ADVANTAGES OF DELAYED VENTRICULOPERITONEAL SHUNTING IN POST HAEMORRHAGIC HYDROCEPHALUS SEEN IN LOW BIRTH WEIGHT INFANTS

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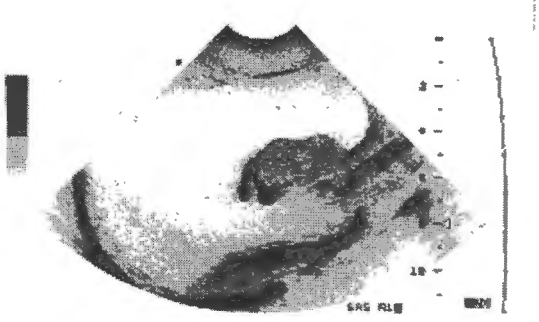

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I wish to thank all individuals and departments who were involved in the care and assessment of the patients' presented in this thesis. A very large multidisciplinary team is required to care for a difficult clinical problem such as intraventricular haemorrhage and I will therefore not mention everyone by name.

CONTENTS

ABSTRACT

INTRODUCTION:

The incidence of intraventricular hemorrhage (IVH) in very low birth weight infants is between 25 and 50%. Approximately 13-60% of these patients will develop progressive post hemorrhagic hydrocephalus (PHH) and of these 22-70% will require CSF diversion. The most common therapeutic intervention is insertion of a ventriculoperitoneal shunt but there is considerable controversy surrounding the timing of the operation. Most authors promote early surgery to prevent secondary injury from hydrocephalus but it was our impression that this was associated with a higher incidence of shunt complications.

METHOD:

The incidence of shunt complications in 36 patients shunted for PHH were retrospectively reviewed. Patients were treated at Red Cross Children's Hospital over an 8 year period.

RESULTS:

Nine (25%) of the 36 patients required shunt revision for obstruction, seven required revision during the initial admission. Shunt infection occurred in 4 patients (11%) all during the initial hospital admission. Four patients died, one from a shunt related complication. There was a clear relationship between the timing of surgery and the incidence of complications (chi square test p,0.01). Nineteen patients underwent surgery before 5 weeks of age and 9 developed early shunt complications. Of those shunted after 5 weeks none had an early complication. Groups were matched for weight and grade of IVH.

DISCUSSION:

A possible explanation for these results is that shunt complications are related to the quantity of blood present in the CSF at the time of shunting. A short delay before intervention is recommended in an effort to reduce the morbidity of shunt complications.

CHAPTER 1: INTRODUCTION

The management of post-haemorrhagic hydrocephalus in the premature infant remains a controversial topic in Paediatric Neurosurgery. Numerous therapeutic options are described ranging from conservative treatment to early ventriculo-peritoneal shunting [48, 64, 68]. There are many reasons for this variety of options. This is a group of patients in whom the incidence of serious complications is high and neurological outcome often disappointing. This in turn translates to high costs, both in terms of money and hours spent caring for these children by their families and medical staff. The range of therapeutic options therefore reflects medical opinion and resources at various centers. Some feel that the outcome in this group of patients does not warrant the cost and effort involved [52], while others feel that intensive active therapy may lead to improved, worthwhile outcome making the cost justifiable [3]. In between these two divergent opinions and actions lie many other therapeutic protocols.

The Red Cross War Memorial Children's Hospital in Cape Town is a referral center for Paediatric Neurosurgery where a significant number of patients with post-haemorrhagic hydrocephalus are treated. When managing these patients we face the same problems as other Paediatric Neurosurgery Institutions, but must also take into account that they are often from a poor background. The burden of caring for a disabled child is felt more acutely in these circumstances and for this reason we have examined ways of limiting complications without compromising neurological outcome. This dissertation consists of a literature review looking at the pathophysiology, management

and outcome of intraventricular haemorrhage (IVH) and post-haemorrhagic hydrocephalus (PHH) in low birth weight infants. This provides the background to a retrospective study of the treatment of PHH at Red Cross Children's Hospital over an eight-year period. The findings of the study are discussed in the context of accepted therapeutic protocols and what is appropriate for our environment.

DEFINITIONS

On review of the current literature it is apparent that many terms are used interchangeably so it is appropriate to define the terms that are to be used in this dissertation.

LOW BIRTH WEIGHT INFANT

By international consensus all infants with a birth weight of 2500g or less are considered low birth weight. This may either be as a result of prematurity or growth retardation or a combination of these factors. Very low birth weight (VLBW) refers to infants under 1500g.

PRETERM INFANT

Any infant born before completing 37 weeks in utero is preterm. Intraventricular haemorrhage is associated with prematurity but in the vast majority occurs only when birth is before 32 weeks. At this gestational age birth weight is usually below 2500 grams. It is for this reason that this study

refers to IVH in low birth weight infants. In the retrospective study done at Red Cross Hospital the gestational age was not always accurately known.

INTRAVENTRICULAR HAEMORRHAGE

Intraventricular haemorrhage is a pathological term used to describe a combination of periventricular and intraventricular haemorrhage that occurs in some preterm infants. Various grading systems have been described based on the extent of parenchymal destruction and the amount of haemorrhage in the ventricular system. When not referring to a particular grading system it is better to use the term periventricular haemorrhage to describe haemorrhage that has not extended into the ventricles. IVH is the most common variety of neonatal intracranial haemorrhage and its importance relates to its high incidence and the gravity of the more severe forms with their attendant complications.

POST-HAEMORRHAGIC HYDROCEPHALUS

Post-haemorrhagic hydrocephalus can be defined as progressive dilation of the ventricular system that develops as a complication of neonatal intraventricular haemorrhage [25]. It does not include hydrocephalus caused by other forms of intracranial haemorrhage occurring in the new-born child. This definition implies that continuing ventricular enlargement will result in clinical signs, necessitating treatment of the hydrocephalus.

INCIDENCE

The incidence of IVH has decreased over the past decade with improvements in both obstetric and neonatal intensive care. Recently reported series indicate an incidence of between 21-50% in premature infants [18, 19, 22, 33, 52, 73]. Some of the variability is accounted for by the differing maximum weight allowed as an exclusion criteria in these studies. The incidence of IVH is higher in very low birth weight infants and has been reported to be as high as 90% [5]. This decrease in the incidence of IVH is demonstrated by a report from the Washington University School of Medicine; the incidence of IVH in neonates less than 2000 grams in the early 1980's was 39%, this dropped to 25% at the end of the decade [73].

It is unfortunate that this decrease has not translated into fewer patients with IVH in all centers. In sophisticated health care environments survival rates for premature infants, particularly those who weigh less than 1000 grams, continue to increase. With the higher incidence of IVH in this group it continues to be a problem in the neonatal intensive care unit.

The incidence of PHH is difficult to ascertain, as there is no accepted grading system that will allow for comparison between different published series. For this reason the diagnosis of PHH is subjective. Filling of the ventricular system with blood in the higher grades of IVH results in ventricular enlargement. As a rule this is not referred to as PHH. The diagnosis is usually made after serial transcranial ultrasound or CT scan shows progressive ventricular dilatation.

Following the development of progressive ventriculomegaly, approximately 50% of cases spontaneously arrest within a month, with partial or total resolution of the ventriculomegaly. In the remaining 50% the ventricular size increases progressively for more than a month and is accompanied by raised intracranial pressure requiring treatment [72].The reported incidence of PHH in series where patients have been followed up over some time is between 13-60% and of these patients between 22% and 70% have received permanent cerebrospinal fluid (CSF) diversion with a shunt [3, 16, 18, 32, 39, 49, 54, 63]. The variation in the percentage of shunted patients may be due to the different therapeutic regimens these patients were subjected to. In the majority of patients the progression of PHH seems to be slow and predictable however in a small percentage of patients the ventricular enlargement is rapid requiring more urgent treatment [76].

CHAPTER 2: PATHOPHYSIOLOGY OF INTRAVENTRICULAR HAEMORRHAGE AND POST-HAEMORRHAGIC HYDROCEPHALUS

PATHOGENESIS OF INTRAVENTRICULAR HAEMORRHAGE

The site of origin of IVH is the subependymal germinal matrix. This is an area immediately ventrolateral to the lateral ventricle and between 10 and 20 weeks contains cerebral neuroblast cells. In the third trimester of pregnancy these cells mature into glioblasts which will become oligodendrocytes and astrocytes. It is also an area that contains many thin walled vessels that are the source of bleeding in IVH. The site of haemorrhage within the matrix varies with gestational age [20]. In infants less than 28 weeks gestation bleeding occurs in the matrix overlying the caudate nucleus body. In infants between 28 and 32 weeks gestation the lesion is at the head of the caudate nucleus. After 32 weeks haemorrhage is more likely to occur from the choroid plexus.

The majority of haemorrhages occur in the first few days of life, with approximately one third of the haemorrhages developing within the first hour of age. Risk factors can either be maternal, such as cocaine use [65], or they can be neonatal. Perinatal and postnatal factors such as, labour, delivery and

respiratory distress are considered contributory to the process [52]. These events either alone or together act in the premature neonate to produce IVH through intravascular, vascular or extravascular pathologies [73].

INTRAVASCULAR FACTORS

It appears that the regulation of cerebral blood flow and pressure in the neonate is easily disturbed if the birth is premature and the child is exposed to complications such as respiratory distress. Factors that relate to platelet-capillary function and blood clotting may contribute but are of less importance.

Fluctuation of cerebral blood flow

Two patterns of cerebral blood flow are observed in patients ventilated for respiratory distress of prematurity. A stable pattern is associated with systolic and diastolic blood flow velocities that are constant where as in an unstable pattern both velocities vary. Patients with an unstable cerebral blood flow are far more likely to develop IVH [50]. The cause of the fluctuation is mechanical ventilation that is not synchronised with the patients breathing and this may be improved by inducing muscle paralysis.

Increase and decrease in cerebral blood flow

In experimental animal models IVH is provoked most readily by a sequence of hypotension followed by hypertension. It appears that autoregulation in the premature child is abnormal for a variety of reasons such as vessel dilatation due to hypoxia (protective shunting of blood from the gut to the foetal brain

occurs) or hypercarbia and cranial trauma. This leads to a pressure passive cerebral circulation with a change in arterial pressure being mirrored by a change in flow. A drop in cerebral blood flow may lead to ischaemic changes in a vascular border zone in the germinal matrix, or cause injury to vessels in this area. If flow then increases, bleeding may occur either because of poor vessel integrity or germinal matrix reperfusion injury. Increased cerebral blood pressure or flow may be caused by a number of factors. Hypercarbia is a common accompaniment of respiratory distress syndrome and is a potent vasodilator. Decreased haematocrit has also been shown to significantly increase cerebral blood flow in an autoregulatory effort to increase oxygen delivery to the brain. A low haematocrit is a common finding in sick premature infants due to iatrogenic blood loss and low initial blood volume. Abrupt elevations of blood pressure may also be brought about by noxious stimuli such as exchange transfusion, pneumothorax and tracheal suctioning.

Increases in cerebral venous pressure

Perfusion pressure in capillary beds is partly dependent on venous pressure. If uncontrolled rapid changes in venous pressure occur perfusion pressure will also change without time for the protective effects of autoregulation to occur. The germinal matrix is particularly prone to the effects of venous pressure as this is an area of venous confluence. The medullary, thalamostriate and choroidal veins unite in the subependymal tissue of the lateral ventricle at the level of the foramen of Monro. This is the most common site of germinal matrix haemorrhage. There can be many causes of raised venous pressure in

premature infants such as labour and delivery, asphyxia and respiratory complications.

Platelet and coagulation disturbance

Disturbances of coagulation are common in premature infants with complications of asphyxia and respiratory distress. It is therefore difficult to establish if coagulopathy has an independent pathogenic role in the development of IVH.

VASCULAR FACTORS

Tenuous capillary integrity

Capillary vessels in the germinal matrix are in the process of involution. As the germinal matrix disappears with cell migration the immature micro-vasculature remodels into a mature capillary bed. These immature vessels are also larger than normal capillaries, composed only of an endothelial layer. It is likely that these changing vessels are more susceptible to rupture and haemorrhage.

Vulnerability to hypoxic-ischaemic injury

The germinal matrix contains a vascular border zone between striate and thalamic vessels. This area is likely to be susceptible to hypoxia in the event of reduced cerebral blood flow. As these capillary endothelial cells also have a high requirement for oxidative metabolism, injury to the vessel wall could easily occur.

EXTRAVASCULAR FACTORS

Deficient vascular support

The germinal matrix provides poor support for the large walled capilliaries that pass through it because it is nearly devoid of mesenchymal elements. Unsupported vessels are more likely to rupture.

Fibrinolytic Activity

Increased fibrinolysis is characteristic of remodeling systems and would predispose to haemorrhage in this area.

PROGRESSION OF INTRAVENTRICULAR HAEMORRHAGE

Various factors after birth may contribute to the enlargement and extension of a germinal matrix haemorrhage. Seizure activity, pneumothorax development, volume overload, hypoxia, acidosis, hypercarbia and other disturbances which result in increased cerebral blood flow have all been shown to exacerbate the lesion [41]. In the study by Shankaran et al 10% of 62 patients with IVH had significant progression of the haemorrhage during the first 2 weeks of life [63]. For this reason it is important that the final grading of IVH is delayed until 2 weeks after birth as this will ultimately help determine prognosis.

PATHOGENESIS OF POST-HAEMORRHAGIC HYDROCEPHALUS

According to Oi there are three pathophysiological aspects to the development of hydrocephalus in the premature child [44]. The first is underdevelopment of major CSF pathways. The second is extremely high intracranial compliance and finally the brain is still undergoing myelination. For these reasons the premature brain is susceptible to developing hydrocephalus after an insult such as IVH. The soft, unmyelinated brain also allows significant ventricular dilatation to occur without any increase in head size. This is illustrated in a study by Levene and Starke who in a longitudinal study of ventricular dilation after IVH found a group of patients who had persistent ventricular dilation but normal head growth over 52 weeks [32].

Prior to the mid 1970's, PHH was thought to be an inevitable occurrence in infants who survived IVH [30]. This is certainly not the case but assessment of the true incidence of PHH is difficult to ascertain. As has been mentioned previously diagnostic criteria for PHH differ from study to study and the natural history is often obscured by early therapeutic intervention. Selection bias also plays a role as many centres are referred only the severe grades of IVH. In the longitudinal follow up of 68 patients with IVH by Levene and Starke 31% showed some degree of ventricular dilation but only 8% of surviving patients were ultimately shunted [32]. Similar results have been shown in other studies where therapeutic intervention has been relatively late [16, 22, 63].

There is a strong correlation between the severity of IVH and the probability of developing hydrocephalus [3, 6, 22, 46, 54, 62, 63]. Most severe grades of IVH start with some degree of ventricular enlargement caused by distension of the ventricular system by blood at the time of haemorrhage [63]. This ventricular dilation does not progress in all cases, in some regression will occur and in others stabilisation. Blood in the ventricular system rapidly reaches the subarachnoid space and it is postulated that clots may block CSF pathways [20]. Possible sites of obstruction include the aqueduct, V4 outflow foramina, the tentorial orifice and the arachnoid granulations [30, 35]. This obstruction to CSF flow and absorption would account for the early development hydrocephalus. It may also provide a reason for the spontaneous resolution of hydrocephalus in some patients. As blood products and debris clear from the ventricle, normal CSF pathways may re-open allowing regression of ventricular enlargement. Liquefaction of a clot in the ventricular system may take 10 days or more [35].

Other mechanisms may account for the persistence of hydrocephalus or the development of delayed hydrocephalus. Fibrosing arachnoiditis in response to haemorrhage has been demonstrated in some patients [30, 73]. It is thought that the presence of blood products and cellular debris initiates a chemical meningitis, particularly in the posterior fossa. The posterior fossa may be more affected as this is where blood tends to collect after IVH [73]. Resolution of the inflammatory process leads to a fibrous thickening of the meninges with obstruction to CSF flow through the subarachnoid space. This process could also account for the hydrocephalus that develops in infants with less severe

IVH as only a small amount of haemorrhage would be required [73]. It is likely though that multiple pathogenic mechanisms account for the hydrocephalus seen after IVH. The differing sites of CSF obstruction that can be inferred from a CT scan illustrate this. In the study by Shankaran et al only 15% of patients with hydrocephalus had enlargement of the third and fourth ventricles caused by obliterative arachnoiditis. This would imply that all other patients had obstruction to CSF flow within the ventricular system even after resolution of intra-ventricular clot [63]. Ependymal disruption and reactive sub-ependymal gliosis may also play a role in the development of delayed hydrocephalus [73].

The interval between IVH and the onset of progressive ventricular dilation varies. In severe IVH dilation has been recorded between day 1 and day 40, in most however dilation starts within the first 2 weeks after IVH [32, 49]. Delayed hydrocephalus after IVH has been reported by Perlman [49]. Of 193 patients with IVH, 4 developed hydrocephalus between 5–12 months after the initial haemorrhage. Three of these patients had minor haemorrhages. If spontaneous resolution of hydrocephalus occurs it usually takes place around the end of the first month after diagnosis of IVH [32, 49].

NEUROPATHOLOGY OF INTRAVENTRICULAR HAEMORRHAGE

Hydrocephalus is only one of the pathological processes that are a consequence of IVH. Two others are germinal matrix destruction and

periventricular haemorrhagic infarction [73]. Both are important as they have a bearing on prognosis after IVH.

Germinal matrix destruction

Germinal matrix destruction results in loss of glial precursor cells which will prevent normal brain architecture and function. Haemorrhage in this area results ultimately in a cystic cavity the walls of which contain haemosiderin laden macrophages and reactive astrocytes.

Periventricular haemorrhagic infarction

Approximately 15% of infants with IVH develop an area of haemorrhagic infarction in the periventricular white matter, just dorsal and lateral to the external angle of the ventricle. The lesion is asymmetrical and tends to occur on the side with the largest amount of ventricular blood. Half of these lesions are large and involve the white matter from frontal to occipital regions, the rest are more focal. Eighty percent are associated with large IVH and are often mistaken for IVH extension. The most likely cause of these lesions is venous haemorrhagic infarction caused by obstruction of the venous confluence in this area [73].

Other neuropathological states are common accompaniments of IVH but are not directly caused by IVH. The two most common are periventricular leukomalacia and pontine neuronal necrosis.

Periventricular leukomalacia

Periventricular leukomalacia is an ischaemic injury of white matter in the premature infant. It is generally symmetrical and non-haemorrhagic and in this way is distinguishable from periventricular haemorrhagic infarction. It is also more likely to occur in the periventricular arterial border zone near the trigone area as opposed to the venous confluence area more anteriorly.

Pontine neuronal necrosis

Hypoxic–ischaemic neuronal injury may accompany IVH in premature infants and a common pool of affected neurones is in the pons. Mortality from this lesion is high due to respiratory failure.

NEUROPATHOLOGY OF POST-HAEMORRHAGIC HYDROCEPHALUS

There is a large body of experimental evidence showing that ventricular dilation especially acute dilation, produces an array of anatomical effects on the cerebral parenchyma. Most of these studies have been performed in animal models using rabbits, monkeys, puppies or mice. It is difficult therefore to extrapolate these findings to premature infants where the brain is not yet myelinated, cells are still migrating and compliance of the cranium is very high. Nonetheless a number of predictable changes occur in these models which are likely to take place in neonates with PHH. Guzzetta et al have noted five main lesions: changes in the ependymal cells, periventricular white matter

oedema, reactive gliosis, axonal changes and collapse of periventricular capillaries [19].

Progressive slow ventricular enlargement results in ependymal stretching, loss of cilia and microvilli as well as increased mitotic activity [15]. In acute ventricular expansion ependymal continuity may be lost and an expansion of the neuropil extracellular space is usually found. Periventricular oedema does not extend far and is sharply demarcated [19]. Hypertrophy and hyperplasia of periventricular astrocytes are usually found in hydrocephalus resulting in stiffening of the subependymal layer. Axonal changes amount to swelling, disruption and demyelination. Periventricular capillaries either collapse or are stretched by ventricular dilation and this change appears to be reversible with early shunting [14, 79].

Weller has demonstrated in a model using puppies that these pathological changes occur at certain times after the development of hydrocephalus. Hydrocephalus was initiated by infusion of silicone oil into the cisterna magna at birth. In the 20 and 40 day old puppies, where CSF pressure was raised, there was disruption of the ependyma, severe periventricular oedema and evidence of nerve fibre degeneration. No damage was seen in the cortex. With time CSF pressure returned to normal and periventricular oedema resolved. In 80 day old puppies a modified ependymal lining had reformed, oedema had resolved and a marked subependymal astrocytosis had occurred. Ectopic myelination of astrocytes was also noted. This is important as some studies use myelin content as a measure of white matter

preservation, which is misleading [75]. Weller goes further and tries to correlate these findings with biopsies taken from 5 hydrocephalic infants at different times after the evolution of hydrocephalus. Post-shunting outcome is then used as a measure of hydrocephalus induced brain injury. This is misleading, as the aetiology of hydrocephalus in each case appears to be different. One can not therefore infer correlation between the histological changes and clinical outcome in these cases.

Synaptic vesicle protein (SVP) is a protein associated with synaptogenesis shortly after birth [70] and reduced amounts of SVP have been shown in rats with congenital hydrocephalus. Hydrocephalus in these animals is also associated with impaired dendritic and neuronal spine development. These changes were temporaly related to the development of raised intracranial pressure in these animals. Partial reversal of this pathology was achieved by early treatment of the hydrocephalus demonstrating a direct causal relationship between hydrocephalus and impaired synaptogenesis [70]. It should be noted however that this is a model of congenital hydrocephalus and that SVP only increases for 3 weeks after birth. This age related increase may not occur in premature infants with IVH/PHH until a later time.

Cranial compliance is so high in premature infants that the development of raised intra-cranial pressure (ICP) is not as prominent as in other age groups. Lin et al recorded ICP in 26 patients with PHH. Average recorded pressures varied from 4 to 40 mm Hg at rest with a mean of 17.8 mm Hg. Normal neonatal ICP is less than 5.6 mm Hg. In these patients no relationship was

demonstrated between ICP and outcome in terms of physical disability, sensorineural deafness, speech problems or visual handicap. It did appear however that raised ICP is associated with seizures. Six out of seven patients who had seizures also had significantly raised ICP [35].

GRADING OF INTRAVENTRICULAR HAEMORRHAGE AND POST-HAEMORRHAGIC HYDROCEPHALUS

Grading of the severity of IVH is essential in determining the possible complications and prognosis after germinal matrix haemorrhage. The first classification of the severity of IVH was described by Papile et al. In 1978 using CT scan [46]. The appearance of various degrees of intracerebral haemorrhage were correlated with the development of hydrocephalus (Table1).

TABLE 1

Severity of IVH according to Papile et al. [46]

GRADE I Subependymal haemorrhage
GRADE II Intraventricular haemorrhage without ventricular dilation
GRADE III Intraventricular haemorrhage with ventricular dilation
GRADE IV Intraventricular haemorrhage with parenchymal extension

Use of this grading system is widespread and it is used in most published studies, however it does have some notable deficiencies. All haemorrhages must involve the parenchyma to some degree as the germinal matrix is located outside of the ventricle but in the hemisphere. There is also a wide spectrum of pathology in grade IV disease. Some patients may have only a small parenchymal clot whereas others may have more hemispheral blood than parenchyma. This may account for discrepancies in some studies where small parenchymal bleeds may be classified as grade III in some but grade IV in others. Other forms of parenchymal injury such as haemorrhagic infarction and periventricular leukomalacia are not included in this grading system, although haemorrhagic infarction may be inadvertently included as it appears to be an extension of matrix haemorrhage. Volpe has made an attempt to overcome this deficiency by including periventricular intra-parenchymal echodensity (IPE) as seen on ultrasound [74]. IPE is used as an approximation of the amount of parenchymal injury (Table 2).

TABLE 2

Grading of severity of IVH by ultrasound according to Volpe [74]

GRADE I Germinal matrix haemorrhage with no or minimal intraventricular haemorrhage (< 10% of ventricular area on parasagittal view)
GRADE II Intraventricular haemorrhage (10 –50% of ventricular area on parasigittal view)
GRADE III Intraventricular haemorrhage (>50% of ventricular area on parasagittal view; usually distends lateral ventricle)
Separate notation Periventricular echodensity (indicate location and extent)

Most grading systems have been described using a particular imaging modality ie. CT or ultrasound [46, 63, 74]. However the most often used imaging technique used in the neonatal Intensive care unit is real time cranial ultrasound and most studies grade IVH based on this. Performing a CT scan has been recommended if accurate determination of the amount of parenchymal injury is important such as in the decision to withdraw treatment. CT scan can more accurately determine parenchymal injury than ultrasound [33]. More accurate assessment of parenchymal damage, after the first postnatal week, from ischaemia has been described using xenon-133 and positron emission tomography. The clinical usefulness of these investigations has yet to be determined [41].

The regression, stabilisation or progression of ventricular enlargement after IVH is well described [16, 25, 32, 42, 49]. Serial ultrasound or CT scan investigations must be performed in order to assess changes in ventricular size and in severe grades of IVH (III & IV) this is usually done weekly. Holt has described objective measurements of ventricular size in order to categorise the degree of ventricular enlargement. Changes in size can then be accurately assessed from week to week and the need for treatment determined [25] (Table 3)

TABLE 3
Grading of ventricular dilatation by ultrasound in PHH [25]

GRADE	CORONAL VIEW *BV:BP RATIO*	SAGITTAL VIEW *VENTRICULAR DIAMETER*	AXIAL VIEW *CORTICAL MANTLE*
MILD	<0.4	10-15 mm	>6 mm
MODERATE	0.4-0.6	15-20 mm	-
SEVERE	>0.6	>20 mm	<5 mm

BV:BP RATIO

The biventricular-biparietal ratio is a ratio between the ventricular width and the width between the inner table of the skull. It is measured in the coronal plane at the level of the foramen of Monro.

VENTRICULAR DIAMETER

The ventricular diameter is measured on the best true sagittal scan of the lateral ventricle. At a point corresponding to the 2 o'clock position on the posterior edge of the thalamus, a measurement is made at a 45^0 angle to the edge of the white matter.

CORTICAL MANTLE

This is the thickness of the brain parenchyma between ventricle and inner table of the skull at its thickest point.

MECHANISMS OF BRAIN INJURY IN IVH / PHH: SUMMARY

Form the preceding discussion it can be seen that there a many insults to the premature brain associated with IVH and later PHH. These insults can be divided into four phases according to the time at which they occur [35] (Table 4). Included in this classification are injuries occurring as a result of the complications of hydrocephalus management. It is important when considering the optimal management of these patients to know which of all the insults causes the most brain injury. This is because one injury may be treated at the expense of increasing injury through some other mechanism. An example is early lumbar puncture therapy to lower raised intracranial pressure which increases the incidence of meningitis [20, 67]. From available studies it appears that the primary injury of IVH is the most important factor in determining prognosis (see outcome studies Chapter 4). This is only true however as long as central nervous system (CNS) infection does not occur as a complication of therapy in the treatment of PHH. Cerebrospinal fluid infection is one of the worst insults that the developing brain can sustain [35, 40, 61, 67].

TABLE 4
The four phases of brain injury following neonatal IVH / PHH [35]

PHASE 1 *The primary insult of IVH* 1. Prenatal hypoxic-ischaemic encephalopathy 2. IVH acting as a space occupying lesion 3. Dissecting injury from haemorrhage
PHASE 2 *Secondary injury from postnatal hypoxic-ischaemia* 1. Shock / coagulopathy 2. Hypotension 3. Disordered cerebral autoregulation 4. Raised ICP 5. Reduced cerebral perfusion pressure 6. Seizure induced increase in cerebral metabolism 7. Apnoea, pneumothorax: Hypoxaemia
PHASE 3 *Tertiary injury from raised ICP and ventriculomegaly* 1. Impaired cerebral blood flow 2. Brain shifts
PHASE 4 *Quaternary injury from raised ICP* 1. Complicating VP shunt block 2. Shunt over-drainage 3. Isolated fourth ventricle 4. CSF infection

CHAPTER 3: MANAGEMENT OF INTRAVENTRICULAR HAEMORHHAGE AND POST-HAEMORRHAGIC HYDROCEPHALUS

PREVENTION OF INTRAVENTRICULAR HAEMORRHAGE

Strategies for preventing IVH are essential as survival rates for low birth weight infants increase. Interventions can be prenatal or postnatal and target the various mechanisms of pathogenesis discussed earlier.

PRENATAL INTERVENTION

Prevention of preterm birth

The incidence of IVH increases as gestational age and birth weight decrease [41]. This illustrates the importance of preventing premature birth or delaying delivery as long as possible.

Transportation in utero

If premature labour and delivery can not be prevented then the pregnant mother should be transported to a regional centre with neonatal ICU facilities. The incidence of IVH is high in premature infants transported after delivery [74].

Prenatal pharmacological interventions

Phenobarbital may reduce the incidence and severity of IVH if given antenatally although evidence is not conclusive. Vitamin K may also be of benefit given that premature infants have only 60% of adult levels of vitamin K dependent coagulation factors [74]. Antenatal steroids which enhance fetal lung maturity have reduced the incidence of IVH.

Atraumatic labour and delivery

Precipitous labour and delivery can lead to deformation of the soft, compliant neonatal skull with resulting injury and loss of cerebrovascular autoregulation. Despite this the role of caesarean section remains unclear.

POSTNATAL INTERVENTION

Resuscitation of the newborn

Over-rapid volume expansion during resuscitation can lead to increased cerebral blood flow, which as discussed previously is a factor in the pathogenesis of IVH. It is also prudent to consider early, atraumatic ventilation as cerebral autoregulation is often disturbed. Hypercarbia is a common finding and can lead once again to increased cerebral blood flow. Hyperventilation and hypocarbia has been shown to restore cerebral autoregulation but also causes cerebral vasoconstriction and limit oxygen delivery. For this reason it is probably best to recommend normo-ventilation only.

Correction of fluctuating cerebral blood flow and arterial and venous pressure

Cerebral blood flow fluctuation is seen primarily in ventilated infants with respiratory distress syndrome. Because of the almost invariable relationship between this and IVH, infants may be given muscle paralysis to restore a stable pattern of cerebral blood flow and venous pressure. Care should also be taken to prevent sharp elevations in arterial blood pressure. Excessive handling and tracheal suctioning should be avoided and intra venous infusions should be administered with caution.

Correction of coagulopathies

Although some infants with IVH will have a coagulopathy that needs intervention not all patients will require action to correct or prevent such abnormalities.

Pharmacological interventions

In an effort to reduce the incidence and severity of IVH, phenobarbitol, vitamin E and ethamsylate have all been administered postnatally with inconclusive results. The benefit of postnatal indomethacin was also doubtful until recently. Ment et al have shown in a large prospective, randomised, placebo-controlled trial that low dose intravenous indomethacin lowers the incidence and severity of IVH. The mechanism of action of indomethacin is unclear but may involve scavenging prostoglandin-mediated free radicals or inhibiting active calcium transport in vascular smooth muscle. Experimentally indomethacin has been shown to decrease cerebral blood flow, decrease post asphyxial reactive

cerebral hyperaemia and accelerate germinal matrix microvasculature maturation. Importantly it also did not result in extension of pre-existing IVH [43].

PREVENTION OF POST-HAEMORRHAGIC HYDROCEPHALUS

It is assumed that hydrocephalus occurring after IVH is as a result of CSF pathway obstruction initially by blood clots and later by subsequent collagen formation. If this is true then early fibrinolysis of the ventricular clot in an effort to clear CSF pathways may prevent the development of hydrocephalus.

In 1992, Whitelaw et al. demonstrated that low dose intraventricular administration of streptokinase enhanced endoventricular fibrinolysis and prevented permanent hydrocephalus in 8 of 9 infants with post haemorrhagic ventricular dilation [77].

A prospective, randomised case control study was performed by Luciano et al. following this positive experience. Using the same dose of streptokinase as Whitelaw et al. 10 patients were treated, 5 in the fibrinolysis group and 5 in the control group. Three patients in each group eventually required ventriculo-peritoneal shunt placement. The fibrinolysis group also had the complications of ventriculitis in one patient and rebleeding from the germinal matrix in another. The conclusion was that streptokinase treatment should not be administered soon after IVH, unless progressive ventriculomegaly occurs [36].

It is difficult to draw conclusions from these small studies however the complications of intraventricular streptokinase are cause for concern. Administration of fibrinolytics in the late phase of IVH/PHH, as suggested by Luciano, is probably also inappropriate. The arachnoiditis caused by IVH may start soon after the haemorrhage and early blood clearance would be preferable. Suggested causes of failure of therapy are firstly that enhanced fibrinolysis seen in ventricular fluid was not obtained at the arachnoid villi and secondly that mechanisms other than fibrinolysis are responsible for the clearance of CSF blood clots [36].

THERAPEUTIC OPTIONS FOR THE TREATMENT OF POST-HAEMORRHAGIC HYDROCEPHALUS

There are a number of issues that need to be considered when deciding on a therapeutic course for an infant with PHH.

Natural history of PHH

Several studies have shown that only a minority of infants with IVH will develop hydrocephalus and most of these patients will have had grade III or IV haemorrhage [32, 42, 63]. Of the infants with dilated ventricles only a minority will progress to PHH requiring a shunt. Results of 3 studies showing the

natural history of the disease where no or minimal intervention occurred are shown in table 5.

TABLE 5

Incidence of PHH in infants with IVH from 3 studies where there was minimal intervention.

	Levene and Starke [32]	Shankaran et al. [63]	Ment et al. [42]
Total patients enrolled	202 Neonatal admissions	242 Neonatal admissions	438 VLBW Infants
Patients with IVH	68	62	133
Surviving patients who developed ventricular dilation	15	26	Unknown
Patients who had progressive hydrocephalus with raised ICP and increasing head size requiring therapy	3	11	5

Given the tendency for some patients to have spontaneous resolution of hydrocephalus up to one month after IVH it is prudent not to rush into a definitive shunting procedure that will leave the patient shunt dependent. Many authors recommend initial "conservative" therapy (combinations of medical therapy and lumbar puncture) in order to identify the patients who will have persisting raised intracranial pressure [12, 16, 32, 42, 63, 64, 68].

Protection of the cerebral mantle

Progressive ventricular enlargement due to abnormal CSF absorption can cause cerebral injury through either raised intracranial pressure or mechanical

disruption of brain tissue from ventricle dilatation. However not all infants with enlarging heads will have raised ICP [29, 35]. This is because of the high intracranial compliance that these infants have. Furthermore there is little evidence to support the contention that raised ICP causes significant neurological injury in this group of patients. In the evaluation of ICP after IVH in 26 patients Lin et al. could show no correlation between raised pressure and poor neurological outcome [35]. On the other hand there is no debate that hydrocephalus in older children and adults requires prompt treatment in order to limit the effects of raised ICP. Studies that recommend early surgical treatment of PHH base their recommendation on experience with these older patients.

Regarding mechanical injury of the brain, it appears that this takes place in an ordered sequence. White matter injury occurs first with remarkable sparing of the cerebral cortex [58]. Reconstitution of the mantle after successful shunting is a well-recognised phenomenon in infants with hydrocephalus [37]. It is presumed that this increase in mantle thickness is from shortening of previously stretched white matter fibres and a reduction of the circumference of the cortex. It would seem logical that there is a limit in terms of time and thickness beyond which this recovery will not take place, but as yet these values are unknown. Consequently, any decision regarding timing of a surgical intervention remains subjective.

Complications of surgical therapy in premature children

In the early stages of IVH patients are often unstable. They are usually nursed in an ICU with invasive monitoring and many require ventilation. Until the development of real time high-resolution ultrasound even investigation of IVH was difficult as it required moving labile patients to a CT scanner.

Any surgical intervention during this early period increases the risk of sustaining iatrogenic complications. It has been noted that excessive stimulation of infants can lead to progression of IVH (see pathogenesis of IVH). Moving infants into the operating room environment also exposes patients to the risks of hypothermia and haemorrhage. Premature patients are also at high risk of developing infections for a variety of reasons such as poor immune system function, skin fragility and colonisation with pathogenic flora. Surgical procedures that result in the implantation of foreign material such as shunts and reservoirs therefore dramatically increase the risk of CNS infection [13, 60, 61].

MEDICAL THERAPY FOR PHH (PHARMACOLOGICAL INTERVENTION & LUMBAR PUNCTURE)

Pharmacological intervention in order to reduce the volume of CSF produced has been proposed as a therapeutic option for PHH [64, 68]. Acetazolamide is a carbonic anhydrase inhibitor that partially blocks the formation of water by the choroid plexus thereby acting directly on CSF production. Furosemide is the

other commonly used agent and has a diuretic effect that ultimately reduces CSF formation secondary to dehydration.

Cerebro-spinal fluid (CSF) turnover per day is approximately 3 times which means that far more CSF is produced per day than is present within the central nervous system at any one time. For this reason even a significant reduction in CSF production (up to one third) does not change intracranial pressure by more than 1.5 cm of water when there is a large imbalance between production and absorption as in PHH [39]. Pharmacological intervention is therefore only likely to be of help as an adjunct to some other form of therapy or when hydrocephalus is only slowly progressive. These agents also have adverse effects causing disturbances of electrolytes, acid base balance and haemodynamic instability.

Lumbar puncture (LP) has been widely used as a method of temporarily treating PHH before a definitive shunting procedure [2, 11,16,47, 67, 78]. The procedure is usually performed daily and either a specific amount of CSF is drained [39, 78] or drainage is continued until a specific pressure is attained [16].

In theory it would seem to provide a comparatively safe way of reducing ICP and limiting brain injury to that caused by the primary insult. It can be performed in the neonatal nursery on a regular basis until the infant is well enough to tolerate a surgical operation. However despite its appeal, studies have not shown any improvement in neurological outcome or a decrease in

the number of patients eventually requiring a shunt. The results of randomised trials evaluating LP therapy are summarised in table 6.

TABLE 6
Outcome of patients randomised to LP or conservative therapy for treatment of PHH

	Whitelaw [78]	Dykes [16]	Anwar [2]
Total patients enrolled LP / Conservative	157 79 / 78	38 22 / 16	47 not randomised
Patients requiring shunt LP / Conservative	41 / 42	No numbers Equal shunts Both groups	10 / 9
Adverse outcome & Death LP / Conservative	58 / 60	12 / 11	Not assessed
Good outcome LP / Conservative	9 / 9	6 / 3	Not assessed
CNS infections LP / Conservative	7 / 4	unknown	unknown

No statistically significant difference in outcome was shown in any of these trials. In addition it appears that in the largest study, by the Ventriculomegaly trial group, there was an increased incidence of infection in the LP group. Although this difference was not statistically significant, other authors have also raised the concern that lumbar puncture could provide a portal of entry for infection in these patients [78].

There are also other potential drawbacks to performing serial LP's. Lumbar drainage of CSF is not possible in all patients, as some will have obstructive hydrocephalus. In the ventriculomegaly trial group up to 25% of patients also required ventricular taps as insufficient CSF was obtained by LP [78]. Premature

infants also have to suffer the stress of frequent painful punctures which may last from 15 to 60 minutes. Finally if lumbar punctures are effective relatively large amounts of CSF may be drained over a short period of time. This can result in disturbances of cerebral circulation [39], apnoea [78], loss of protein and electrolyte disturbances [20].

VENTRICULAR TAP, VENTRICULAR DRAINAGE & VENTRICULAR RESERVOIR

VENTRICULAR TAP

The anterior fontanelle is open in premature infants so transcutaneous aspiration of ventricular CSF by needle puncture is a simple procedure. A short spinal needle is introduced into the ventricle at least 1 cm off the midline at the level of the coronal suture. This technique has been described as a temporising treatment for PHH when LP fails [78]. It does have potential complications however. Firstly repeated taps carry the risk of parenchymal tract injury [24] and haemorrhage and secondly there is a chance of introducing infection. For these reasons ventricular tap has not been a popular method of treatment.

VENTRICULAR DRAIN

External ventricular drainage has been described by a number of authors as an effective therapy for PHH [16, 20, 23, 38, 76]. It offers the advantages of

continuous CSF drainage, pressure monitoring and when ideally performed requires only a single brain parenchymal tract. Weninger has also reported, in a series of 27 infants, being able to insert the ventricular catheter in the incubator using local anaesthetic. Because the patient does not have to be moved the drain can be inserted early when the infant may still be unstable. In this series drains were inserted at a mean age of 14 days (range 3-28 days) and all patients showed a decrease in ventricle size within 2-3 days. Three patients died, 7 had resolution of their hydrocephalus and 17 went on to VP shunt placement. No serious complications were associated with drain placement or maintenance although 12 revisions were required for drain blockage, accidental dislocation and CSF leak. It is notable that there were no cases of clinical ventriculitis in this group even although CSF culture was positive on 7 occasions. These cultures were presumed to be positive because of exogenous contamination [76]. This is in contrast to another series reported by Hahn where 9 out of 15 patients (60%) required treatment for infection while undergoing ventricular drainage [20]. There are no reports comparing this form of therapy to any other and numbers in all reported series are small so assessment of the effectiveness of the intervention is unclear. In Weninger's series all patients with grade IV IVH had a poor outcome and these patients were felt not to benefit from early hydrocephalus treatment. Of the patients with grade III IVH 41% had a good outcome and it is suggested that these patients may have obtained benefit from early treatment [76]. Technical improvements in external ventricular drainage such as Broviac ventriculostomy have been reported in an effort to improve on the frequent complications of catheter dislodgement and infection [10]. In this instance a

catheter with a dacron cuff is tunnelled subcutaneously before exiting into a bag. The cuff ensures that the catheter does not move and a fibrous response to the dacron limits retrograde bacterial colonisation of the catheter.

VENTRICULAR RESERVOIR

In order to overcome the complications of external ventricular drainage some authors have suggested inserting a ventricular catheter with a reservoir under the scalp [37, 39, 52]. As with lumbar puncture or ventricular tap, CSF is removed on a daily basis until either the hydrocephalus resolves or the patient is stable enough to undergo definitive shunting. McComb reported on the outcome of this procedure in 20 patients. Reservoirs were inserted on average by the 12th day of life (3-30 day range) in an operating room and improvement in cortical mantle thickness was observed in survivors [39]. It is unfortunate however that 13 patients died in this series and although the causes were not thought to be procedure related most deaths occurred within 30 days of operation. This is considered to be an operative mortality in most reports. In another series of 12 patients, catheter placement occurred at a later age (mean 23 days) [37]. Cortical mantle thickness was improved on follow-up CT scan in surviving patients. Only 1 patient avoided a VP shunt, 7 patients died and 2 developed catheter related infections. The numbers in these series are very small and the mortality was high in both so it is not possible to make any comment on the effectiveness of this therapy.

VENTRICULAR SHUNT

VENTRICULOSUBGALEAL SHUNT

The insertion of a ventricular catheter that drains into an undermined subgaleal space has the possible advantage of allowing continuous CSF diversion from the ventricle. Sklar et al described this operation as a temporising procedure in 62 infants with PHH before VP shunts were inserted [66]. The operation was performed in an operating room under general anaesthesia. No information is given regarding the age at which this intervention was made but 80% of infants were reported to show a decrease in ventricle size. Seven patients died with one death directly related to scalp necrosis and infection at the site of the operation. The overall infection rate was 10% and a further 10% avoided a permanent shunt. More recently Rahman has reported a small series of patients undergoing the same treatment [56]. Fifteen patients had ventriculosubgaleal shunts inserted at an early age. All showed stabilisation of ventricular size but 80% went on to require insertion of a VP shunt. No infection was reported in this series. Again an opinion on whether outcome was improved by early intervention can not be made based on these reports. Some critical observations regarding this technique have been made [12]. First, the addition of tunneling and abdominal insertion of a distal catheter to the shunt does not substantially increase the time required for surgery or its morbidity. The omission of these steps only reduces the incidence of peritoneal complications such as respiratory compromise or retrograde spread of infection with necrotising enterocolitis. Second, use of the described "Omaya reservoir connectors" should be

avoided in this patient population because of the high incidence of ventricular catheter disconnection. This is a procedure that has not gained universal acceptance.

VENTRICULOPERITONEAL SHUNTS

Ventriculoperitoneal shunting is the definitive therapy for PHH although it is seldom the only intervention. Most patients are initially managed with one of the previously described treatments in an effort to exclude those who will have resolution of their hydrocephalus and allow for stabilisation prior to a surgical procedure [6, 18, 20, 26, 27, 33, 38, 50, 51, 52, 55, 60, 63]. However there are a few reported series where insertion of a VP shunt is described as the only therapy [4, 34, 48].

Ultimately shunts are inserted for two reasons. Firstly, a VP shunt provides a reasonably physiological way of maintaining normal intracranial pressure and in this way limits brain injury. Secondly, a shunt may be required for cosmesis. Even the infant with irreversible severe neurological injury may benefit from a shunt to decrease head size to a dimension that is easily nursed. This not only allows parents to bond with their child but also prevents complications such as pressure sores.

There is no doubt that shunts are required for the long term treatment of PHH, however their use is fraught with complications in this group of patients [6, 13 27, 33, 35, 38, 55, 59, 60, 61]. Table 7 shows the complications related to VP shunting in 5 representative series.

TABLE 7

Complications of ventriculoperitoneal shunts in PHH

	Scarff et al [60] 1983	James et al [27] 1984	Lin et al [35] 1992	McCallum et al [38] 1994	Levy et al [33] 1997
Total number of shunted patients	20	53	27	50	47
Average age at the time of shunting	4.5 weeks	31.5 days	8 weeks	26 days	52 days
Number of shunt infections (%)	5 (25%)	18 (27%)	13 (48%)	8 (17%)	3 (6.3%)
Number of patients with shunt obstruction	10 (50%)	14 (26%)	24 (89%)	47 (94%)	39 (83%)
Total number of revisions	16	23	~92	163	209
Operative mortality	0	1	0	3	0
Follow-up period	short	Nursery stay	9mth– 3 years	2-5 years	Up to 16 years
Adjunctive therapy prior to shunting	LP	LP	EVD	Reservoir	Ventricular Tap

LP – Lumbar puncture

EVD – External ventricular drain

These results demonstrate the high incidence of infective and obstructive complications in PHH and this is confirmed in studies that have stratified complications according to the aetiology of hydrocephalus [13, 61].

Many reasons for the high incidence of complications have been proposed. Shunt infection is higher in infants under 6 months of age [13]. Renier and co-workers attributed this high incidence of infection to declining levels of maternal IgG during the first 6 months of life prior to the build up of specific antibodies. In addition compliment activity and cellular immunity are lower and

less efficient than in adults [57]. This theory remains controversial however as other authors maintain that immunoglobulins, compliment and cellular immunity have little effect once organisms have entered the ventricles [53]. Another reason could be the age-related skin changes and the presence of high- density colonies of coagulase negative staphylococcus in young infants [53]. IVH also seems to constitute a specific risk factor for infection irrespective of patient age. Haemorrhage remnants in the ventricles probably diminish the effectiveness of local defence systems [61].

Controversy also exists regarding the reasons for the increased incidence of shunt obstruction. Many authors cite the high protein levels found in the CSF after IVH as the cause [24, 26, 27, 51, 60]. Mechanisms whereby the high protein has been postulated to affect shunt performance include, increased CSF viscosity, valve sticking due to protein, protein deposition in the lumen and a greater susceptibility to infection. Other groups, however have shown CSF protein levels to have no relationship to shunt malfunction [4, 8, 9, 55]. In a study looking specifically at shunt complications and CSF protein levels in 95 patients Brydon et al showed no statistical relationship between protein levels and either obstruction or infection [9]. In another study by the same authors reduced bacterial adhesion to shunt catheters was demonstrated in the face of increased protein levels, illustrating that protein may in fact protect against infection [7].

High red blood cell counts in the CSF have been shown to increase the incidence of shunt obstruction [8,55]. Several reports have also shown a higher

complication incidence in patients who were shunted at a young age presumably with more RBC and their products still present in the CSF [6,18, 26, 55]. CSF protein content correlates well with the extent of IVH and this has perhaps been the confounding variable in studies looking at CSF protein [28]. Blood clearance from the ventricles after IVH is variable but in most cases clears considerably in the first month [39]. The timing of shunt placement remains controversial as a balance must be achieved between the incidence of complications with early surgery and the probability of neurological injury with delayed shunting. Other complications such as skin breakdown over the shunt and CSF accumulation around the burrhole have also been described [48].

In order to overcome the complications of shunting in these patients some technological innovations in shunt design have been suggested. In 1979 Bada recommended using distal catheters with a 1cm triple-slit to limit obstruction due to coagulum [4]. James et al later suggested a low-pressure system with the distal catheter open below the level of the slit valve to further reduce the chance of obstruction [27]. More recently the Ammar shunt has been specifically designed for premature infants with PHH [1]. The shunt is made of soft silicone, has a small configuration and the entire shunt acts as a low-pressure valve. No trial has yet been conducted to assess if any of these innovations are beneficial.

CHAPTER 4: OUTCOME OF PATIENTS WITH INTRAVENTRICULAR HAEMORRHAGE AND POST-HAEMORRHAGIC HYDROCEPHALUS

IVH AND OUTCOME

Intraventricular haemorrhage is the commonest cause of morbidity and mortality in very low birth weight infants (VLBW). In a review of 22 publications documenting the outcome of VLBW infants it was shown that more and more infants are surviving the respiratory complications of prematurity [69]. As this occurs the neurological deficits in survivors are becoming more prominent.

The strongest predictor of outcome in patients who sustain IVH is the grade of haemorrhage [16, 28, 45,22]. For this reason it is important to serially evaluate the extent of IVH in the germinal matrix as progression can occur over days. Correlation between outcome and grade of IVH from several representative reports are shown in table 8.

TABLE 8

Relationship between IVH Grade and outcome.

Outcome	IVH Grade				
	Krishnamoorthy 1979 1yr [28] N = 15	∝I n=3	II n=9	III n=0	IV n=3
	Normal	1	6		-
	Mild-Moderate	2	3		1
	Severe	-	-		2
	Dykes 1982 1yr [16] N = 59	Mild n=10	Moderate n=26	*Severe n=26	
	Normal	5	8	4	
	Abnormal	-	9	6	
	Died	5	7	15	
	Papile 1983 1yr [45] N = 198	∝I	II	III	IV
	Normal	16	9	2	2
	Mild	14	7	7	2
	Severe	3	2	5	13
	Multi Handicap	2	0	4	10
	Hanigan 1991 18 mth [22] N = 97	∝I	II	III	IV
	Normal	15	2	1	0
	Suspect	15	3	2	1
	Abnormal	7	5	5	7

∝IVH grading according to Papile

*In the study by Dykes et al. the severe grade of IVH included Papile grades III & IV.

PHH AND OUTCOME

Regarding the outcome of infants with PHH it is far more difficult to ascertain which factors other than grade of initial IVH have an effect. Most patients who develop PHH have either grade III or IV IVH and a high percentage are therefore severely disabled. Studies reviewing this topic show a worse neurological outcome related to IVH grade, increased number of shunt revisions, CNS infection and seizures [6, 11, 16, 20, 22, 24, 26, 28, 33, 35, 38, 39, 54, 62, 63, 76]. These factors may of course also be inter-related. The incidence of shunt infection increases with the number of times the shunt needs to be revised and seizures may be related to extensive IVH resulting in cortical injury. In a logistic regression analysis Levy et al demonstrated that grade of haemorrhage was by far the most important variable in determining cognitive outcome, motor function and the presence of seizure activity ($P < 0.0001$). In the same study a logistic model of survival determined that grade of haemorrhage and multiple shunt revisions (more than 5) were the most important determinants of survival ($P < 0.0001$)(Levy).

Outcome results from studies dealing only with patients with PHH are shown in table 9.

TABLE 9
Developmental outcome in patients' treated for PHH in previously published reports.

STUDY	Patients	Normal %	Delayed %	Severely delayed %	Dead %
Cooke 1987	54	44	31	17	7
Hanigan et al. 1991	16	6	19	75	
McCallum 1994	47	38	11	40	11
Resch et al. 1996	63	15	67.5	17.5	
Levy et al. 1997	72	24	11	22	43

Variations in the results of these studies probably reflect differing distributions of poor grade patients rather than differences in management. In the study by Levey et al. there were 18 patients with grade IV haemorrhage. None of these patients had a normal outcome and most were severely disabled having both spastic quadriparesis and a developmental quotient more than 2 standard deviations below the mean [33].

The effects of hydrocephalus on outcome

Does hydrocephalus alter outcome in patients with IVH? This is a difficult question to answer as the complications of VP shunt insertion may obscure the pathological effects of ventricular enlargement and raised ICP. Opinion in the literature remains divided on this issue. Some authors have indicated that hydrocephalus is a predictor of poor outcome [31, 62, 71]. In a study by Laurent et al. looking at outcome in 43 patients IVH grade was not as good a predictor of handicap as the presence or absence of hydrocephalus [31]. Papile et al also

showed that although patients of similar grade IVH with and without hydrocephalus had the same incidence of handicap, the hydrocephalus group tended to have more multi-handicapped patients [45]. Failure of ventricular decompression after shunt insertion has also been suggested as an indicator of poor outcome [62]. The reasoning that this is because hydrocephalus related injury has become irreversible is flawed however, as this may only represent progressive atrophy after parenchymal injury from other causes.

There is also a body of evidence indicating that hydrocephalus per se is not a factor in neurological outcome [11, 22, 28, 35, 62]. In a study looking at the effects of ICP in PHH in 26 infants no correlation was shown between raised ICP and outcome [35]. Cooke also demonstrated a strong correlation between the presence of porencephaly on ultrasound and outcome in 54 infants [11]. These abnormalities were noted before the onset of hydrocephalus. As has been mentioned previously many studies show a clear relationship between shunt complications in the treatment of hydrocephalus and increased morbidity and mortality [16, 24, 33, 35, 54, 62, 71].

The cost of treating PHH

There have been two published reports on the cost of treating infants with PHH. Both studies only looked at the treatment of infants with grade IV IVH. In 1994 McCallum looked at the cost of initial hospitalisation in 50 infants with PHH. The average cost was US$ 194 776 per patient. The additional costs thereafter of complicated and uncomplicated shunt revisions were US$ 4 692/patient/year (Infection incidence = 4.9%/patient/year and shunt

obstruction = 0.49 revisions/patient/year). There were only 15 patients in this study who were considered to be self sufficient and if the figures are adjusted to show cost per self sufficient child then the average is US$ 808 125 for the first 20 years of life [38]. This only includes the costs of hospitalisation and the fees of the neurosurgeon and neonatologist. It does not take into account the costs of rehabilitation or visits to other specialists.

In a more recent publication reviewing a series of 52 patients treated between 1977 and 1987 Pikus et al. estimated the cost of first hospitalisation at US$ 150 000 per patient. No patient in this study had a normal outcome [52]. The conclusion in both of these papers was that the cost-benefit analysis of the treatment of PHH after high grade IVH was discouraging.

CHAPTER 5: REVIEW OF SHUNT COMPLICATIONS AFTER THE TREATMENT OF POST-HAEMORRHAGIC HYDROCEPHALUS OVER AN 8-YEAR PERIOD.

INTRODUCTION

The incidence of intraventricular haemorrhage in very low birth weight infants has been reported to be decreasing in a number of neonatal centres over the past decade. Recent reports indicate that the incidence of IVH is around 25% to 50% in this group of patients [18, 19, 22, 33, 52, 73]. Nonetheless with advances in neonatal care more premature infants with IVH are surviving. Approximately 13-60% of the patients with IVH will develop progressive haemorrhagic hydrocephalus (PHH) and 22% to 70% of these will require CSF diversion [3, 16, 18, 32, 39, 49, 54, 63]. The most commonly performed procedure for the treatment of PHH is insertion of a ventricoloperitoneal shunt (VP shunt) as this offers the most permanent solution. Unfortunately VP shunts in low birth weight infants with IVH have a universally high complication incidence [6, 13, 27, 35, 38, 55, 59, 60, 61]. This tends to add to an already high morbidity, mortality and cost. It was the

aim of this study to review the timing of surgery for VP shunt insertion to ascertain if this in any way influenced the complication incidence.

PATIENTS AND METHODS

Forty one patients were referred to the paediatric neurosurgery department at Red Cross War Memorial Children's Hospital during the 8 year period from January 1989 to December 1996. A retrospective review of the patients' clinical notes was undertaken looking at birth weight, IVH grade, patient age at the time of surgery and complications occurring after surgery. Complications included VP shunt obstruction, shunt infection and death.

Only 36 of these patients are included in the study as insufficient data was available for 5 patients. All patients were referred from 3 surrounding neonatal units (Mowbray Maternity Hospital, Somerset Hospital, Groote Schuur Hospital) once progressive hydrocephalus became apparent on serial trans-fontanelle ultrasound, or on clinical examination. In all cases the diagnosis of IVH and subsequent Papile grading [46] was made using transfontanelle ultrasonography. Most patients also had a cranial computed tomography (CT) scan prior to insertion of a VP shunt. Before surgery was performed no attempt was made to treat the hydrocephalus by lumbar puncture or ventricular tap. There was also no administration of thrombolytic agents to try and clear the IVH.

VP shunts were inserted in an operating room with perioperative antibiotic cover for 24 hours. Two types of VP shunt were used; Codman and Chadbara. Both were distal slit valve medium pressure shunts with distal and proximal catheters connected by a right angle connector. A right occipital burrhole was used to place the ventricular catheter into the frontal horn of the right ventricle where possible and a subcostal inscision was used for peritoneal access. One patient had a ventricular reservoir inserted on day 31 which was tapped intermittently prior to VP shunt insertion 60 days later, and another had an external ventricular drain placed at 32 days of age with shunt insertion on day 52.

In most patients a routine post-operative CT scan was performed prior to discharge to assess the ventricular position of the VP shunt and size of the patients ventricles. During the study all patients were under the care of one consultant Neurosurgeon and one of 5 rotating registrars. The shortest follow-up interval was 5 months and the longest 5 years with an average interval of 2.2 years.

RESULTS

All of the patients tolerated the surgical procedure well with no intra-operative or immediate post-operative complications. Birth weight was below 2000 grams in all but 1 patient with a range from 740 to 2100 grams (mean 1312 grams).

The IVH grade was I in 1 patient III in 23 patients and IV in 12 patients.

Surgery for VP shunt insertion was undertaken between day 13 and 124 after birth with a mean of 42 days.

Complications were divided into VP shunt obstruction requiring revision, shunt infection and death.

Shunt Obstruction:

Nine out of the 36 patients (25%) required revision of their shunt after obstruction during the study period with a total of 21 revision procedures performed. The range in the number of revisions performed was 1 to 6 per patient. This excludes patients who had shunt failure related to infection.

Seven of the patients (19%) had revision of their shunt during the initial admission prior to discharge (early revision). This is an important result as it excludes the patients who had later revisions documented because of a long follow-up period. Of the patients who had early revisions 2 went on to require later revisions after their discharge from hospital.

Infection:

Shunt infection occurred in 4 patients (11%), all during the initial hospital admission. Two patients acquired Klebsiella shunt infections with the insertion of the initial shunt and were treated with external ventricular drains and antibiotics. One patient had the external drain converted to a shunt after the cerebrospinal fluid cell count dropped below 5 white cells and cultures grew no organisms. The other patient underwent a prolonged course of antibiotic administration and ventricular drainage. There was no improvement in the cerebrospinal fluid cell count during this time and eventually the ventricular drain was removed and the patient was discharged home for a period of months. A follow-up CT scan on this patient demonstrated locculated, isolated ventricles of differing density. Further CSF diversion was not attempted and the hydrocephalus was allowed to progress. One patient developed infection with Staphylococcus epidermidis after conversion of a ventricular reservoir to a VP shunt. Five further revisions were performed before this patient was discharged in a severely disabled state. The last patient had infection with a Staphylococcus aureus organism and died from the infection after 3 shunt revisions.

Mortality:

Four patients died. One patient had a VP shunt related death and died from a shunt infection at age 8 months. In the other 3 patients mortality was related to pneumonia. Two patients died at age 1 year and 1 at the age of 2 years.

Neurodevelopmental outcome

Sixteen patients had a record of neurodevelopmental outcome recorded in their hospital folder. Results are shown in table 10.

TABLE 10

Neurodevelopmental outcome

Outcome	Shunted before 5 weeks	Shunted after 5 weeks
Normal	0	1
Mild handicap	2	2
Moderate handicap	2	0
Severe handicap	4	5

CT scan appearance after shunting

Scans done at variable intervals after insertion of a shunt were reviewed in 18 patients. Thirteen patients had recovery of cerebral mantle thickness and 5 showed atrophy. Of the patients shunted after 5 weeks only 1 showed atrophy, 4 patients shunted in the earlier group developed atrophy. There was no relationship shown between cerebral mantle recovery and neurological outcome.

Relationship between complications and age/weight at the time of surgery (Table 14)

Mortality from causes other than VP shunting are not included in this analysis. Shunt revisions that occurred after the initial admission period are also not

included as they are less likely to be influenced by the timing of surgical intervention.

During their initial hospital admission nine patients had complications; either infection or mechanical shunt obstruction. In all cases surgical intervention was performed within the first month of birth. If day 35 (5 weeks) of age is used as a cut off then 19 patients underwent early intervention of which 9 developed complications (47%) and 10 did not. No patients had early complications when surgery was performed after day 35. A comparison of the incidence of complications in 2 groups of patients; those undergoing surgery before day 35 and those having surgery after this time, shows a significantly higher incidence of complications in the early surgery group (x^2 test $p< 0.01$) (Table 11). A comparison of complications occurring in patients with a birth weight below 1200 grams and those with a birth weight above this value showed no statistical correlation (x^2 test $p> 0.7$) (Table 12). There was also no tendency to operate on patients at a particular time because of a certain birth weight (x^2 test $p> 0.73$) (Table 13).

Table 11
Chi-square table comparing complications after early and late surgery

	COMPLICATIONS	NONE	TOTAL
SURGERY <35 d	9	10	19
SURGERY >35 d	0	17	17
TOTALS	9	27	36

Chi-square 10.737 p-value <0.001

Table 12

Chi-square test comparing complications occurring below and above 1200 grams

	COMPLICATIONS	NONE	TOTAL
WEIGHT <1200 g	5	13	18
WEIGHT >1200 g	4	14	18
TOTALS	9	27	36

Chi-square 0.148 p-value <0.7003

Table 13

Chi-square table comparing the timing of surgery and patient weight above and below 1200 grams

	WEIGHT <1200 g	WEIGHT >1200 g	TOTAL
SURGERY <35 d	9	10	19
SURGERY >35 d	9	8	17
TOTALS	18	18	36

Chi-square 0.111 p-value < 0.7385

TABLE 14a
Data for patients shunted before 5 weeks.

#	BIRTH WT GRAMS	IVH GRADE	AGE AT SURGERY IN DAYS	EARLY REVISIONS	TOTAL REVISIONS	INFEC	MORTALITY	DEVELOPMENT DELAY	CT FINDINGS
1	800	IV	13	1	2		PNEUMONIA		
2	850	III	14	1	2			SEVERE	RECOVERY
3	1350	IV	14	1	1			MODERATE	RECOVERY
4	1000	III	14	0	1	KLEBS		SEVERE	ATROPHY
5	1600	III	14	0	0			MODERATE	ATROPHY
6	1040	IV	19	0	0				
7	1250	III	20	1	1				ATROPHY
8	1500	III	23	0	0				
9	1650	III	26	0	0				
10	1080	III	26	0	0				
11	1700	IV	27	0	0				RECOVERY
12	1150	III	30	3	3	STAPH A	SHUNT INFEC		
13	1924	III	30	0	0			MILD	RECOVERY
14	900	III	30	0	0			MILD	
15	1180	III	30	2	2				
16	1500	III	30	0	0	KLEBS		SEVERE	
17	1240	I	RESV 31/VP93	6	6	STAPH		SEVERE	ATROPHY
18	1900	IV	EVD 32/VP52	0	0				RECOVERY
19	980	IV	32	0	0				
Ave	1294g		24 d						

TABLE 14b
Data for patients shunted after 5 weeks.

#	BIRTH WT GRAMS	IVH GRADE	AGE AT SURGERY IN DAYS	EARLY REVISION	TOTAL REVISION	INFEC	MORTALITY CAUSE	DEVELOPMENT DELAY	CT FINDINGS
20	1110	IV	37	0	0				
21	1180	III	38	0	0			NORMAL	RECOVERY
22	1180	III	40	0	0				
23	1050	III	41	0	0			MINOR	RECOVERY
24	1800	IV	42	0	0				
25	1500	IV	42	0	2			SEVERE	RECOVERY
26	2100	III	45	0	0			SEVERE	
27	1360	IV	47	0	0		PNEUMONIA		RECOVERY
28	1140	IV	55	0	0		PNEUMONIA		RECOVERY
29	1560	III	57	0	0				
30	1900	III	62	0	0				RECOVERY
31	740	III	68	0	0			SEVERE	RECOVERY
32	1800	III	72	0	0				
33	1120	III	90	0	1			SEVERE	RECOVERY
34	925	III	90	0	0				
35	840	III	98	0	0			SEVERE	ATROPHY
36	1350	IV	124	0	0			MINOR	
Ave	1333g		62d						

IVH GRADE – According to Papile [46]
EARLY REVISION –Includes all shunts revised during the initial admission.
INFEC. – Refers to organism cultured after proven shunt infection.
CT FINDINGS – Refers to recovery of the cerebral mantle or atrophy as seen after shunting.
RESV – Subcutaneous ventricular reservoir.
EVD – External ventricular drain.

DISCUSSION

The best algorithm of treatment for PHH is currently not established. A limited number of controlled studies with long term follow-up are reported comparing conservative or preventive treatment modalities such as lumbar puncture, and fibrinolysis [21, 78]. None have convincingly demonstrated an improved outcome when used to treat this group of patients. Ultimately there are a significant number of patients who will require VP shunting for progressive hydrocephalus.

It is unfortunate that almost all studies reporting on the outcome of VP shunting in PHH demonstrate a high incidence of shunt complications including obstruction, infection and wound breakdown [6, 13 27, 33, 35, 38, 55, 59, 60, 61]. In comparison with other reports this series has a relatively low incidence of complications (Table 15). To some extent this is probably as result of selection bias. Our neurosurgical service is remote from the surrounding neonatal centres and it is likely that only patients who appear to have a reasonable chance of survival are referred.

TABLE 15

Comparison of VP shunt complications from this and other reports.

	Scarff et al [60] 1983	James et al [27] 1984	Lin et al [35] 1992	McCallum et al [38] 1994	Levy et al [33] 1997	Taylor 1999
Total number of shunted patients	20	53	27	50	47	36
Average age at the time of shunting	4.5 weeks	31.5 days	8 weeks	26 days	52 days	42 days
Number of shunt infections (%)	5 (25%)	18 (27%)	13 (48%)	8 (17%)	3 (6.3%)	4 (11%)
Number of patients with shunt obstruction	10 (50%)	14 (26%)	24 (89%)	47 (94%)	39 (83%)	9 (25%)
Total number of revisions	16	23	~92	163	209	21
Operative mortality	0	1	0	3	0	1
Follow-up period	short	Nursery stay	9mth– 3 years	2-5 years	Up to 16 years	5mth-5 years
Adjunctive therapy prior to shunting	LP	LP	EVD	Reservoir	Ventric. Tap	1-EVD 1- Res

In the results from this study it is apparent that most of the complications occur in the period soon after shunt insertion. Seven of the 9 patients who had shunt obstruction required revision during their initial hospital admission and all the infectious complications also occurred in this period. This finding has also been noted in other reports [18, 24, 26, 38, 60].

It is probable that along with other factors blood within the ventricles, during this period of haemorrhage resolution, is responsible for both shunt occlusion and infection. High red blood cell counts in the CSF have been shown to

increase the incidence of shunt obstruction [8, 55] and haemorrhage remnants in the ventricles probably also diminish the effectiveness of local defence systems [61].

It is for this reason that many authors have recommended various forms of therapy to delay the insertion of a shunt while still treating the hydrocephalus. However, despite the use of lumbar puncture, ventricular drains and reservoirs the incidence of complications remains high (Table 7). In this study (Taylor) a diminished complication incidence was noted when VP shunt insertion was delayed beyond one month. It is probable that haemorrhage products reach a critical level around this time and that shunt function is no longer compromised. This finding is supported by reports from other authors of higher complication rates when surgical intervention is performed at an early age [6, 20, 26, 38, 55] (Table16).

TABLE 16

Complications of VP shunts at different ages of insertion

Study	Obstruction with shunt insertion < 3 weeks	Obstruction with shunt insertion > 3 weeks
Boynton et al. [6] 1986	92%	60% P < 0.05
	Obstruction with shunt insertion < 8 weeks	Obstruction with shunt insertion > 8 weeks
Resch et al. [55] 1989	94%	44%
	Obstruction with shunt insertion < 5 weeks	Obstruction with shunt insertion > 5 weeks
Taylor 1999	47%	11% P < 0.01

When choosing the correct time for operative intervention surgeons must find a balance between early shunt insertion, in order to limit the damaging effects of hydrocephalus, and delaying surgery in an effort to minimise the complications. Despite a lack of evidence in the form of controlled trials randomising patients to early or late therapy for PHH most authors emphasise the need for early surgery [4, 6, 27, 34, 62, 76]. This position is based mostly on evidence of brain injury related to hydrocephalus observed in animal models and pathological evidence noted in adults and older children. Few clinical studies have demonstrated that early surgical treatment of PHH results in an improved outcome.

Liechty et al concluded that CSF shunting before 6 weeks resulted in a better neurological outcome than after this time [34]. In this study there were 8 patients in either the early or late surgery group and an outcome difference between them was shown in psychomotor development but not mental development (Bayley scales of infant development). The study was flawed however in that patients shunted after 6 weeks were treated in the first 2 years of the trial when routine grading of IVH was not performed. It is possible that this group contained more high-grade haemorrhages and that neonatal care was not as advanced as later in the study. The same problem is not addressed in two other studies showing good outcome after early surgery [4, 17]. Neither trial graded IVH which is the strongest predictor of outcome. Furthermore shunting was performed prior to one month of age when there is still a possibility that

hydrocephalus will stabilise [16, 42, 63]. It is therefore also possible that patients who did not require a shunt were operated on.

Contrary to this, there is a large body of evidence showing that outcome is not altered by the timing of surgical intervention [6, 11, 16, 33, 39, 54, 76]. Resch et al. compared outcome in patients shunted before 6 weeks (n=7) and those shunted after 6 weeks (n=12) and showed that patients in the late surgery group had a better prognosis although the difference was not significant [54]. Boynton et al. also demonstrated that early shunting is still associated with a high incidence of neurodevelopmental abnormalities. Ventriculoperitoneal shunts were placed at a mean age of 29 days in their study and outcome analysis showed that 60% of patients still had multiple handicaps [6]. Outcome data from the study presented here are insufficient to draw any conclusions from. Some reports have also shown worse neurological outcome after multiple shunt revisions and shunt infection in the treatment of PHH [54, 62]. As these complications are commoner after early surgery it is possible that early surgery may lead to a worse outcome.

By far the strongest predictor of outcome in patients' with IVH is the grade of haemorrhage that is sustained [16, 28,45]. This is also true of patients who develop PHH with the added prognosticators of seizures, multiple shunt revisions and infection [6, 11, 16, 20, 22, 24, 26, 33, 35, 38, 39, 54, 62, 76]. It is because the primary neurological insult of IVH has such a dominant influence on outcome that the role of other insults is hard to ascertain. Hydrocephalus undoubtedly causes secondary neurological injury but at which point this occurs or

becomes irreversible in the immature brain is unknown. It is possible that the complications of early surgical intervention have a more detrimental effect on the brain than early hydrocephalus.

Evidence from this study and the literature supports the contention that delayed VP shunting in PHH offers the definite advantage of reduced complications and possible advantage of improved outcome.

CONCLUSION

Consideration should be given to delaying the insertion of a VP shunt until 5 weeks of age in infants with PHH. This gives time for stabilisation and regression of hydrocephalus in some patients, obviating the need for surgery. It also allows the ventricles to clear of blood improving the chances of normal shunt function and limiting the occurrence of infection. Based on evidence in the literature this period of delay does not appear to adversely affect neurological outcome.

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