Intraventricular haemorrhage in prematurity

One of the neurological conditions commonly seen in prematurity is intraventricular haemorrhage (IVH). IVH remains a serious condition with significant associated mortality and morbidity. In this category of patients, management of post-haemorrhagic hydrocephalus (PHH) is very challenging. Different surgical options for the treatment of PHH are reviewed in this article.

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Key points

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1. Prematurity and low birth weight are the most important risk factors for intraventricular haemorrhage (IVH).
2. Infants with severe IVH are at risk of developing post-haemorrhagic hydrocephalus and often suffer from neuromotor deficits in the long term.
3. Management is a combination of medical and surgical treatments. Several surgical options are available and their indication is still controversial.

Preterm birth, defined as live birth at a gestational age of less than 37 weeks, remains very common occurring in an estimated 12.3% of all live births in the USA in 2008[1] and 7.9% of live births in the UK in 2005.[2] Premature infants often have very low birth weights, and often suffer from a huge range of diseases affecting multiple systems making treatment difficult. With improving neonatal care survival of these infants has improved dramatically in the past few decades, however, some diseases of prematurity remain difficult to manage, contributing towards an increasing number of surviving ex-premature infants with poor long-term outcomes.[3]

One of the neurological conditions commonly seen in prematurity is intraventricular haemorrhage (IVH), where bleeding from periventricular structures is thought to occur due to fragility of the germinal matrix and changes in cerebral perfusion. The severity of IVH is often graded according to Papile's classification (**TABLE 1**).[4] While Grade I and II IVH tend to resolve without major long-term disability, infants with Grade III and IV IVH have a significant risk of developing post-haemorrhagic hydrocephalus (PHH) and often suffer from marked neuromotor deficits in the long term. Transfontanelle ultrasound is the diagnostic exam of choice.

Incidence

As the risk of developing IVH and PHH is partly determined by the population studied, medical management of the infant, gestational age, birth weight and many other parameters, the precise incidence in any given population is difficult to determine.[5] Some centres in the USA have quoted the incidence of IVH as 15-20% in infants weighing less than 1,500g at birth, while others suggest it is higher. A 19-centre study of over 15,000 infants claims a 33% incidence for IVH, 13% of whom had grade III or IV bleeds.[6] The incidence rises to 46-47% in infants born at less than 750g, supporting the view that low birth weight is an important risk factor. In a cohort of over 9,500 American infants of 22-28 weeks' gestational age and birth weight between 401-1,500g, 16% were found to have severe IVH (grade III and above). Another study further claims that there has been a significant reduction over the past 10-15 years in the need for either temporary or permanent shunting in extremely preterm neonates with IVH,[7] mainly due to improved medical management.

However, regardless of the precise incidence, IVH remains a serious condition with significant associated mortality and morbidity. A multicentre study between Boston, USA, and Christchurch, New Zealand, found that 22% of their 248 very low birthweight infants developed IVH. Among these, about a quarter developed PHH, which failed to resolve in 62% of cases and led to death in over 10%.[8] Survivors of severe IVH are rarely free of morbidity: a study of over 6,000 children (birth weight under 1,000g) showed that severity of IVH and requirement of a permanent cerebrospinal fluid (CSF) shunt were both risk factors for neurodevelopmental disability at age 18-22 months, with 92% of subjects with Grade IV IVH requiring shunting showing some degree of neurodevelopmental impairment.

Management of IVH and PHH

Despite the fact that many infants with PHH ultimately require permanent CSF diversion, early insertion of

ventriculoperitoneal (VP) shunts is generally contraindicated due to a high complication rate. A small study of 19 premature infants showed that 58 shunt procedures were required in total, with 12 cases of infection, 29 blockages and three deaths, although risk of complications were relatively lower in infants with greater weight and lower CSF protein.[6]

Failure of early permanent shunts is likely to be multifactorial. The presence of blood in the CSF may lead to clotting around the proximal shunt catheter, causing blockage. The fragile skin of the preterm infant is a relatively poor barrier, ulcerating easily after surgery and providing an easy route for infection. Poor immunity and the multiple comorbidities often seen in preterm infants further complicate matters. As most of these factors are directly attributable to the physiology of prematurity, optimising VP shunt insertion and maintenance is unlikely to be successful.

As such, most centres advocate temporising measures to manage the rise in intracranial pressure until weight increases to 2,000 or 2,500g, CSF protein levels drop and the patient is free of systemic infection. The rationale for temporising measures is to reduce the higher risk of complication at the time of the insertion of the permanent shunt, which is due to an immature immune system and reduced peritoneal absorption in the premature infant. Infants who undergo early shunt insertion require twice as many revisions compared to those having temporary shunts. Furthermore, up to 15% of infants with IVH will not require a permanent shunt.[6]

Non-surgical management of PHH

Non-surgical measures to manage hydrocephalus secondary to IVH have shown scant success. Serial tapping of CSF either by lumbar puncture or ventricular puncture, removing at least 10mg/kg of CSF with each tap, has previously been used as a method of temporisation.[9] However, a Cochrane review in 2001 showed no significant difference between the serial tapping and conservative treatment and raised the suggestion of an increased risk of CSF infection.[10] As such, this method is no longer recommended as a treatment.

Diuretics such as acetazolamide and furosemide have also previously been advocated for management of IVH.

Grade I	Haemorrhage limited to the sub-ependymal matrix
Grade II	Haemorrhage extending into the ventricular system (<50%), without acute ventriculomegaly
Grade III	Haemorrhage extending into the ventricular system, with acute dilatation because of flooding of 50% or more of one or both lateral ventricles
Grade IV	Haemorrhage grade I, II or III with extension into brain tissue

TABLE 1 Classification of intraventricular haemorrhage according to Papile.[4]

However, a randomised controlled trial (RCT) of 177 infants showed no significant difference in death and shunt placement risk ratio between the treatment arm and the control arm. Furthermore, neurodevelopmental outcome was thought to be worse in the treatment arm.[11]

Intraventricular fibrinolytic agents such as streptokinase have equally been reviewed and found to be ineffective, with concerns about increased risk of meningitis and secondary intraventricular bleeds.[12]

Trials

There have been a variety of trials carried out with the rationale of preventing the high rates of morbidity and mortality related to IVH.[11-15] The most recent one is a combination of novel interventions called DRIFT (drainage, irrigation and fibrinolytic therapy) and aims to remove intraventricular blood, inflammatory cytokines and iron, which are associated with hydrocephalus before it becomes established.[13]

The results of DRIFT showed that, although it did not significantly lower the need for permanent shunt surgery, severe cognitive disability at two years was significantly reduced.[15]

The National Institute for Health and Care Excellence (NICE) has reviewed DRIFT and concluded there is insufficient evidence for DRIFT to be recommended across the UK and its use should be limited to research studies. NICE recommended a larger randomised trial. On this basis, the DRIFT 2 trial is planned involving a larger number of infants to validate previous data about long-term cognitive impairment, percentage of infants requiring a permanent shunt and complications related to shunts.

The timing of insertion of a ventricular access device is still controversial and centre-related. In a retrospective study from the Netherlands, early insertion (before crossing the 97th centile + 4mm ventricular index line), showed lower rates of VP shunt need. The Early versus Late Ventricular Intervention Study (ELVIS) is currently randomising between the two treatment thresholds, with death or shunt-dependence and disability at two years the main treatment outcomes.

The limited success of medical treatment for PHH means that most patients ultimately require surgical management for progressive hydrocephalus.

Surgical measures

The primary aim in early surgical management of PHH is to achieve short-term control of intracranial pressure with relatively non-invasive procedures with lower complication rates than immediate placement of permanent shunts. This should allow for spontaneous resolution of hydrocephalus in some cases, and 'buy time' for infants with persistent hydrocephalus to grow to a stage where permanent VP shunts are relatively well tolerated. A range of different approaches has been used on infants with hydrocephalus secondary to IVH, each with its own theoretical advantages, however, there remains no clear consensus on the best method to use.

External ventricular drainage

External ventricular drains (EVDs) are one of the earlier methods of temporisation. A catheter is placed into the ventricle through a hole in the skull and connects to an external drainage system. A study in the 1980s of 37 patients with EVDs inserted for PHH showed a 10% risk of apnoea, 8% risk of haemorrhage and 6% risk of ventriculitis.[16] Another study in 1992 of 27 newborns with EVDs inserted had 23 survivors, 16 of whom needed either VP or ventriculo-atrial (VA) shunts. Interestingly, although ventriculostomy catheter tips from seven of the patients showed positive bacterial cultures, none of the infants showed clinical or biochemical evidence of ventriculitis.[17-18]

A study of 37 patients treated with a total of 51 EVDs, reported eight deaths and two cases of ventriculitis, equating to a 5.4% infection rate per patient and 3.9% per drain.[18] A larger Viennese study of 76 infants treated with EVD quoted a 7.1%

risk of infection and 45.2% risk of blockage, leading to a mean of 1.57 shunt revisions per patient.[17]

Overall, complication rates in the studies varied widely, which may be due to relatively small sample size and variations in local practice including methods of infection control, theatre conditions and threshold for diagnosis of complications. Of the surviving infants in the above studies, 29-38% did not require permanent shunts after EVD removal, showing spontaneous resolution of hydrocephalus after a period of temporisation.[19-20]

Recent outcome studies suggest that inserting an EVD early in the course of disease (in the first 25 days of life) may improve neurodevelopmental outcome, particularly in terms of cognitive and social function, highlighting the importance of achieving rapid stabilisation of intracranial pressure in the fragile developing brain of the preterm infant.[21]

Ventricular access devices/reservoirs

Serial tapping of subcutaneous ventricular access devices has been used for management of IVH for at least 25 years.[22] Reports of outcomes have estimated:[23-25]

- 5-10% risk of peri-operative infections
- 20% shunt revision rate
- 15% major skin defects or CSF leak
- 12-25% of survivors remaining shunt-free.

In one smaller study, 36% of survivors showed grossly normal neurology later in childhood, although most of those with shunts required revision within two years.[26]

A Parisian study of 64 preterm infants presented a higher infection rate of 21.8%, and concluded that this, in conjunction with the relatively high mortality rates compared to serial tapping (between 11 and 26% in studies around that time) meant that ventricular access devices were not particularly beneficial in treating PHH.[23] However, it should be noted that over a quarter of their infants were treated with fibrinolytic agents through the reservoir (a practice now thought to increase infection risk), which may have adversely affected outcomes. Later studies from the Netherlands demonstrated decreasing infection rates with ventricular reservoirs during the period of the retrospective study, from 19.2% around 1992-1997 to 4% from 1998-2003.[24] The authors point out that the technique of accessing the reservoir and prophylactic antibiotic policies had not changed in the period – the main changes had been in infection control policies such as prevention of exposure and handling. Studies in the past few years have mostly had small sample sizes and have shown either few to no complications, or a relatively large (57%) risk of major complications.[25]

One other complication that has been reported in the literature is hyponatraemia as a result of serial tapping of the ventricular access device. Twelve of 16 preterm infants with IVH and a Rickham reservoir had serum sodium levels of less than 130mmol/L at some point during treatment, a figure not accounted for by inappropriate ADH secretion, salt wasting or drugs.[25] As such, volume replacement with saline is probably indicated in all infants undergoing serial tapping of reservoirs.

A 2009 study of 32 preterm infants comparing reservoirs and VP shunts suggested that reservoir patients who later needed shunts eventually had fewer shunt revisions, despite being smaller and younger, which are both risk factors for complications.[26] As such, whether or not reservoirs are superior to other temporisation methods, it is at least the prevalent consensus that they are beneficial compared to early VP shunting.

Ventriculosubgaleal shunt

First described in 1977, the ventriculosubgaleal shunt (VSGS) has been promoted by its proponents as allowing continuous rather than intermittent CSF diversion, providing sustained relief without the need for constant tapping.[27] The shunt connects the ventricles to the subgaleal space – the space between the scalp and the skull. No clear evidence exists, however, that they are clearly better in terms of intracranial pressure control or improvements in cerebral perfusion.

Earlier descriptions of the VSGSs used in infants with IVH suggested it is a safe method of temporisation, with 0-5.9% shunt infection risk, and a small (less than 5%) risk of intracranial haemorrhage and wound leakage.[28-30] However, most of these studies looked at VSGSs placed in patients other than preterms with PHH – a number of the other patients had tumours, intraventricular abscesses and infection, which may have skewed complication rates. A recent paper also looked at VSGS as the initial intervention for neonates with IVH and meningomyeloceles, suggesting that the shunt revision rate and incidence of slit ventricles was lower than other methods described in the literature.[30]

Other small studies from the past three years have been generally optimistic. One study described VSGSs controlling progression of PHH in nine neonates, two of whom avoided permanent shunting and none had infections or CSF leaks, although one required a VSGS revision to extend the interval before insertion of a permanent shunt.[31] A Turkish study of 25 premature infants with PHH and VSGS showed a slightly worse prognosis, with:[32]

- eight inadequate subgaleal CSF collections requiring revision or immediate VP shunts
- seven deaths (four of which were sepsis-related)
- seven cases of CSF leak
- two cases of meningitis
- two cases of catheter displacement
- one subdural haemorrhage.

Other methods

One method of temporisation described in the literature utilises temporary valveless VP shunts, which may be converted into a valve-regulated shunt at a later date. A study of 13 infants with valveless shunts compared to 27 with immediate implantation of normal VP shunts showed more shunt infections in the valveless shunts, but equal infection risk (14.8 vs 15.4% per patient), despite the valveless group being younger and less heavy.[33]

Endoscopic third ventriculostomy (ETV) has also been used in PHH of prematurity. ETV is an endoscopic procedure aiming to restore CSF circulation, by bypassing an obstruction; it is a very effective treatment in obstructive hydrocephalus. Some IVH could cause an obstruction of the normal CSF pathway: in ETV a new channel is created between the ventricles and the subarachnoid space restoring the flow of CSF. In fact, a 2003 article on preterm infants with acquired obstruction due to severe IVH described ETV as being an effective treatment in two of four infants selected for the procedure.[34] In another study of 18 patients with access devices (such as reservoirs), seven patients ultimately remained shunt-free at follow up because of ETVs.[35]

A recent study has also suggested that a combination of ETV and choroid plexus cauterisation may be effective in PHH as long as the prepontine cistern remains unobstructed on MRI.[36]

Comparison of the methods of temporisation and overall comments

The popularity of various methods of surgical management of PHH have varied somewhat over the past three decades, based on local experience and reports favouring one method over another. A late 1980s study in Virginia, USA, of 39 premature neonates with PHH on ultrasound, described a switch from using EVDs as the main form of surgical management to utilising ventricular reservoirs and low pressure 'neonatal shunts', with a significant reduction in morbidity and mortality.[37] However other groups, especially in Europe, have continued to use the EVD with reportedly acceptable complication rates.[21,22]

Most of the recent comparative studies have focused on comparing ventriculosubgaleal shunts and ventricular access devices. Lam et al compared 32 preterm neonates with PHH, half of whom had ventricular access devices needing daily tapping and half who had VSGS implants, 25% of which needed further daily taps. There were more complications in the VSGS group compared to the reservoir group – the VSGS infants had one infection, one CSF leak and three obstructions, while the reservoir group had one obstruction. However, 28.57% of VSGS patients but only 6.25% of patients with reservoirs were shunt-free at the end of the follow-up period, leading the authors to propose that ventriculosubgaleal shunts may be superior.[38] However, the study was of a relatively small sample size, and while the groups were broadly similar in terms of baseline characteristics, there was no obvious calculation of power showing that the outcomes were significantly different between groups.

A later study of 325 infants revealed no statistically significant difference between reservoirs and VSGSs in terms of shunt requirement, infection, need for revision, subsequent shunt infection, shunt revision rates or mortality rates.[39]

A recent multicentre study described temporisation in four large centres in the USA and Canada, where 73 of 110 infants with Grade III/IV IVH, birth weight <1,500g and a gestational age of <37 weeks, had either a reservoir (50 infants) or a VSGS (23 infants) inserted and 37 infants were given a VP shunt immediately. Although the study looked mainly at factors affecting the decision to temporise (increasing ventricle size and bradycardia but not apnoea, head circumference or fontanelle assessments) rather than outcomes, it was noted that only 11% of the temporised infants did not need conversion to permanent CSF shunting, a figure which is lower than most other estimates. This finding may reflect a higher incidence of severe progressive hydrocephalus of the population studied or a lower threshold for permanent shunting.[40]

Summary

This article describes the treatment and subsequent outcome of preterm infants with IVH and PHH. As a result of improvements in neonatal care during the last decades and earlier and more effective intervention, IVH is related to a less unfavourable outcome. Infants with severe IVH are at risk of severe neurological sequelae. Approximately 80% of IVH occurs by 72 hours after birth but a considerable proportion of IVH is visible on the first scan performed within a few hours of birth.

Neonatologists have made several practice changes in the past decade that have impacted on the incidence of IVH and PHH. Similarly, paediatric neurosurgery has made significant progress in the past five years in decreasing perioperative complications, particularly surgical-site infections. Although it is likely that fewer preterm infants will suffer IVH in the future, the prevention, treatment and outcomes of IVH in preterm infants remain challenging.

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