may cross the placenta to cause foetal tachycardia, hypoglycaemia and hyperinsulinism.

Calcium channel blockers are smooth muscle relaxants and are effective tocolytics. In comparison to other tocolytics they reduce the rate of delivery within 7 days of receiving treatment and delivery prior to 34 weeks gestation. They appear to have fewer side effects for the mother and there is some evidence to suggest lower morbidity for the newborn.

Antenatal interventions directly aimed at prevention of IVH

There is a good body of evidence that shows preterm babies born in perinatal centres have a lower morbidity and mortality than those that are born outside these centres. Over the past decade neonatal care has been reorganized in the UK with the emergence of neonatal networks and transport teams. These have improved access to tertiary level care for all infants and mothers who threaten to deliver prematurely should be transferred into these centres.

Corticosteroids: there have been over 20 different randomized controlled trials that have looked at the effects of antenatal steroids on neonatal morbidity. They have been subject to systematic review and there was a significant reduction in intraventricular haemorrhage compared to infants whose mothers were not treated (relative risk 0.54, 95% confidence intervals 0.43–0.69). This review included infants over a wide range of gestations. More recently some groups have looked at the effectiveness of corticosteroid on the morbidity and mortality of infants in different gestational age groups. Some groups have shown that antenatal corticosteroids decrease mortality in extremely preterm babies 24–28 weeks. In infants less than 24 weeks there remains considerable controversy but there is a trend towards improved survival and one group has shown a significant difference in severe IVH.

There is controversy over single or repeat courses of corticosteroids with a recent Cochrane review showing a significant benefit on the severity of neonatal lung disease in the group with repeated courses. However, there is concern that newborns subject to multiple courses of antenatal corticosteroids have lower birth weights and head circumference. However, the significance of this is as yet unclear as there are only a few long-term follow-up studies that give conflicting results.

Antenatal phenobarbitone: phenobarbitone was an area of interest as some studies demonstrated a reduction in IVH in infants whose mothers received it antenatally. A Cochrane systematic review showed a significant effect on reduction of IVH, but the authors questioned the quality of several trials and when only good quality trials were analysed, no benefit was found. Maternal antenatal phenobarbitone administration for the prevention of neonatal IVH is not supported.

Antenatal magnesium sulphate: magnesium sulphate is used antenatally for seizure prophylaxis in pre-eclampsia. However, it has also been used to provide neuroprotection of the infant. The mechanism of action is not fully elucidated but it is thought to stabilize foetal cerebral blood flow, block excitatory neurotransmitters, act as an antioxidant and reduce platelet adhesiveness. There have been several large randomized controlled trials (e.g. BEAM, ACTOMgSO4, PREMAG, Magpie, Magnet), which have specifically looked at maternal magnesium sulphate and its foetal neuroprotective effect. Several systematic reviews have been done and these confirm that in preterm infants born after maternal magnesium sulphate there is a lower incidence of cerebral palsy and death. However, there has not been found to be any effect on the incidence of IVH. A non-randomized study of maternal magnesium and aminophylline administration with standard tocolysis and corticosteroids showed a significantly lower rate of IVH compared to the group that only received standard tocolysis and corticosteroids.

Antenatal vitamin K: coagulopathy in the preterm infant is a common finding. It was this observation that led to several studies on the foetal effects of maternal antenatal vitamin K. A systematic review within the Cochrane Database shows benefit of this therapy in reducing both mild and severe PVH, but some of the included trials were of poor quality and when excluded from the analysis the results became non-significant. Follow-up studies failed to show any difference in neurodevelopmental follow-up except one study, which showed a detrimental effect but lost many participants to follow-up.

Postnatal

Phenobarbitone: this was the first agent that was reported to reduce IVH. Its use was based on observations that phenobarbitone reduced fluctuations in cerebral blood flow, partially protecting the brain after hypoxic ischaemic damage. It was shown to protect hypertensive newborn beagles from intracranial haemorrhage, but it is also known to cause respiratory depression in newborn infants and hypotension. A trial of postnatal phenobarbitone in 1981 showed great promise for the prevention of PVH but subsequent systematic analysis of 10 randomized controlled trials have failed to confirm this benefit but did show an increased need for mechanical ventilation in the treatment arm.

Indomethacin: indomethacin is a non-steroidal anti-inflammatory drug that has been used extensively in neonates for closure of patent ductus arteriosus. It is a potent cyclooxygenase inhibitor and subsequently blocks the prostaglandin production, which is thought to be necessary for maintenance of ductal patency. Experimental evidence has shown that the drug can promote germinal matrix maturation and improve blood–brain barrier permeability, when it has been damaged by ischaemia. It is thought to affect cerebral blood flow and improve cerebral autoregulation thereby reducing the risk of haemorrhage to the vulnerable neonatal germinal matrix. It has also been shown to cause vasoconstriction that is associated with the significant side effects of renal impairment, intestinal perforation and necrotizing enterocolitis.

There have been many studies now that have shown the benefit of administering prophylactic indomethacin in reducing the rate of PVH. A systematic review of 19 randomized controlled trials comparing prophylactic indomethacin to placebo showed that whilst there were short-term benefits to prophylactic administration of indomethacin in infants at risk of IVH, this did not translate into improved neurodevelopmental outcome. Mortality rates and rates of severe disability, defined as deafness, blindness, cerebral palsy or a developmental quotient 2 standard deviations below the mean, were the same in the placebo and indomethacin groups.

This finding has raised considerable debate on the role of indomethacin and there is now suggestion that there may be an underlying genetic reason behind the effect. The COX-2 gene (involved with prostaglandin synthesis) has two different variants which may respond differently to indomethacin and this may go in part to explain that whilst the short-term benefits of indomethacin are significant this does not translate into

improved long-term outcome because the developing brain responds differently to the treatment. It has been reported that premature infants born with one variant of the gene have a lower cognitive performance at 2 and 5.5 years compared to those with the alternative variation.

More recently, Ment has reanalysed their data on the basis of gender. They found that the IVH rate in males after indomethacin prophylaxis was significantly lower, a finding that was not replicated in females. This also was seen looking at long-term neurodevelopmental outcome; independent of PVH, indomethacin treated boys performed better than the similar group of girls.

Ibuprofen is another non-steroidal anti-inflammatory drug that has been shown to be effective in closing the ductus arteriosus, but had no effect on the incidence of PVH.

Ethamsylate: ethamsylate is another non-steroidal drug that has been shown to reduce bleeding following some surgical procedures, from wounds and in menorrhagia. The mechanism of action is thought to be a promotion of platelet aggregation that may be mediated through the prostaglandin pathway and stabilization of the capillary basement membrane. Ethamsylate is not thought to have any affect on cerebral blood flow.

A recent Cochrane systematic review found seven suitable trials (1410 infants) that randomized infants less than 35 weeks to ethamsylate or placebo/no treatment. The analysis showed no long-term neurodevelopment benefit in the treated infants and no difference in mortality. Ethamsylate treated babies less than 31 weeks had significantly less PVH than controls and there was a significant reduction in severe, grade 3 or 4 IVH in the whole group of infants, but this difference was not seen in the group of infants less than 32 weeks. Even though there is a reduction in IVH overall the lack of long-term benefit does not support the routine use of ethamsylate in this group for prevention of PVH.

Factor VII: Factor VII participates in the clotting cascade by both a tissue factor-dependent path and an independent path. It has been suggested that it may be effective in arresting bleeding in a wide array of situations and has been artificially manufactured for use in patients with Haemophilia. Because it is dependent on tissue factor it would have to be given after the onset of PVH to promote clot formation and its effect should be limited to the site of injury/PVH. It has been shown that preterm infants in the first days of life may have low levels of Factor VII and those with the lowest levels have been found to have more severe PVH.

Likewise the role of Factor VIII and fresh frozen plasma have been explored but the evidence surrounding their role in the prevention of PVH is limited.

Pancuronium: it is known that one of the risk factors for PVH is fluctuations in cerebral blood flow. When an infant is mechanically ventilated they are often said to be ''fighting'' the ventilator. What is meant by this term is that the infants breathing efforts and that of the machine are asynchronous. It has been shown that this asynchrony can lead to an increase in air leaks. Perlman in 1985 showed that fluctuating cerebral blood flow velocity on the first day of life leads to an increased risk of PVH and this is a blood flow pattern that would be seen in an infant that is breathing asynchronously with the ventilator.

Pancuronium is a non-depolarizing neuromuscular blocking agent that is used in neonatal intensive care to paralyse patients and hence stop ''fighting the ventilator''. Perlman went on to show a significant decrease in incidence of PVH in infants that were paralysed compared with those spontaneously breathing on the ventilator. A systematic review for the Cochrane Database included six trials that compared infants that received neuromuscular blockers to those that received none or selective blockade. The review included 486 infants and showed a significant decrease in the incidence of PVH and a trend towards less severe PVH in the paralysed infants who had had evidence of ventilator asynchrony. They also showed a trend towards fewer air leaks. However, the authors conclude that as the long-term effects of prolonged use of pancuronium in the preterm infant are known its routine use cannot be recommended.

Morphine: morphine has been shown to decrease stress response and improve ventilator synchrony in the ventilated preterm infant. Infants who had been given morphine for sedation for ventilation in the newborn period have not been shown to have a better neurodevelopmental outcome than their non-sedated counterparts. Compared with midazolam sedation or placebo, morphine sedated infants showed less PVH. Subsequently the NEOPAIN study of 898 infants' randomized ventilated preterm babies to masked placebo or morphine infusions. All babies were allowed additional ''open-label'' morphine if it was clinically needed. Morphine infusions did not decrease the rate of PVH compared to the placebo infants but additional bolus ''open-label'' morphine was associated with increased rates of PVH. There is no evidence that morphine prevents PVH.

Surfactant: exogenous surfactant therapy has revolutionized the management of the preterm infant with respiratory distress syndrome. Many studies have looked at the role of surfactant and the prevention of PVH. A systematic review has shown that there is no significant effect on the incidence of PVH in infants who are given prophylactic versus rescue surfactant. There has not been shown to be any affect on PVH whether the surfactant is a natural or synthetic product.

Surfactant administration can alter lung compliance rapidly and consequently carbon dioxide (CO_2) levels may rapidly fall. Hypocarbia has a well-established link to periventricular leukomalacia but hypocarbia has also been reported to have an association with PVH. This was a retrospective analysis of over 300 babies and the group found that a single arterial CO_2 of less that 30 mmHg in the first 48 h of life was associated with an increase in severe PVH (34% versus 16% in babies without a low CO_2). Whilst the study has some methodological flaws it is an area that should be further researched. In the meantime we should be aiming for normocarbia in this vulnerable group. A small randomized study of permissive hypercarbia ($PaCO_2$ 45–55 mmHg) in the first days of life did not show any increase in PVH.

Vitamin E: vitamin E is an antioxidant and free radical scavenger. Preterm infants have low serum levels of vitamin E. Twenty-six randomized trials were analysed in a Cochrane systematic review and it was found that vitamin E significantly reduced the rate of PVH but with an increased rate of sepsis. There was significant heterogeneity between the trials which makes the findings less

robust but sub-group analysis showed decreased PVH with vitamin E given by routes other than intravenously.

Inositol: inositol is a six-carbon sugar alcohol found widely throughout mammalian tissue. It is an essential nutrient and promotes synthesis and maturation of surfactant components. A meta-analysis of two randomized trials involving nearly 300 infants showed that infants who received inositol supplementation in the first few days of life had a significant decrease in PVH. No information was provided on long-term outcome and the numbers are small.

Inhaled nitric oxide: inhaled nitric oxide (iNO) is currently used for the treatment of hypoxic respiratory failure and persistent pulmonary hypertension in the term and near-term infant. It promotes pulmonary vasodilatation and thereby improves arterial oxygenation. It has therefore been used in preterm infants to see if it has similar effects with the aim of reducing ventilatory support and hence ventilator induced lung injury.

Early studies of iNO in preterm infants showed no difference in PVH between treatment and control arms. Two randomized controlled trials have reported the effect of iNO as a neuroprotective agent in preterm infants when given in low dose in the first week after birth. One study aimed to see if iNO reduced death or chronic lung disease, which it did but there was a marked significant reduction in both severe PVH and PVL in the treatment group. Likewise Kinsella's study of 793 infants received iNO 5 ppm for 21 days showed no difference in death or chronic lung disease (there was a difference when analysed by birth weight with a better outcome for infants 1000—1250 g) but did show significantly decreased periventricular leukomalacia (PVL) in the iNO group. The combined outcome of severe PVH, ventriculomegaly and PVL was significantly reduced in infants 750—999 g. These two studies involving nearly 1000 participants showed significantly better short-term neurological outcomes for preterm infants given iNO.

The smaller study followed up its infants at 2 years with detailed neurodevelopmental assessment. Children in the iNO group had approximately half the risk of abnormal neurodevelopmental outcome than the placebo group; a finding that did not change when all cofounders were considered.

Another study looked at iNO in preterm infants with severe respiratory failure. iNO was only continued if there was a response in oxygenation so infants had the gas for variable times and were far sicker than infants in the above trials. They reported higher mortality and severe PVH rates in infants less than 1000 g. Whilst this is concerning, the population is very different in this trial to the 2 above as mean oxygenation index in this trial was approximately 22 compared with 6 in the two trials above.

Conclusions

There are few proven treatments shown to prevent PVH, but antenatally administered corticosteroids are effective in their role in decreasing IVH and promoting lung maturation. Postnatally a number of interventions have been tried but none have as yet good evidence to support their routine use. Most recently interest has been sparked in the neuroprotective properties of inhaled nitric oxide. Improved short-term and markedly improved long-term outcomes provide hope that this may prove a useful tool in the prevention of PVH. ◆

FURTHER READING

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Practice points

- Antenatal corticosteroids reduces the risk of subsequent PVH
- There is little evidence for other antenatal strategies preventing PVH
- Indomethacin given after birth significantly reduces risk of PVH but appears to have little effect in reducing long-term neurodevelopmental abnormality although boys may be better protected than girls
- Inhaled NO may reduce incidence of PVH and improve neurodevelopmental outcome but this observation must be substantiated by further trials