Treatment and outcome of neonatal haemorrhagic brain injury

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Treatment and outcome of neonatal haemorrhagic brain injury

Behandeling en uitkomst van neonatale intracraniële bloedingen
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag 21 juni 2011 des middags te 4.15 uur

door

Annemieke Jacoba Brouwer

geboren op 18 november 1962
te Winschoten

Promotor: Prof. dr. L.S. de Vries

Co-promotor: Dr. F. Groenendaal

Roezegar ast ke ghah ezzat dehad.
Ghah ghar darad.
Zo doet het leven.
Het speelt met je.
Tjarge bazighar azin bazitjeha.
Besjaar darad.
Soms heeft het je lief.
Soms vernedert het je.
"Het huis van de moskee" Kader Abdolah

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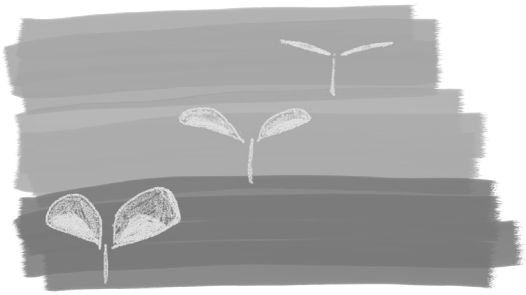
General Introduction



Germinal Matrix Intraventricular haemorrhage (GMH-IVH) remains the most common, neurological complication of premature birth, occurring in roughly 25%-30% of preterm infants with a gestational age below 30 weeks.[1] The presence of an IVH grade III and IV is one of the most important predictors of neurological outcome in preterm infants.[2,3] Post haemorrhagic ventricular dilation (PHVD) occurs in 25%-50% of all preterm infants with an IVH grade III or grade IV.[4] The presence of associated white matter injury, either a grade IV haemorrhage or more diffuse changes in the white matter and development of PHVD are two significant problems and increase the risk for an adverse neurodevelopmental outcome. Preterm infants with PHVD tend not to present with signs of raised intracranial pressure due to the open fontanelle and compliance of the neonatal brain.[5] Early recognition of PHVD therefore mainly depends on sequential cranial ultrasound.

Cerebrospinal fluid (CSF) is mainly produced by the choroid plexus in the lateral ventricles and the roof of the third ventricle. Following a large intraventricular haemorrhage, multiple clots may obstruct the reabsorption of CSF. Following the onset of a large IVH, there may be a period of reduced CSF production for some days, but when CSF production returns, the lateral ventricles will start to enlarge.[6] Progressive ventricular dilatation tends to occur during the second week after birth. The progressive accumulation of CSF will change the shape of the lateral ventricles from slit like to a balloon shape. The expanding ventricles may distort the white matter adjacent to the lateral ventricle and the intracranial pressure will eventually start to rise. The normal CSF pressure does not exceed 6 mmHg.[7] As the preterm skull is very compliant, the ventricles can expand without an initial rise in pressure but eventually the pressure can be as high as 10-15 mm Hg.[7]

Treatment of PHVD in preterm infants is more complicated than in any other type of hydrocephalus, because of the large amount of blood in the ventricular system and the high protein level in the CSF combined with the small size and instability of the patient. All these factors make early placement of a ventriculoperitoneal shunt (VP shunt) more difficult.

Neuroimaging / Diagnosis

Cranial ultrasound (cUS) is the method of first choice in the diagnosis of GMH-IVH. Ultrasonography can reliably detect all grades of GMH-IVH, from isolated germinal matrix haemorrhage to a major IVH, with or without periventricular haemorrhagic infarction. [1] Four grades identified for GMH-IVH, according to the classification of IVH by Papile, based on computed tomography (CT) examination [8] are:

Grade I or mild haemorrhage is confined to the germinal matrix without evidence of blood in the ventricular lumen.

Grade II or moderate germinal matrix haemorrhage involves minimal filling (10-40%) of the lateral ventricles with little or no ventricular enlargement.

Grade III or severe germinal matrix haemorrhage is associated with substantial filling of the lateral ventricles (>50%) with acute ventricular enlargement.

Grade IV or periventricular haemorrhagic infarction is an IVH associated with an intraparenchymal haemorrhage.

As this classification was based on CT, an adapted classification, based on cranial ultrasound scan was proposed by Volpe [1]:

Grade I: Germinal matrix haemorrhage with no or minor intraventricular haemorrhage (<10% of ventricular area on parasagittal view)

Grade II: Intraventricular haemorrhage (10%-50% of ventricular area on parasagittal view)

Grade III: Intraventricular haemorrhage (>50% of ventricular area on parasagittal view; with acute dilatation of the lateral ventricle)

Additionally a separate notation is made for *Intraventricular haemorrhage and apparent periventricular haemorrhagic infarction.*

Intervention and therapy

There are different ventricular parameters on cUS which can be used to diagnose PHVD. The measurement of the ventricular index [9] is the most commonly used parameter in the diagnosis of PHVD.[10] Other parameters are the anterior horn width (AHW) and the thalamo-occipital distance (TOD). The AHW is measured in a coronal view as the distance between the medial wall

and floor of the lateral ventricle at the widest point [11]. The TOD is measured in the parasagittal view; the TOD is measured from the outermost point of the thalamus, at its junction with the choroid plexus, to the outermost part of the occipital horn posteriorly. [11] (Fig 1)

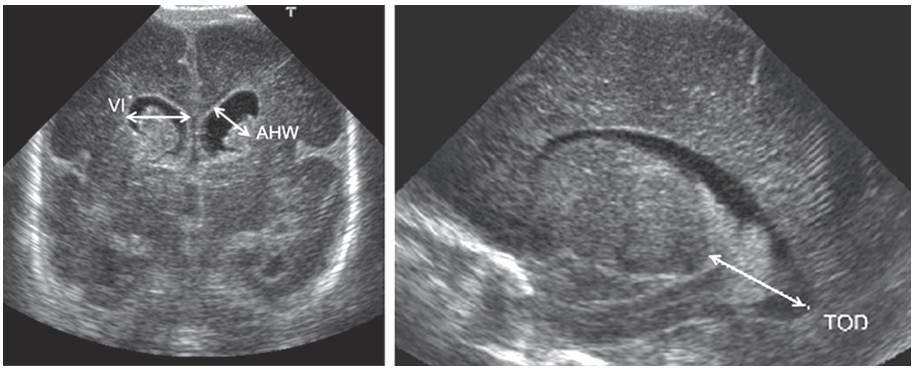


Figure 1: VI: ventricular index, AHW: anterior horn width and TOD: thalamo-occipital distance

At present there is no consensus regarding optimal timing or type of (neurosurgical) intervention to treat PHVD. Clinical management of PHVD varies greatly among centres, even among individual clinicians at any single centre.[12]

Lumbar punctures or ventricular taps. Repeated lumbar punctures (LP) have been advocated as the first method to treat rapidly progressive ventricular dilatation. There is, however, discomfort for the infant and a risk of almost ten percent for subsequent development of meningitis. [13,14] There is no evidence that early tapping of CSF by early lumbar or ventricular punctures reduces the risk of shunt dependence, disability, multiple disability or death.[13] The use of repeated lumbar or ventricular punctures was however associated with an increased risk of central nervous system infection. Lumbar punctures are often not successful and the amount of fluid, which one expects to drain, is often not obtained. Less often aqueductal stenosis is present, which makes it impossible to perform a successful LP, and one will therefore sometimes decide to perform a

ventricular puncture instead. Ventricular punctures do however have the risk of needle tracks and when many ventricular taps are performed the needle tracks may coalesce and form a porencephalic cyst like lesion. (Fig 2)

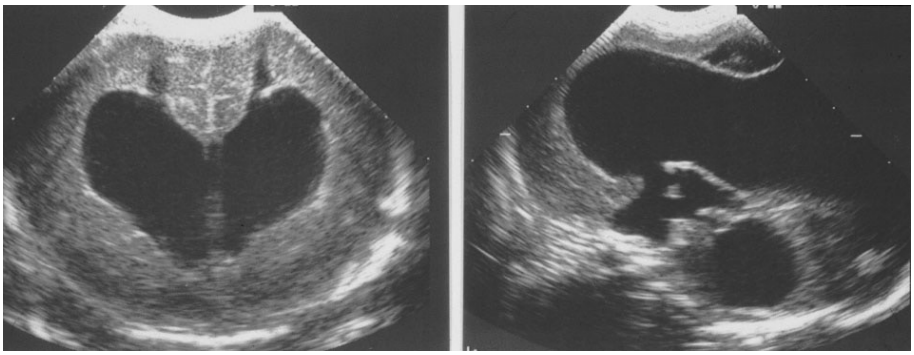


Figure 2: Utrasound, coronal view (left), showing needle tracks following bilateral ventricular taps. The mid sagittal view (right), shows a very dilated third and fourth ventricle, suggesting outflow obstruction at the level of the foramina of Luschka and Magendie

Drug treatment to reduce CSF production. [15] Acetazolamide and furosemide, which both reduce the production of CSF, have been suggested as non-invasive therapies to reduce the risk to develop hydrocephalus and the need for a VP shunt. Two RCT's [16,17] have been performed and both were unable to show a beneficial effect. [18] There was no decreased need for a VP shunt or death with acetazolamide and furosemide therapy. Acetazolamide and furosemide therapy were neither effective nor safe in treating PHVD, and can therefore not be recommended as therapy for post haemorrhagic hydrocephalus. [19] Isosorbide is another drug, investigated in a trial by Lorber et al. [20-22], treating various types of childhood hydrocephalus for long periods. Infants with moderate hydrocephalus usually respond well to isosorbide, adverse effects were uncommon, mild or moderate, and reversible on stopping treatment or reducing the dosage. Lorber concluded that isosorbide did not replace surgery, and was less effective than surgery.

Intraventricular fibrinolytic therapy. Treatments involving fibrinolytic agents carry a high risk of triggering new haemorrhages. Two RCT's have been conducted [23,24], both evaluating intraventricular streptokinase in infants who developed PHVD. The numbers of deaths and infants with shunt dependence were similar in the control group and treatment group. There was cause for concern about meningitis and a secondary IVH, but numbers were too small to quantify the risks [23,24]. It is therefore not recommended to use intraventricular fibrinolytic therapy before one month of age in infants developing PHVD. [25]

Ventricular Access Device (VAD). Insertion of a subcutaneous ventricular access device (VAD), to facilitate repeated tapping of adequate CSF volumes, is widely practiced, without having been tested in a randomised trial. A recent retrospective multicentre study [12] presented evidence that the use of VADs appeared to have a lower incidence of subsequent permanent shunt placement than that associated with subgaleal reservoirs. In the study of Limbrick et al. [26] there was no difference in the number of infants who required a VP shunt following either insertion of a VAD or a subgaleal reservoir. The VAD is a frequently used method in the management of PHVD; it avoids the risk of producing repeated needle tracks throughout the brain. Reservoirs can be tapped several times a day, but two taps per day is usually sufficient. An important drawback of VADs is that the removal of CFS is intermittent, resulting in a gradual increase of intracranial pressure (ICP) between taps, and there is a modest risk of infection. [27,28]

Subgaleal shunt. There is limited literature available about this type of intervention. In one study the placement of ventriculo-subgaleal shunts was effective as a temporary method for withdrawal of CSF. [29] However, in this study the subgaleal shunt was associated with an unacceptably high CSF infection rate (66.6%). A potential cause for infection is CSF stasis just beneath the extremely thin skin of the premature infant, promoting colonization by skin flora. More research is needed before this form of intervention can be recommended.

External ventricular drain (EVD). Placement of an EVD has also been used as the next invasive step in the management of PHVD. The catheter is tunnelled underneath the skin before it is placed in the dilated ventricle and is subsequently connected to a drainage system. The main complication is infection. In the literature infection rates vary from unacceptably high rates: 20-50% [30] to very low rates (0%).[31,32] The risk is especially increased when the external drain is present for more than 10-14 days. The use of antibiotic-impregnated shunt (AIS) system has been recommended to reduce the risk of infection.[33] Catheter related infection has been shown to be an independent predictor for poor neurodevelopmental outcomes. [1]

Ventricular lavage (DRIFT). The DRIFT (drainage, irrigation, and fibrinolytic therapy) procedure attempts to remove intraventricular blood, inflammatory cytokines, and iron that are associated with hydrocephalus before it becomes established. The results were promising in the first study [34], with only 26% of the infants needing a VP shunt. This first study was followed by a RCT [35], which unfortunately had to be stopped before all infants could be enrolled, because of a significant increase in secondary IVH in the DRIFT group compared to the standard group. DRIFT did not reduce the need for VP shunt surgery or death in preterm infants with ventricular dilatation after IVH when compared with tapping of CSF, usually from a subcutaneous reservoir. It was concluded that secondary IVH was a factor that counteracts the possible benefits from washing out old blood, and is therefore at present not recommended. Although DRIFT did not significantly lower the need for shunt surgery, severe cognitive disability at 2 years Bayley (Mental Developmental Index < 55) was significantly reduced. Median MDI was improved by more than 18 developmental points in the DRIFT group. [36] The DRIFT technique is now referred to as *ventricular lavage*.

Ventriculoperitoneal shunt: When all methods mentioned above fail, the definite treatment for hydrocephalus in preterm infants is still the VP shunt. Most neurosurgeons will first insert a VP shunt, once the infant has a weight of at least 2 kg. There are many problems with this method. Firstly, the surgical

treatment is still complicated by high revision rates. Shunt failure rates are high in this group of patients, with failure rates of 39% during the first year, up to 53% over a 2 year period. [37] Correlations were seen between the number of shunt revisions and outcome; number of neuroimpairments and fine motor development. [38] Secondly, the prematurity of the patients and their relatively incompetent immune system favours shunt infections.[30,39] The infection rates for shunts inserted in patients younger than 6 months is about 16 percent and is almost three times higher than that for children when they are older (5.6%).[40]

Neurodevelopmental outcome

Despite a decrease in mortality, the risk of subsequent adverse neurodevelopmental outcome remains high among surviving infants with a large intraventricular haemorrhage. The risk of a poor outcome has been reported to increase with the presence of PHVD following a large GMH-IVH (40-60%) and even further in those who require insertion of a VP shunt (75-88%) [14,38] Preterm infants who suffer from a grade III-IV IVH are at high risk for CP and also subsequent cognitive impairment. [4,41-43] This is partly due to associated lesions, present in the brain parenchyma before the onset of PHVD. It is however also likely that some of the dysfunction is the result of prolonged periods of raised intracranial pressure which has been shown to lead to periventricular oedema and distortion of the developing axonal pathways and impaired myelination in animal models.[44] Timing and best methods of treatment of PHVD remain an unsolved issue in the neonatal intensive care unit.[45]

Intracranial haemorrhage in the full-term infant

While subarachnoid haemorrhage, IVH and cerebellar haemorrhages are more commonly seen in the preterm infant, subdural haemorrhage (SDH) and intraparenchymal haemorrhage are more often diagnosed in the term infant.[46]

Intracranial haemorrhage (ICH) in the term infant, including SDH, with or without parenchymal involvement, used to be a common cause of neonatal death following a traumatic delivery, but the incidence has decreased with improved obstetric care. In recent years subdural haemorrhage is more often recognized,

mainly because neuro-imaging by magnetic resonance imaging (MRI) is now also performed routinely in infants not presenting with clinical symptoms.[47] ICH in the term infant usually presents with non-specific neurological signs and symptoms. Signs can be non-specific and may not point directly to the brain as the source of the problem.[48] ICH in the newborn is frequently associated with a prolonged or precipitous delivery, a vaginal breech delivery, an instrumental delivery, using a forceps or ventouse extraction and primiparity or extreme multiparity. [48-51] Haemorrhage may be due to rupture of veins in the subdural space, with bleeding from the venous sinus or from haemorrhage within the cerebellum. [48] Accumulation of blood in the posterior fossa can cause neurological symptoms, which become manifest within the first few days after delivery, such as a tense or bulging fontanelle, increasing head circumference, apnoeas, bradycardia and/or seizures. [49] The true incidence of ICH is probably higher than reported, because only part of the infants with an ICH present with clinical symptoms. [47]

Aims and outlines of this thesis

The general aim of this thesis is to evaluate the treatment of infants with a GMH-IVH and subsequent development of PHVD, and to describe the neurodevelopmental outcome of these children.

Aims of this thesis are:

1. To gain insight in the different perspectives on the diagnosis and treatment of PHVD in European centres with a special interest in neonatal neurology. (Chapter 2)
2. To assess the incidence of infections of subcutaneous reservoirs in the treatment of PHVD in preterm infants. (Chapter 3)
3. To describe our unit's management of PHVD and report on the outcome of our pilot project of nurse-managed subcutaneous reservoir punctures. (Chapter 4)
4. To report the evolution and short-term neurodevelopmental outcome of preterm infants with GMH-IVH grade III and IV, using routine low-threshold intervention of associated PHVD. (Chapter 5)
5. To evaluate neurodevelopmental and cognitive outcomes at 5-8 years of age, among preterm infants who had a severe IVH (grade III or IV) and required neurosurgical intervention, either a subcutaneous reservoir and/or a VP shunt. (Chapter 6)
6. To describe precipitating factors, presenting symptoms and neuro-imaging data as well as neurodevelopmental outcome of full-term infants in whom an imaging diagnosis (CT or MRI) of ICH was made. (Chapter 7)

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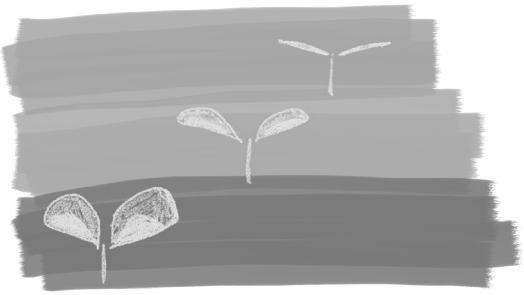
2

European perspective on the diagnosis and treatment of Post-Haemorrhagic Ventricular Dilatation



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Arch Dis Child, in press

ABSTRACT

Background: Post-haemorrhagic ventricular dilatation (PHVD) is a serious complication of prematurity with considerable subsequent disabilities. The diagnostic and therapeutic approaches to PHVD are known to vary among neonatal centres.

Aim: To gain more insight into the different diagnostic criteria and treatment policies on PHVD among Neonatal Intensive Care Units across Europe.

Methods: A questionnaire was designed, including sections related to the incidence, diagnostic criteria, timing and mode of intervention of PHVD, and sent out to neonatologists with a known interest in neonatal neurology in 37 European centres.

Results: A positive response was obtained from 32/37 (86.5%) centres located in 17 European countries. An overall estimated incidence of 7% was reported for severe intraventricular haemorrhages (IVH; grade III or IV according to Papile) among very premature neonates born below 30 weeks' gestation. About half of these infants developed PHVD, of whom three-quarter required intervention. Measurements of the ventricular size on cranial ultrasound were most commonly used to diagnose PHVD (93.8%). However, no consensus existed on which ventricular parameters needed to be enlarged and to what extent. The same applied for the timing of treatment of PHVD. Early intervention (i.e., initiated after the ventricular index (VI) exceeded the 97th percentile (p97) according to Levene) was provided in 8/32 centres (25.0%), whereas 23/32 centres (71.9%) first started therapy once the VI had crossed the p97+4mm line and/or when neonates presented with a progressive increase in head circumference or with clinical symptoms of raised intracranial pressure. Wide variation was seen with respect to the applied therapy modalities for cerebrospinal fluid drainage.

Conclusion: This study underlines the need to collaborate to achieve an international consensus on the diagnosis and intervention in neonates with PHVD. More uniformity in the diagnostic criteria of PHVD would facilitate eligibility and recruitment of sufficient numbers of infants to assess optimal timing and mode of intervention.

INTRODUCTION

A substantial number of survivors of preterm birth exhibit subsequent disabilities. A variety of intracranial lesions are known to account for a spectrum of cognitive and behavioural problems in 25-50% of the very low birth weight infants who survive, while major motor deficits occur in 5-10%.[1] Among the different lesions that may cause brain injury, severe intraventricular haemorrhage (IVH) grade III and IV according to Papile [2] and subsequent post-haemorrhagic ventricular dilatation (PHVD) pose a significant threat to the developing neonatal brain.[3-5] However, preterm infants who develop progressive PHVD in the absence of associated parenchymal lesions may have a normal neurodevelopmental outcome. In a recent retrospective cohort study, we found that 90% of the preterm born infants that were treated for PHVD following an IVH grade III had a Developmental Quotient (DQ) > 85 at 2 years corrected age.[6] As was to be expected, outcome was not so promising for those infants with PHVD following a grade IV haemorrhage. They more often had cognitive and motor impairments, and 49% went on to develop cerebral palsy; nevertheless, 67% of these infants with an IVH grade IV had a DQ > 85 at the age of 2 years. Results of other studies also suggest that the extent of associated parenchymal lesions is the main predictor for especially motor outcome in neonates with progressive PHVD.[7,8]

At present there is no consensus about optimal timing of intervention for PHVD. In the same retrospective study we observed that early intervention was associated with a reduced need for ventriculo-peritoneal (VP) shunt placement and a trend for a better cognitive outcome.[6] In the prospective randomised DRIFT (Drainage, Irrigation and Fibrinolytic Therapy) study, severe cognitive disability (Mental Development Index < 55) was significantly less common at the age of 2 years in those infants with PHVD who had received DRIFT intervention. [9] In addition to differences in timing and mode of intervention, diagnostic approaches to PHVD seem to vary among neonatal centres.

The aim of this study was to gain more insight in the diagnostic criteria and different treatment policies for PHVD among Neonatal Intensive Care Units across Europe.

METHODS

The survey was conducted between May and August 2010. An online questionnaire was designed, and the invitation to participate was sent by email to neonatologists with a known interest in neonatal neurology in 37 European neonatal centres. Questions did not request the personal opinion of the recipients but explored the formal protocols for the diagnosis and treatment of PHVD.

The questionnaire (see Appendix) included sections related to the diagnostic criteria for PHVD and the timing and mode of intervention. In addition, participants were asked how many very preterm infants (gestational age (GA) < 30 weeks) were admitted annually, how many of them developed a severe IVH (grade III or IV), how many subsequently developed PHVD and how many received intervention.

Since this study related to unit policies and not to clinical information of individual patients, requirements for informed consent and Ethics Committee approval did not apply.

RESULTS

A positive response was obtained from 32 out of a total of 37 European centres (86.5%), located in 17 different countries.

Incidence of PHVD

Incidence rates of severe IVH (grade III and IV) and PHVD were reported by 27/32 respondents. Most respondents provided estimates of the last 1-3 years. Severe IVH was diagnosed in less than 10% of the neonates below 30 weeks' GA in most centres (range 3-20%). About half of these infants subsequently developed PHVD, of whom three-quarter required any type of CSF drainage (Figure 1). The majority of centres treated less than 5 preterm infants with progressive PHVD each year.

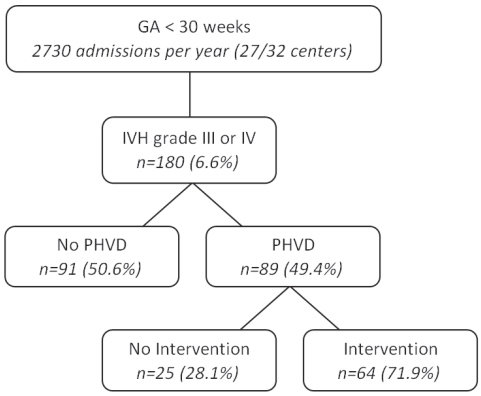

Figure 1: Estimated incidence rates of severe intraventricular haemorrhage (IVH) (grade III or IV) and post-haemorrhagic ventricular dilatation (PHVD) in very preterm infants below 30 weeks' gestational age (GA) in 27/32 of the responding centres; a distinction is made between infants with progressive PHVD who received any type of intervention and infants with PHVD receiving no intervention.

Diagnosis of PHVD

The diagnosis of PHVD was based on measurements of ventricular size by cranial ultrasound (cUS) in 93.8% of the centres (Figure 2). In infants with an IVH, cUS was conducted twice a week in most centres (range: daily – once a week). Once PHVD had been diagnosed, cUS was performed more frequently, mainly daily or every other day; a few centres, however, continued performing cUS once a week.

In more than half of the centres (n=18), the diagnosis of PHVD was exclusively based on the ventricular index (VI) and corresponding reference curve according to Levene.[10] In 10 centres, the VI was measured in combination with additional ventricular dimensions. The anterior horn width (AHW) was assessed by 8 respondents, using either the reference curve of Davies et al. [11] or – less often – Couchard et al. [12]. A few centres measured the frontal horn ratio (FHR) [13] or took occipital horn size (thalamo-occipital distance, TOD) [11] into account. The diagnosis of PHVD was based on visual assessment of ventricular shape and the presence of ballooning on either cUS or computed tomography in 2 centres (Table 1).

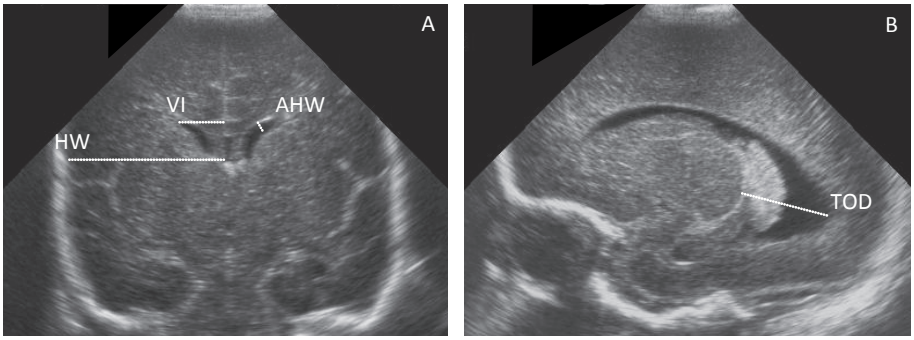

Figure 2: Measured ventricular parameters on cranial ultrasound (cUS) to diagnose post-haemorrhagic ventricular dilatation (PHVD).

A) Measurements of the anterior horn width (AHW) - the maximal diagonal width of the anterior horn -, the ventricular index (VI) - the distance between the falx and the lateral wall of the anterior horn - and the frontal horn ratio (FHR) – the ratio between the VI and corresponding hemispheric width (HW) – in the coronal plane at the level where the AHW appears maximal.

B) Measurement of the thalamo-occipital distance (TOD) - the distance between the outermost point of the thalamus at its junction with the choroid plexus and the outermost part of the occipital horn posteriorly – in the parasagittal plane.

Table 1: Diagnostic approach to PHVD; n (%)

Measurement ventricular size on cUS	**30/32**	**(93.8)**
AHW	1/30	(3.3)
FHR	1/30	(3.3)
VI	18/30	(60.0)
VI+AHW	4/30	(13.3)
VI+TOD	3/30	(10.0)
VI+AHW+FHR	1/30	(3.3)
VI+AHW+TOD	2/30	(6.7)
Visual assessment ventricular shape on cUS orCT	**2/32**	**(6.2)**

AHW: anterior horn width, CT: computed tomography, cUS: cranial ultrasound, FHR: frontal horn ratio, TOD: thalamo-occipital distance, VI: ventricular index

There was wide variation among the respondents regarding the criteria to diagnose PHVD. The thresholds for ventricular size that were most often applied were either a VI above the 97th percentile (p97) according to Levene or a VI exceeding the p97+4mm line (Table 2).[10]

Table 2: Criteria to diagnose PHVD; n (%)

Enlarged ventricular size on cUS	**30/32**	**(93.8)**
VI>p97	13/30	(43.3)
VI>p97 and ballooning	1/30	(3.3)
VI>p97 and AHW>6mm	1/30	(3.3)
VI>p97, AHW>6mm and/or TOD>24mm	1/30	(3.3)
VI>p97, AHW>5mm and 3rd ventricular width>4-5 mm	1/30	(3.3)
VI>p97 and aqueduct diameter>5mm	1/30	(3.3)
VI>p97+4mm	9/30	(30.0)
VI>p97+4mm and ballooning	1/30	(3.3)
AHW>5-10mm (moderate); >10mm (severe)	1/30	(3.3)
FHR>10x8mm	1/30	(3.3)
Visual assessment of ventricular ballooning on cUS or CT	**2**	**(6.2)**

AHW: anterior horn width, FHR: frontal horn ratio, TOD: thalamo-occipital distance, VI: ventricular index

In addition to measurements of the lateral ventricles, 7 respondents took into account the size of the third ventricle; 6 respondents measured both third- and fourth ventricular size.

Timing of intervention

The decision whether or not to start intervention, and when, was mainly based on ultrasound measurements of ventricular size in 20 centres. A rapid increase in head circumference (HC) (1.0-2.0 cm per week, depending on the centres' criteria) and clinical symptoms of raised intracranial pressure (ICP) (e.g., a bulging fontanel, apnoeas and/or seizures) were the main indications for cerebral spinal fluid (CSF) drainage in 3 and 6 centres, respectively. For another 3 respondents, the decisive factor was the presence of cerebral blood flow velocity abnormalities, recorded using Doppler ultrasound measurements.

Early intervention – defined as intervention once the VI has crossed the p97 line according to Levene – was used by a quarter of the respondents.[10] In the other centres, therapy was first started after the VI had exceeded the p97+4mm line (late intervention), when a more marked increase in AHW was noted, and/or when neonates presented with a progressive increase in HC or with clinical symptoms of raised ICP. Isolated dilatation of the occipital horns (TOD > 24mm) was regarded as an indication for treatment in 2 centres (Table 3).

Table 3: Criteria to start intervention in neonates with progressive PHVD; n (%)

Early intervention	**8/32 (25.0)**
VI>p97	6
VI>p97, AHW>6mm, TOD>24mm (ELVIS)	2
Late intervention	**23/32 (71.9)**
VI>p97+4mm	12
VI>p97+4mm + increased HC and/or clinical symptoms raised ICP	6
AHW>10mm + overt 3rd ventricular dilatation	1
FHR>10x8 mm + ballooning	1
Increased HC + ballooning and transependymal exudation on CT	1
Increased HC and/or clinical symptoms raised ICP	2
Missing	**1/32 (3.1)**

AHW: anterior horn width, ELVIS: early versus late intervention study, FHR: frontal horn ratio, HC: head circumference, ICP: intracranial pressure, TOD: thalamo-occipital distance, VI: ventricular index

Treatment modalities

When CSF drainage was considered necessary in neonates with progressive PHVD, the majority of respondents (26/32, 81.3%) started with lumbar punctures (LPs). Six centres (18.7%) started with placement of either a subcutaneous ventricular reservoir (n=3) or an external drain (n=3). Osmotic diuretics (isosorbide or acetazolamide) were administered before or in addition to CSF drainage in 2 centres (Table 4). In general, the infants' GA did not influence the offered treatment.

Table 4: Applied treatment modalities in neonates with progressive PHVD; n (%)

Osmotic diuretic	2/32	(6.3)
Lumbar puncture	26/32	(81.3)
Ventricular tap	11/32	(34.4)
Subcutaneous ventricular reservoir	21/32	(65.6)
Subgaleal shunt	1/32	(3.1)
External drain	11/32	(34.4)
Ventriculo-peritoneal drain	32/32	(100.0)
Ventricular lavage (DRIFT)	2/32	(6.3)
Ventriculocisternostomy	1/32	(3.1)

Most centres performed a few LPs (median: 3, range: 1-20) before switching to any surgical intervention, depending on the effectiveness of the LPs in decreasing ventricular size or ICP. Five centres did not limit the number of LPs, but continued to do LPs until they were no longer effective due to a lack of communication or until the infant's weight and CSF protein content were appropriate to place a VP-shunt.

All centres consulted a neurosurgeon once ventricular taps or placement of a ventricular reservoir, subgaleal shunt, external drain or VP-drain were required. In 4 hospitals, infants had to be transferred to another centre for neurosurgical intervention. In the other hospitals, either a paediatric neurosurgeon (16/28, 57.1%) or general neurosurgeon (12/28, 42.9%) was on service for neurosurgical interventions. Prophylactic antibiotics (i.e., amoxicillin+clavulanate, ampicillin, cefazolin, cefuroxim, flucloxacillin in combination with gentamycin, teicoplanin or vancomycin) were administered in 65.6% of the centres (21/32) prior to neurosurgical intervention. (3 missing)

Neonates with isolated occipital horn dilatation were treated in 2/32 centres (6.3%) with either an osmotic diuretic agent (isosorbide or acetazolamide) or a combination of an osmotic diuretic agent and additional CSF drainage in case of progressive dilatation or signs of raised ICP.

Ventricular reservoir

Twenty-one centres used a ventricular reservoir (65.6%). Punctures from the reservoir were mainly performed by the attending neonatologist (n=18), resident (n=11) and/or neurosurgeon (n=6). In a few hospitals, physician assistants (n=2), advanced neonatal nurse practitioners (n=2) and nurses (n=1) also performed punctures.

Reservoir punctures were in 90.5% of the centres (19/21) carried out under strict aseptic conditions, including hand scrubbing and the use of a cap, mask and sterile gown and gloves, whereas the protocol in 2 hospitals only prescribed hand washing and the use of gloves. While 38.1% of the respondents (8/21) allowed the CSF to drop freely from the needle following insertion into the reservoir, 61.9% (13/21) attached the needle to a syringe and used gentle suction. The most common approach was to withdraw 1 ml/min, aiming for 10 ml/kg (n=14). Others either stopped the procedure when 10 ml/kg CSF had dropped freely from the needle (n=2) or used a time limit of fifteen minutes for CSF withdrawal, irrespective of the amount of fluid that had been removed (n=4). (1 missing)

Ventriculo-peritoneal shunt

With respect to placement of a VP-shunt, different indications were reported (Table 5). A combination of bodyweight and concentration of protein in the CSF was most frequently considered when deciding whether insertion of a VP-drain could be performed (17/32, 53.1%). Either bodyweight or the CSF protein concentration was the main criterion in 8/32 (25.0%) and 5/32 (15.6%) centres, respectively. (2 missing) The minimal bodyweight required to insert a VP-drain varied between the hospitals from 1000-3000 grams. Thresholds for CSF protein concentration ranged between 1.0 g/L and 1.5 g/L. In one centre, the concentration of erythrocytes in the CSF was evaluated in addition to the bodyweight, and this had to be less than 100/mm^3.

Table 5: Indications for placement of a VP-drain; n (%)

When taps from reservoir are still needed > 4 weeks	10/32 (31.3)
When taps from reservoir are still needed > 4 weeks + clinical symptoms of raised ICP and/or increased HC	7/32 (21.9)
Clinical symptoms of raised ICP and/or increased HC	5/32 (15.6)
When trying to stop tapping has failed	3/32 (9.4)
When trying to stop tapping has failed + clinical symptoms of raised ICP and/or increased HC	1/32 (3.1)
More than 4 lumbar punctures	1/32 (3.1)
Missing	5/32 (15.6)

HC: head circumference, ICP: intracranial pressure (ICP)

DISCUSSION

This questionnaire offers insight into the variety of different perspectives regarding the diagnosis and treatment of PHVD among 32 neonatal centres with a special interest in neonatal neurology in 17 European countries. From this survey, it can be concluded that there is considerable variation in the diagnostic and therapeutic approaches to neonates with PHVD.

According to these data, the pooled estimated incidence of severe IVH (grade III or IV) was 7% among neonates born below 30 weeks' gestation. In the literature, the incidence of severe IVH in preterm infants with a GA < 30 weeks or a birth weight < 1500 gram varies between 7-18%.[14-18] Almost half of the very preterm infants that were diagnosed with a severe IVH developed subsequent PHVD, which is line with previous reported data.[1] Of these neonates, about three-quarter required intervention for their PHVD.

Measuring ventricular size on cUS was the most common method to diagnose PHVD. However, there was no consensus on which ventricular parameters needed to be enlarged and to what extent. The same applied to the timing and mode of intervention. Some centres advocated early intervention, initiated when the VI had crossed the p97 line according to Levene but had not yet reached the p97+4mm line, whereas others started intervention only once the VI had exceeded the p97+4mm threshold or in neonates who showed symptoms of an increased ICP.[10] When CSF drainage was deemed necessary, LPs were most often considered

as intervention of first choice, whereas placement of a VP-shunt, in general, was the last treatment option after failure of other therapeutic interventions. Consensus was missing regarding the use of other treatment modalities for CSF drainage. Differences in the organisation of neonatal care among hospitals may to some degree account for the reported variety. Whether or not an infant has to be transferred to another hospital for neurosurgical treatment, as well as the availability of specialized NICU care, will be taken into account when deciding for a specific type of intervention or placement of a particular ventricular device. Ethical considerations and personal beliefs may also play a role. Neurosurgeons may be less willing to place a shunt or reservoir in extremely low birth weight infants or in infants who lack clinical symptoms of a raised ICP (e.g., a bulging fontanel) or a rapid increase in head circumference, even though a raised ICP is unlikely to be present in the context of these signs in the preterm infant.[19] Concerns for an increased risk of infection following placement of a ventricular device may also affect decisions that have to be made. Due to a high number of missing answers (40.6%), it is not possible to draw conclusions from this survey regarding the infection rate associated with reservoirs and VP-drains, which varied significantly from 0-50%.

Since the last decades, the amount of research focussing on gaining more evidence for distinct treatment approaches has been increasing. Several studies have investigated optimal timing of intervention[20,21], and currently, the prospective randomized ELVIS trial (Early versus Late Ventricular Intervention Study, trial number: ISRCTN43171322) is conducted to assess the potential beneficial role of early intervention (i.e., initiated once the VI has crossed the p97 line according to Levene) over late intervention (i.e., initiated after the VI has exceeded the p97+4mm line)[10]. A few randomized controlled trials have been conducted to gain evidence for the role of diuretics.[22,23] Others have focussed on the specific benefits of several modalities of CSF drainage, but conclusions regarding the optimal treatment approach varied.[9,24 -26] A common concern among neonatal centres is the risk of infections associated with neurosurgical interventions and devices. Results of recent studies that considered infections following neurosurgical treatment are, however, reassuring and suggest that concerns for ensuing infections should not be a limiting factor.[27-29]

Several limitations should be considered with regard to this survey. The centres participating in this survey only represent a part of neonatal centres across Europe. Hence, no conclusions can be drawn regarding the diagnostic and therapeutic approaches for PHVD in other European hospitals or outside Europe. In addition, the provided incidence rates for severe IVH and PHVD should be interpreted as estimates. Management in individual centres may have been limited by available treatment modalities and specialists. From this questionnaire it was, however, not possible to determine to what extent this did influence the choice for a particular approach to infants with PHVD.

In general, the results of this study underline the need to collaborate on an international consensus on the diagnosis and treatment of neonates with PHVD. More uniformity in diagnosing PHVD would be a significant step forward. Management of infants with PHVD is controversial because the benefits of any specific treatment regimen have not yet been established. More research is needed to define optimal timing of intervention and the most preferable treatment strategy. The use of cUS on a regular basis is recommended to monitor the rate of progression of PHVD and to evaluate the effectiveness of therapy. Since most hospitals treat only a few neonates with progressive PHVD each year, centralization of care in specialized centres with neonatal intensive care and neurosurgery on site will be important to gain more experience, develop expertise and maintain consistency in the management of infants with PHVD, thus optimizing care. In addition, collective registration of data regarding the infection rates associated with the different ventricular devices would be of great value, since little is known about these specific infection risks.

At present, several centres in Europe are involved in the ELVIS study. Awaiting the results of this randomized trial, we hope the ELVIS protocol may be an impetus to a European protocol for the diagnosis and treatment of PHVD to achieve optimal care and neurodevelopmental outcome of these neonates.

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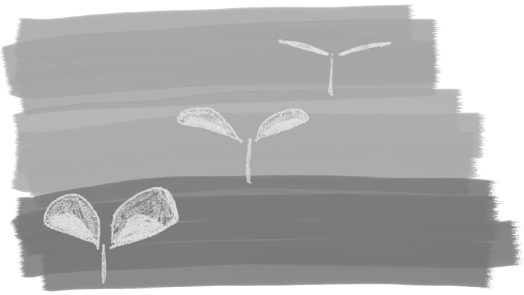
APPENDIX

Please, find attached the weblink to the questionnaire. https://spreadsheets.google.com/viewform?hl=en&pli=1&formkey=dEZDNm4yWndRRjFORnl4QjNvcVh5dXc6MA

3

Incidence of Infections of Ventricular Reservoirs in the Treatment of Post- Haemorrhagic Ventricular Dilatation: A Retrospective Study (1992-2003)



AJ Brouwer
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M Verboon-Maciolek
P Hanlo
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SUMMARY

Background: Since 1992, infants with a progressive post-haemorrhagic ventricular dilatation (PHVD) have been treated in the Neonatal Intensive Care Unit, Wilhelmina Children's Hospital, Utrecht, The Netherlands, with a ventricular reservoir.

Objective: To retrospectively study the incidence of infection using this invasive procedure.

Methods: Between January 1992 and December 2003, 76 preterm infants were treated with a ventricular reservoir. Infants admitted during two subsequent periods were analysed, group 1:1992-1997 (n=26) and group 2 those admitted during1998-2003 (n=50). Clinical characteristics and number of reservoir punctures were evaluated. The incidence of complications over time was assessed, with a focus on the occurrence of infection of the reservoir.

Results: The number of punctures did not change during both periods. Infection was significantly less common during the second period (4% (2/50) *v* 19.2% (5/26), p=.029).

Conclusion: The use of a ventricular reservoir is a safe treatment to ensure adequate removal of cerebrospinal fluid (CSF) in preterm infants with PHVD. In experienced hands, the incidence of infection of the ventricular reservoir or major complications remains within acceptable limits.

Keywords: neonate, prematurity, hydrocephalus, ventricular reservoir, infection

Abbreviations: CSF: Cerebrospinal fluid, GMH-IVH: Germinal Matrix-Intraventricular Haemorrhages, PHVD: post-haemorrhagic ventricular dilatation.

INTRODUCTION

Germinal Matrix-Intraventricular Haemorrhages (GMH-IVH) in the neonatal period are an important clinical problem. Although the incidence of IVH has decreased over the last decade, it is still a common problem in the very low birth weight infant.[1]

About 30-50% of infants with an IVH develop post-haemorrhagic ventricular dilatation (PHVD); the more severe the GMH-IVH, the higher the risk of developing PHVD.[2-4] PHVD usually develops within 10 - 20 days after the onset of the GMH-IVH. Ventricular dilatation, seen using cranial ultrasonography, precedes the development of clinical symptoms by days or even weeks. The clinical signs are a full fontanelle, diastases of the structures and a rapid increase in head circumference. Once it has been recognised that the ventricles are enlarged, frequent assessments by ultrasonography are mandatory. The most widely adopted measurement system is that of Levene and Starte, which measures the ventricular width.[5] Another measurement that is increasingly being used is the anterior horn width.[6]

Repeated lumbar or ventricular punctures have been proven to be ineffective in the treatment of PHVD. Others therefore choose to use an external drain or a subcutaneous reservoir.[7]

The aim of the present study was to retrospectively assess the incidence of infections of ventricular reservoirs in the treatment of PHVD in preterm infants.

PATIENTS AND METHODS

Patients

Between January 1992 and December 2003, a total of 76 preterm infants with a ventricular reservoir were studied. We specifically looked at the incidence of infection of the reservoir in these children. We compared two periods: 1992-1997 (group 1, n=26) and 1998-2003 (group 2, n=50). The period of 12 years was divided into two periods of 6 years to examine whether there were any

significant differences over time. We started this treatment policy in 1992 and gained a great of experience over the years. Owing to an increased number of referrals for this procedure, which is performed only in 4 of the 10 Dutch neonatal intensive care units, the number of infants in the second period is twice that in the first 6-year period. (Fig.1)

The notes were reviewed for the clinical characteristics and the number of punctures from the reservoir. Data regarding the total number of punctures were missing for five children, because of incomplete (administrative) data. Clinical characteristics, the number of punctures and the occurrence of infection were compared between the two groups.

Informed parental consent was obtained from the parents before insertion of the reservoir.

PHVD treatment

The policy in the Neonatal Intensive Care Unit, Wilhelmina Children's Hospital, Utrecht, The Netherlands, is to carry out lumbar punctures in those infants who develop PHVD, especially when there is a rapid progression of the ventricular size usually associated with a change in anterior horn width leading to a change in ventricular shape, the so-called 'ballooning', both changes suggestive of raised pressure in the ventricular system. If PHVD is not stabilised in the following 5-10 days despite of daily lumbar punctures, or when lumbar punctures are not successful, a ventricular reservoir is inserted by the paediatric neurosurgeon to enable further control of the intracranial pressure.[8] In our unit, this treatment is often combined with the administration of isosorbide (8 g/kg/day in six doses), an osmotic diuretic that reduces the production of cerebrospinal fluid (CSF).

Ventricular reservoir

During the whole study period, prophylactic intravenous vancomycin was given to all infants for a period of 48 h, and the first dose was given 1 h before placement of the reservoir. A strict sterile procedure was followed during the puncture by the reservoir; sterile gloves, mask and hood, sterile gown and sterile materials. The extent of the PHVD was assessed on the basis of a daily ultrasound

examination, and it was decided how often and how much CSF needed to be removed. Routinely, we start with withdrawal of 10 ml/kg CSF, divided over two taps. The amount of CSF removed is adjusted every day according to the ultrasound findings. CSF is removed at a rate of 1 ml/min to reduce the risk of rebleeding. The ventricular reservoir is not removed when tapping is no longer required, as the surgical removal of the reservoir is an extra procedure which can give rise to complications such as leakage of CSF.

Furthermore, the reservoir can be used for evaluation of the intracranial pressure in case of delayed symptoms of slowly progressive ventricular dilatation.

Routinely the CSF was analysed for red cells, white cells, and total protein and glucose, and one CSF culture was undertaken per day. Diagnosis of infection was based on a positive CSF culture. Clinical symptoms of infection were observed.

When a ventricular reservoir infection was diagnosed, treatment with intravenous vancomycine in combination with other antibiotics (amikacine or ceftazidim) was started until the causative microorganism was identified. Thereafter, the antibiotic treatment was based on the resistance pattern of the causative micro organism.

Statistics

Differences between the groups for all variables were tested by Student's t test, Mann-Whitney U test, $\chi 2$ test and Cross tabs where appropriate. Data were statistically analysed using SPSS V.11.5 for Windows. Significance was set at a p-value of 0.05.

RESULTS

From 1992 to 2003, 76 preterm infants had an intraventricular reservoir inserted for treatment of their PHVD. The clinical characteristics, gestational age, birth weight, Apgar score and the male:female ratio (Table 1) between the two groups were comparable, as was the number of days of inserting the reservoir and the total number of punctures.

Table 1: Clinical characteristics of the study population

	Group 1 (n=26)	**Group 2 (n=50)**
Male / Female	12 / 14	24 / 26
Gestational age, wk (mean ± SD)	30.2 ± 2.8	30.2 ± 2.9
Birth weight, g (mean ± SD)	1465 ± 615	1480 ± 540
Apgar score at 1 min, median (range)	5 (1-9)	6 (1-10)
Apgar score at 5 min, median (range)	8 (4-10)	8 (5-10)
Number of punctures, median (range)	23 (6-126)	22 (5-117)
Day of placement of reservoir, median (range)	15 (1-49)	15 (1-86)

Infection occurred in 5 of the 26 (19.2%) infants in group 1 and in 2 of the 50 (4%) infants from group 2 (Fig 1). We found a significant decrease in the number of infants who developed an infection of the reservoir in group 2 compared with that in group 1 (p=.029). In five of these seven infants, *Staphylococcus epidermidis* was cultured from the CSF, sampled from the reservoir. The reservoir was not removed. After identification of *S epidermidis*, vancomycin was given intravenously to all infants for 9-16 days. In two infants *Candida albicans* was cultured from the CSF sampled from the reservoir. The reservoir was immediately removed, and both infants were given intravenous fluconazole for 16-24 days.

CSF analysis, carried out at the time of diagnosis of infection, showed pleocytosis in only two infants, 160×10^6/L and 167×10^6/L, respectively. None of the seven infants developed clinical symptoms of an infection.

We found no relationship between the number of punctures and the occurrence of an infection (p= .093); also, there was a wide range of the number of punctures (5 – 126).

In addition to infections, the ventricular reservoir had to be removed in 3 of 26 infants from group 1 and 1 of 50 infants from group 2. Revision of the reservoir was necessary in one patient from group 1 and in four patients from group 2. Placement of a second reservoir, due to lack of communication of the lateral ventricles, was required in one patient from each group. Dehiscence of the wound occurred in one patient from group 1 and in two patients from group 2. We found no significant difference in the occurrence of these problems in both groups (p=.504).

In all, 34 of 76 (44.7%) infants required a ventriculo-peritoneal drain: 12 of 26 (46%) from group 1, 22 of 50 (44%) from group 2. We found no significant difference between the groups regarding the number of infants who required a permanent ventriculoperitoneal drain (p= .858).

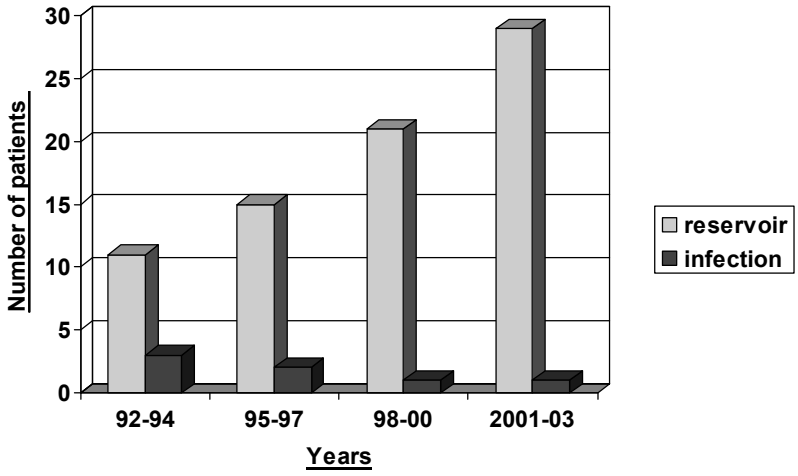

Figure 1: Number of infections of ventricular reservoirs

DISCUSSION

In this retrospective study we looked at the incidence of infections of ventricular reservoirs in preterm infants. The number of infants with an infection of the reservoir decreased considerably over the two 6-year periods. This marked decrease could be due to a several factors. Firstly, we gained a great deal of experience over the years in the removal of CSF using a subcutaneous reservoir. As soon as there was any regrowth of hair, the hair was removed by carefully shaving the area around the reservoir, which was the practice every fortnight. In the second second period (1998-2003), we were more careful to prevent the presence of hair in this area. After the operation, a transparent dressing (Tegaderm, 3M Health Care) was put over the wound and the reservoir, which

was not removed before the puncture in period 1, as opposed to the procedure in the second period. Secondly, in period 1 children were nursed in an open incubator or cradle, whereas in period 2 they remained in a closed incubator or in a hooded cradle to reduce exposure and excessive handling. Neither the technique of the puncture itself -cleaning the reservoir area before the puncture with iodine (Bethadine, Mandipharma, Basel/Switzerland) leaving it there for at least 1 min, cleaning the reservoir area after the puncture with 70% alcohol, covering the puncture place with a sterile gauze afterwards- nor the use of antibiotics has been changed. Since 1992 prophylactic vancomycine is administered intravenously for 48 h.

One of the major risks of a ventricular reservoir is the occurrence of an infection. Invasive punctures will be carried out over a prolonged period, usually twice a day, sometimes even three times a day. This should be carried out under conditions of utmost sterility, as in general these patients are vulnerable for infections because of their underdeveloped immune system.[5] Monitoring the occurrence of micro-organisms in the CSF by undertaking a CSF culture every day is of great importance. The lack of clinical signs of infection in our infants was of interest and probably a result of early detection of the infection. In this study it was clearly shown that the risk of infection could be as low as 4% as long as strict precautions were taken.

In treating infants with PHVD, it is important to protect the brain from additional damage secondary to raised intracranial pressure and to minimise the need for a permanent shunt with the complications of infection and blockage requiring multiple revisions. [3,9] Therefore, the policy in our unit is to assess the degree of PHVD on a regular basis using cranial ultrasonography. If PHVD is not stabilised over 5-10 days despite lumbar punctures, a reservoir is placed.

We have no experience in the treatment of PHVD with intraventricular streptokinase. Previous studies have shown that the use of streptokinase is not recommended.[9,10] Neither do we use isosorbide as monotherapy; its administration is always in combination with CSF removal, because the use of only diuretics has proved to be ineffective.[11] The initial drainage fibrinolytic therapy using two intraventricular catheters to flush the ventricular system had an

infection rate of 8%. No data are available about the associated risk of infection in the ongoing prospective Drainage Irrigation and Fibrinolytic Trail (DRIFT).[3]

To the best of our knowledge, data on the incidence of infections of ventricular reservoirs are limited. Hudgins et al [2] found an infection rate of 8% and a revision rate of 20%. More recently, Richard *et al* showed an infection in 21% of the children, which increased during their study period.[12] In contrast with their data, our incidence of infection of the ventricular reservoir is decreasing.

Recent data from Persson et al show a decrease in the prevalence of infantile hydrocephalus to 6 in 1000 live births at ≤ 32 weeks gestation, with a high rate of cerebral palsy (88%) seen among the survivors.[13] Early intervention of PHVD may help to prevention development of infantile hydrocephalus and its cerebral complications. In the Netherlands, a multi-centre investigation has started in 2006 to study the effect of early versus later insertion of the ventricular reservoir, as recommended in a previous retrospective study. [14]

CONCLUSION

Ventricular reservoirs are a safe and effective method to ensure controlled CSF removal in preterm infants with PHVD. In experienced hands, the incidence of an infection or major complications remains within acceptable limits.

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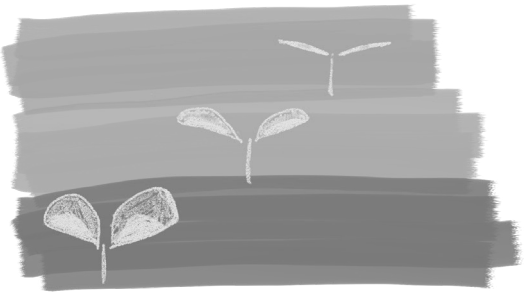
4

Ventricular Reservoir Punctures performed by Nurses:

An Improvement of Quality of Care



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ABSTRACT

Management strategies of the treatment of infants with Post Hemorrhagic Ventricular Dilatation include the placement of a ventricular reservoir. Traditionally, ventricular punctures of these reservoirs have been performed only by physicians. In the pilot project described in this article, we taught nursing staff to perform punctures of a cerebral ventricular reservoir in neonates with hydrocephalus to give nurses more control in their daily care of these infants.

All consecutive punctures performed between August 2006 and March 2007 (n=302) were studied. The chart was reviewed for the infant's state during the puncture, the caregiver who performed the puncture and the timeliness of the puncture with respect to schedule and to infant state. During the day shift, there was no significant difference in timeliness, whether the puncture was performed by a physician, nurse, physician assistant (PA) or nurse under the supervision of a physician. On the night shift, punctures were performed on schedule significantly more often when they were carried out by nurses ($p<.001$). This pilot project demonstrated that nurses can learn to perform cerebrospinal fluid removal from a ventricular reservoir. Because it increased the timeliness with which punctures were performed and gave nurses more control in planning rest periods for these infants, this policy change was judged a succes.

Key words: CSF, nursing, PHVD, ventricular reservoir

INTRODUCTION

Germinal Matrix Intraventricular Hemorrhage (GMH-IVH) in the neonatal period remains an important clinical problem. Although the incidence of IVH has decreased over the past decade, it is still common in very low birth weight infants, with 20-25 percent of these infants experiencing an IVH.[1] About 30-50 percent of infants with an IVH develop posthemorrhagic ventricular dilatation (PHVD); the more severe the infant's GMH-IVH the higher the risk of his developing PHVD.[2-4] Repeated lumbar or ventricular punctures in the treatment of PHVD have not proven to be effective.[3] Some practitioners prefer to use an external drain or a subcutaneous reservoir to control PHVD.[5,6] With an external drain the cerebrospinal fluid (CSF) is removed gradually, but there is considerable risk of infection.[7,8] Removal of CSF through a ventricular reservoir is usually done over a 24-hour period in two equal taps to prevent fluctuations in intracranial pressure. The risk of infection was been shown to be low.[9]

Until this pilot project, ventricular punctures were performed only by physicians in our unit. During the day shift, there are usually enough physicians in the NICU to perform these punctures at the scheduled times. At night, however, there is only one physician (usually a resident) available for the NICU. This physician is often very busy and may be unable to puncture the ventricular reservoir as scheduled. In addition, before the pilot project was begun, punctures were being done at the time most appropriate for the physician, but not always for the patient. To provide continuity in the removal of CSF and optimal timing for the infant, we started a training program for nurses. This article describes our unit's management of PHVD and reports on the outcome of our pilot project of nurse-managed ventricular reservoir punctures.

TREATMENT OF PHVD

It is the policy in our unit to perform lumbar punctures on those infants who develop PHVD, especially when ventricular width progresses rapidly, from a value exceeding the 2SD of Levene to the 2SD+4 mm line. Such progression is usually associated with a change in anterior horn width, leading to a change in ventricular shape, called ballooning. Both changes suggest heightened pressure within the ventricular system.[10] If PHVD does not stabilize within five to ten after daily lumbar punctures are begun, or when lumbar punctures are not successful, it is our practice to have a ventricular reservoir inserted by the paediatric neurosurgeon.[11] This permits further control of intracranial pressure. In our unit, this treatment is often combined with administration of isosorbide (8 g/kg/day divided over 6 doses). This osmotic diuretic is believed to reduce the production of CSF.[12]

VENTRICULAR RESERVOIR: PLACEMENT AND USE

A ventricular resevoir is a small (approximately 4 cm in length) tube topped with a reservoir the size of a drawing pin or thumbtack (Fig 1). The reservoir is placed subcutaneously, and the tube is placed within the ventricle. Compared with the more invasive lumbar puncture, it is easy to obtain CSF through this reservoir, and the infection rate is low.[9]

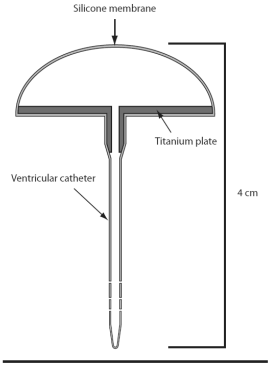

Figure 1: The Ventricular Reservoir: Rickham-style Reservoir, Intrega™ LifeSciences Corporation

After the reservoir has been placed, caregivers use a daily ultrasound examination to assess the extent of the PHVD and to decide how often CSF should be removed and how much should be removed. Routinely, we start with a withdrawal of 10 mL/kg of CSF divided over two taps within 24 hours. The amount of CSF removed is adjusted every day according to the ultrasound findings (see: Protocol for Ventricular Reservoir Punctures). CSF is removed at a rate of 1 mL / minute to reduce the risk of rebleeding.

Protocol for Ventricular Reservoir Punctures

Goal: Reduce of intracranial pressure

Procedure:

- Shave hair if necessary.
- Follow aseptic procedure: hand scrubbing, sterile gown, hood, sterile gloves and materials.
- Position infant flat, in a comfortable position. Place reservoir within reach.
- Disinfect infant's skin with alcoholic chlorhexidine gluconate 0.5%.
- Place aperture drape.
- Again disinfect of the skin with alcoholic chlorhexidine gluconate 0.5%.
- Puncture the reservoir with an infusion set (Microflex 0.4 mm/G27, Vygon) plus a syringe.
- Remove the amount of CSF called for by the day's ultrasound findings slowly (1 mL / minute).

Aftercare:

- Cover the puncture location with a sterile gauze.
- Monitor heart rate, respirations, and oxygen saturation levels for 4 hours following the procedure.
- Measure blood pressure every 15 minutes for 1 hour.
- Record the the amount of CSF removed, its color and consistency, and the infant's state during the puncture.
- Position the infant flat for 6 hours.
- Observation for CSF leakage.
- Be aware of signs of infections.
- Check urine forsodium:potassium ratio two times a week
- Check CSF for cells and protein daily. Culture CSF three times a week.
- Keep the infant comfortable

A strict sterile procedure is followed during the puncture of the reservoir: sterile gloves, mask, hood, sterile gown and sterile materials are used. Prophylactic intravenous vancomycine is administered to all infants for a period of 48 hours starting 1 hour before placement of the reservoir. Infants have to lie flat for six hours after the ventricular puncture to prevent hypotension, bradycardia, nausea and vomiting.

Because surgical removal of the ventricular reservoir can cause complications, such as leakage of CSF, the reservoir is left in place and not removed when tapping is no longer required. The reservoir can be used to evaluate intracranial pressure should delayed symptoms of slowly progressive ventricular dilatation appear.

QUALITY IMPROVEMENT INITIATIVE

Physician workload issues and the need to perform ventricular reservoir taps in a more developmentally supportive way led us to design a pilot project to educate nurses to perform the taps. The goal of this practice change was to improve the timing of ventricular reservoir punctures and to have the punctures done in a developmentally supportive manner. Developmental Care (DC) aims to decrease stressful events in the NICU and to support the infant's well-being. Because of the potential deleterious effect of sleep deprivation on brain development, appropriate intervention strategies should be planned to promote restful periods.[13,14]

Caregivers and parents are "coregulators" for infants, supporting them by accurately reading and interpreting their behavioral signs.[15] Nurses are good at interpreting infant behavioral signs and state and are therefore well qualified to decide when punctures should be done. Therefore it is necessary that nurses are able to take the infant's behavioral state into consideration, when deciding when the punctures should be done. Performing a puncture when the infant is in an agitated or restless state is difficult and is not recommended. The infant should be kept as comfortable as possible during the procedure and not be manipulated unnecessary.

TRAINING PROGRAM

To gain the support of the neonatal nurses for this practice change, we arranged meetings to explain the background for this implementation. Every nurse could make comments, which were taken into consideration when the implementation plan was made.

All nurses were trained in how to perform a ventricular puncture. The neonatologist instructed them about the pathophysiology of PHVD, the risks of a ventricular reservoir, and techniques for removing CSF.

Nurses were trained in operation room procedures for hand washing, including the correct way to put on a sterile gown and hand gloves. Posters picturing the correct procedure of hand-scrubbing were placed near every sink at the NICU. Nurses did not perform the punctures until they had been fully instructed in preperation of the equipment, how to perform the puncture, and assessment of patient reaction to the intervention.

Following this didactic session, each nurse had to perform three ventricular punctures supervised by a neonatologist with expertise in this technique. After three supervised procedures, the nurse could perform punctures without supervision. A register system made clear which nurses had received instructions and how many times each nurse performed a ventricular puncture.

Of the 101 nurses working in our NICU, 81 (80 percent) received instructions. By March 2007, 22 nurses (22 percent) were qualified in puncturing a ventricular reservoir. Most of the infants with a ventricular reservoir were admitted to the high-care (HC) neonatal unit, which is part of our NICU. Nine (53 percent) of the HC nurses were qualified to perform the ventricular reservoir puncture. It is common on our ward that (IC) nurses are working two months per year on the HC unit. Of the 83 IC-nurses, 13 (16 percent) were qualified.

STATISTICS

Differences between the groups for all variables (timing of the puncture and state of the infant) were tested by *t* test or chi square where appropriate. Statistical analyses were performed using SPSS for Windows, version 12.0.2 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at a p-value of 0.05.

PROJECT EVALUATION

Patients

Between August 2006 and March 2007, seven neonates with ventricular reservoirs were admitted to our Level III NICU. A total of 302 punctures were performed on these patients and studied. Three of the infants had grade III IVH with PHVD, two had grade IV with PHVD, one had a PHVD as a result of an aqueductal stenosis, and one infant developed a PHVD after meningitis.

The patient charts were reviewed for the infant's state during the puncture (asleep, awake, crying, hungry), adjustment of care, the person who performed the puncture (nurse, physician or PA), and point in time (timeliness) of the puncture (too early, on time or too late). "Too late" and "too early" were defined as a deviation of one hour or more from the scheduled plan of care when the deviation was not related the infant's state. Data collection continued until more than 90 percent of the punctures were performed by nurses (a period of seven months).

Attitude of the nursing staff

The nursing staf expressed concerns and some resistance to the implementation of this program. Several meetings were organized to create a solid base for successful implementation. The main nursing comment was the increase of workload because puncturing a ventricular reservoir is time-consuming. Many nurses percieved that physicians were passing on their task to the nurses. The meetings resulted in agreements about responsibilities. Puncturing the reservoir

is a shared responsibility of physicians and nurses. Most nurses saw the benefit for the patient and were enthusiastic to perform the punctures.

Puncture Procedure

Of the 302 punctures, 75 punctures were performed once a day, 100 twice a day (every 12 hours) and 9 punctures three times a day (every 8 hours). At the start of each shift it was decided who would perform the puncture: physicians, nurses, PAs, or nurses under supervision.

Of the 185 punctures performed during the day shift, 17 (9 percent) were performed by physicians, 87 (47 percent) by nurses, 6 (3 percent) by a physician assistant and 75 (41 percent) by nurses supervised by a neonatologist. Of the 117 punctures performed during the night shift: 53 (45 percent) were done by physicians, 60 (51 percent) by nurses, and 4 (3 percent) under supervision. (Table 1)

Table 1: Performance of Ventricular Punctures

Puncture Performed by	Day Shift n=185 (%)	Night Shift n=117 (%)
Physician	17 (9)	53 (45.3)
Nurse	87 (47)	60 (51.3)
Nurse + supervision	75 (41)	4 (3.4)
Physician Assistant	6 (3)	0

Of the 185 punctures performed during day shift 172 (93 percent) were done on schedule and 13 (7 percent) were performed with a delay of more than 60 minutes. There was no significant difference in timeliness whether the puncture was performed by a physician, a nurse, PA, or under supervision. Of the 117 punctures performed during night shift 91 (77.8 percent) were done on schedule, 4 (3.4 percent) were performed too early and 22 (18.8 percent) were performed with a delay of more than 60 minutes. ($p<0.001$) Of the 53 punctures performed by physicians, 33 (62 percent) were done on time compared to 54 (90 percent) of the 60 punctures performed by nurses. (Figure 2)

Regarding infant state, infants were asleep throughout 164 (54 percent) of the 302 procedures. For 92 of the 302 punctures (30 percent) infants were

asleep when the puncture started, but woke up, cried, or were in distress during the procedure. There was no significant difference in state whether the puncture was performed by a physician, PA, a nurse, or under supervision.

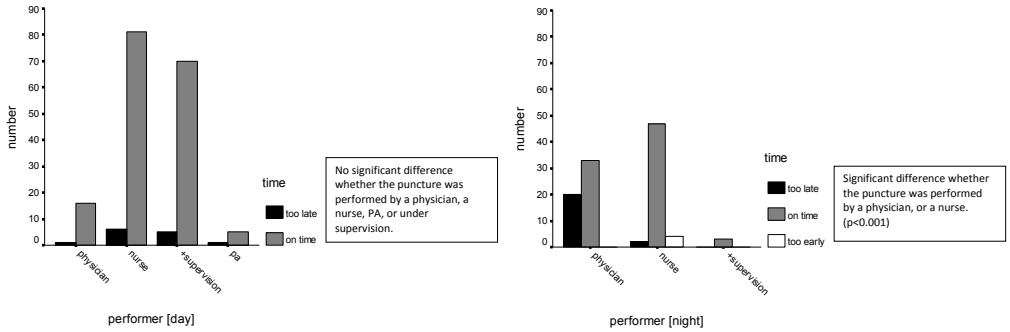

Figure 2: Timeliness of ventricular puncture, by performer and shift

DISCUSSION

This pilot study involved implementing nurses' performance of ventricular punctures. Where we expected resistance from the nursing staff, surprisingly, they were very eager in learning how to perform punctures from the ventricular reservoir. They percieved that proficiency in this procedure would allow them to better organise the daily infant care and infant rest periods, taking the need of the infant and the parents into consideration. To overcome concerns, a stringent implementation plan was put into place.[16] Most of the resistance from nurses was overcome in the preparation phase of this pilot project. A possible source of bias in the results was that health care workers were very focused on timing the punctures during the implementation phase.

Caregivers (and parents) support infants by accurately reading and interpreting their behavioural signs.[15] It is in the best interest of the infant for a nurse to synchronize punctures to the infant's behavioural state. Nurses (rather than physicians) performing reservoir punctures are able to observe and acknowledge the infant's behavior and to provide care to facilitate his self-calming. Nurses will

recognize signs of stress that may need to be managed. Attention to the infant's thresholds and need for rest or cessation of handling is essential.[15] Because nurses observe the infants in their charge 24 hours a day, they are often more adept than physicians at interpreting infant signs.

One of the major risks of performing ventricular reservoir punctures is infection. These invasive punctures are performed over a prolonged period of time, usually twice a day, but sometimes even three times a day. The puncture must be done under sterile conditions because, in general, these patients are vulnerable to infections.[17] We concluded in our previous study that "ventricular reservoirs are a safe and effective method to ensure controlled CSF removal in preterm infants with PHVD. In experienced hands, the incidence of infections or major complications remains within acceptable limits." [9] Special attention was given to the sterile performance of the puncture to keep the infection rate as low as it was prior to the practice change.[9] Continuous surveillance of CSF infections in patients with ventricular reservoirs is routine in our unit. Because of the small number of infants in this study, no additional information can be surmised regarding the number of infections when nurses perform the punctures. Over the next five years, data will be collected prospectively about the incidence of infection. Whenever surveillances data are analyzed, it will show if infection rate is higher or lower when nurses (rather than doctors) perform the reservoir punctures.

Our nurses have been on a steep learning curve since the beginning of this implementation. Considering the limited number of infants who require a ventricular reservoir, it is easier to achieve good care when trained nurses (rather than an ever-changing array of residents who stay on our unit for three to six months and lack the time to perfect a puncture routine) perform punctures of the ventricular reservoir.

CONCLUSION

This practice innovation was successfully adopted by nurses and physicians. This successful change in policy means that punctures are now performed on schedule and nurses have more control in planning rest periods for the infants in their care. We hope that this policy will improve long-term outcome.

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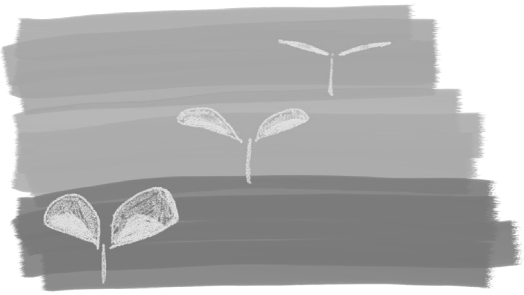
5

Neurodevelopmental Outcome of Preterm Infants with Severe Intraventricular Hemorrhage and Therapy for Post-Hemorrhagic Ventricular Dilatation



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ABSTRACT

Objective: To evaluate the neurodevelopmental outcome of preterm infants with a grade III or IV hemorrhage and to assess the effect of routine low-threshold therapy of post-hemorrhagic ventricular dilatation (PHVD) on neurodevelopmental outcome.

Study design: Of the 214 preterm infants (≤ 34 weeks GA), 94 (44%) had a grade III intraventricular hemorrhage (IVH) and 120 (56%) infants a grade IV hemorrhage. We evaluated the natural evolution of IVH, the need for intervention for PHVD, and neurodevelopmental outcome at 24 months corrected age.

Results: PHVD developed significantly more often in the surviving infants with a grade III hemorrhage (53/68, 78%) than in infants with a grade IV-hemorrhage (40/76, 53%; p=.002). Intervention for PHVD was required significantly more often in the grade III group, than in the grade IV-group (p<.001). In the grade III-group, cerebral palsy developed in 5 of the 68 surviving infants (7.4%), compared with 37 of the 76 infants (48.7%) with a grade IV hemorrhage (p<.001). The mean developmental quotient (DQ) in the grade III group was 99, and in the grade IV-group it was 95 at 24 months corrected age.

Conclusions: Short-term neurodevelopmental outcome of preterm infants with grade III or IV hemorrhage was better than reported earlier. Requiring intervention for PHVD only had a negative effect on DQ in infants with a grade IV hemorrhage. Infants with cerebral palsy had significantly lower DQs, irrespective of the severity of IVH.

Abbreviations

aEEG	Amplitude-integrated electroencephalogram	GMH-IVH	Germinal matrix-intraventricular hemorrhage
CA	Corrected age	IH	Infantile hydrocephalus
CP	Cerebral palsy	IPL	Intraparenchmal lesion
CSF	Cerebrospinal fluid	IVH	Intraventricular hemorrhage
DQ	Developmental Quotient	NICU	Neonatal intensive care unit
GMDS	Griffiths Mental Developmental Scales	PHVD	Post-hemorrhagic ventricular dilatation
GMFCS	Gross Motor Function Classification System	VP	Ventriculo-peritoneal

INTRODUCTION

Although the incidence of germinal matrix-intraventricular hemorrhage (GMH-IVH) in preterm infants decreased in the last decades, it is still a serious problem and the most common type of intracranial lesion in the preterm newborn [1,2]. In the years 1997-2004, the incidence of grade III or IV hemorrhage classified according to Papile [3] in neonates with a gestational age < 32 weeks was 5.6% in the Netherlands (data provided by The Netherlands Perinatal Registry). GMH-IVH may be associated with focal or more diffuse white matter injury. The more severe the hemorrhage, the greater the risk the hemorrhage may be complicated by post-hemorrhagic ventricular dilatation (PHVD) [2], defined as a ventricular width above the 97th percentile according to Levene. [4]

Despite a decrease in mortality, the risk of subsequent adverse neurodevelopmental outcome remains high among the survivors. [5-7] Timing and methods of treatment of PHVD remain an unsolved issue in the neonatal intensive care unit. [8] Previously, several multicenter studies have been performed, randomizing infants for early lumbar punctures. These studies were not able to show a reduced need for shunt insertion in those treated early. [9] Administration of acetazolamide even had an adverse effect on outcome [10] and intraventricular administration of tPA or urokinase also did not result in a reduced need for later shunt insertion. [11] A randomized trial using Drainage Irrigation and Fibrinolytic Therapy (DRIFT) showed promising results in the phase 1 trial, but the trial was stopped as rebleed developed in approximately one-third of the DRIFT-infants. [12,13]

A reduction in the prevalence of infantile hydrocephalus (IH) was recently shown in a Swedish population of preterm infants with a gestational age (GA) ≤ 32 wks from 13 per 1,000 live births in the period 1989 to 1991 to 6 per 1,000 live births in the period 1996 to 1998. [10] The neurodevelopmental outcome of subjects with IH was poor, however, with cerebral palsy (CP) developing in 88% of the infants. Learning disabilities and visual problems also developed in many of the children. [14,15]

We report the evolution and short-term neurodevelopmental outcome of preterm infants with GMH-IVH grade III and IV, using routine low-threshold intervention of associated PHVD. Because this was an observational study, infants were not randomized to 'low-' versus 'high-' threshold therapy of their PHVD.

METHODS

Patients

Between January 1990 and December 2003, 3,643 preterm neonates (≤ 34 weeks GA) were admitted to our level three neonatal intensive care unit (NICU). A search was performed in the ultrasound scanning database. All records and images were retrieved for infants in whom imaging diagnosis of a grade III or IV hemorrhage was made according to the classification of Papile. [3] Of 214 preterm infants with a severe IVH (5,9%), 91 (42%) had a GA of 25.0 to 27.6 wks, 81 (38%) a GA of 28.0 to 30.6 wks, 30 (14%) had a GA of 31.0 to 32.6 wks, and 12 (6%) had a GA 33 to 34 wks. Of these 214 infants, 94 (44%) had an IVH grade III according to Papile [3] and 120 (56%) infants had a grade IV hemorrhage. (Table 1)

The notes were reviewed for the clinical characteristics, timing and type of intervention, and early neurodevelopmental outcome. Developmental quotients (DQ) of 4 infants were missing. The clinical characteristics and mortality were determined and compared between the grade III and grade IV hemorrhage groups. (Table 1) Informed parental consent was obtained from the parents before reservoir or shunt placement.

Table 1: Clinical characteristics of the study population

	IVH - Grade III (n= 94)	IVH - Grade IV (n= 120)	Statistics
Male / Female	58 / 36	70 / 50	NS
Gestational age, wk (mean ± SD)	28.1 ± 2.2	29 ± 2.4	p = .017
Birth weight, g (mean ± SD)	1147 ± 381	1240 ± 450	NS
Apgar score at 1 min, median (range)	5 (0-10)	6 (1-10)	NS
Apgar score at 5 min, median (range)	7 (1-10)	8 (1-10) •	p = .046
Mortality	26 (27.6%)	44 (37%)	NS

NS, Not significant

• 5 min Apgar in grade IV is significantly higher than 5 min Apgar in grade III

Cranial Ultrasound Scanning Examination

Cranial ultrasound scanning was performed within 6 hours of admission, 2 to 3 times during the first week, at least once weekly until discharge, and again at 40 weeks postmenstrual age during the first visit to the follow-up clinic. Grade III hemorrhage was defined, according to the classification of Papile [3], as a severe IVH, with blood filling the ventricular system > 50% associated with acute dilatation of the ventricular system. A grade IV hemorrhage was defined as a unilateral parenchymal hemorrhage, associated with an ipsilateral IVH. This lesion is considered to be caused by impaired venous drainage of the medullary veins in the periventricular white matter, and the lesion is therefore usually referred to as either "venous infarction" or "hemorrhagic parenchymal infarction". Special attention was given to associated white matter lesions, periventricular echogenicity, and lesions in the basal ganglia in infants with grade III hemorrhage and contralateral cystic periventricular leukomalacia (c-PVL) in infants with a grade IV hemorrhage.

The ventricular width was measured according to the criteria of Levene [4] and PHVD was defined as a measurement >p97. Once PHVD was established, cranial ultrasound scanning was performed at least every other day, and often on a daily basis, during the phase of intervention.

Amplitude-Integrated Electroencephalogram Recordings

Since 1992, amplitude-integrated electroencephalogram (aEEG) recordings were routinely used in all infants with a high-grade hemorrhage to assess the background pattern and to aid in the detection of subclinical seizures.

Intervention in Progressive PHVD

The policy in our NICU is to perform lumbar punctures, aiming for withdrawal of 10 mL/kg, in those infants in whom PHVD develops with rapid progression of the ventricular width, from a value exceeding the 97th percentile of Levene toward the p97+4 mm line, which is associated with a change in anterior horn width (>6 mm), leading to a change in ventricular shape (so-called 'ballooning'). Some infants were treated after exceeding the 97th +4mm line because of an unexpected rapid increase of the dilatation or because infants were referred from other tertiary NICUs, where it was not possible to perform neurosurgical procedures. When stabilization of PHVD was not achieved in the next 5-10 days despite daily lumbar punctures, or when lumbar punctures were not successful because of a lack of communication, a ventricular reservoir was inserted by the pediatric neurosurgeon to allow further control of the PHVD through daily or twice daily punctures from the reservoir. Cerebrospinal fluid (CSF) can be tapped more easily and at a controlled speed (1mL/kg/min) from the reservoir. In our unit, this treatment is often combined with the administration of Isosorbide (8 g/kg/day orally in 6 doses), an osmotic diuretic that is considered to reduce the production of CSF. [16]

This treatment regimen was the routine regimen during the entire study period, and most of the medical staff involved in treating these infants remained the same during this period.

Assessment of Neurodevelopmental Outcome

The surviving infants were seen in the follow-up clinic at regular intervals. Assessment of outcome was based on clinical examination at discharge and the Griffiths' Mental Developmental Scale (GMDS) at 24 months of corrected age (CA). [17]

The GMDS provides a subscale and general developmental age and quotient equivalents (mean, 100; SD, 15) of raw scores. Five domains of functioning are tested: locomotor, personal-social, hearing, and speech, eye- and hand coordination, and performance. [18] The GMDS shows continuing validity with time and across cultures. [15] A DQ >85 at 2 years is considered within the reference range. [17] In our hospital, all preterm infants were assessed by developmental pediatricians / neonatologists using the GMDS at 24 months CA. The DQ was calculated for the corrected and chronological age.

Postural and motor control was assessed with the Alberta Infant Motor Scale [19,20] by a pediatric physiotherapist (I.C.H.) who was unaware of the clinical history and imaging findings.

CP was defined as "an umbrella term covering a group of non-progressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of development". [21,22] The diagnosis CP was made according to the criteria of Hagberg et al. at a minimum age of 24 months. [22] Maximal locomotor function of infants with CP was graded according to the Gross Motor Function Classification System (GMFCS). [23,24] At 18 months, a distinction was made between level I (sits with hands free, creeps or crawls on hands and knees, pulls to stand, walks with hands held, and cruises), level II (uses hands for sitting support, creeps on stomach, may pull to stand), level III (sits with external support of lower trunk, rolls, may creep), level IV (good head control in supported sitting, can roll to supine), level V (unable to maintain antigravity of head/trunk).

Statistics

Differences in the groups for all variables were tested with Students *t* test, Mann-Whitney test, Chi-square, independent samples *t* test and 1-way analysis of variance, as appropriate. Statistical analyses were performed by using SPSS software for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at a p-value of .05.

RESULTS

Between January 1990 and December 2003, 94 preterm infants with a grade III hemorrhage and 120 infants with a grade IV hemorrhage were admitted to our tertiary NICU. The clinical characteristics of the infants are described in Table 1.

Mortality

In the grade-III group 26 of 94 infants (28%) died (Figure1). 16 infants died because of multiple problems related to their preterm birth. Intensive care was withdrawn in 12 of the 26 infants because of a combination of the cranial ultrasound scanning findings and neurophysiologic data, consisting mostly of severely abnormal continuous aEEG data, which tended to show a very depressed background pattern with electric discharges that persisted despite administration of different anti-epileptic medications. In most of these immature infants, this was combined with severe respiratory problems, circulatory problems, or both.

Of the 120 infants in the grade IV group, 44 (37%) died. Intensive care treatment was withdrawn in 35 patients when the hemorrhage was extensive involving the fronto-parietal and occipital white matter, often associated with a midline shift, suggestive of a very poor prognosis with multiple disabilities. [22] Care was withdrawn for 3 infants after the development of c-PVL contralateral to the side of the parenchymal hemorrhage. 34 infants who died showed involvement of ≥2 territories, 10 infants had bilateral hemorrhages, and 11 infants had a midline shift. In most of these immature infants, the imaging findings were combined with severe respiratory or circulatory problems. aEEG data tended to show a very depressed background pattern with electric discharges that persisted despite administration of different anti-epileptic medications in most of these 36 infants.

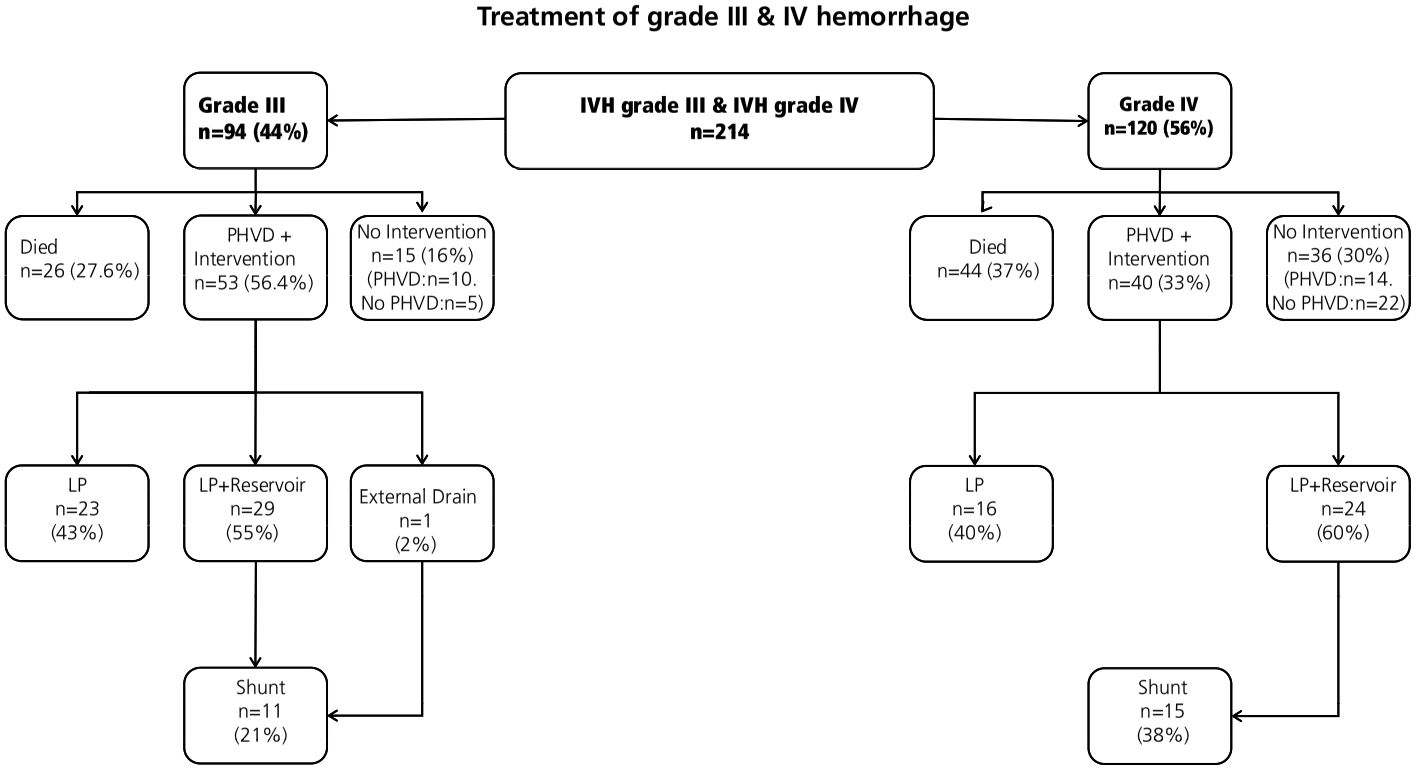

Figure 1: Description of the study population with regard to the severity of hemorrhage and treatment given.

Development of PHVD and Intervention

Of the 144 surviving infants, progressive PHVD requiring intervention developed in 93 (65%). Development of PHVD occurred significantly more often in infants with a grade III hemorrhage (53/68, 78%), compared with infants with a grade IV hemorrhage (40/76, 53%; p<.001). After the development of PHVD, a significantly larger number of infants with a grade III hemorrhage required lumbar punctures to control their PHVD (p<.001), but there was no difference in the number of infants requiring a ventricular reservoir in the 2 groups (p=.2; Figure 1)

Once intervention was considered necessary, more infants with a grade IV hemorrhage subsequently required a ventriculo-peritoneal (VP) shunt (15/40; 38%) than infants with a grade III hemorrhage (11/53; 21%; p=.554). 26 of 93 infants with either grade III or IV hemorrhage (28%) who required any form of intervention eventually required a VP shunt.

Neurodevelopmental Outcome

Neurodevelopmental outcomes are shown in Table II. Of the 68 surviving infants with a grade III hemorrhage, 61 (91%) had a DQ > 85 corrected for prematurity, compared to 58 of the 76 infants (79%) with a grade IV hemorrhage. (p=.055) CP developed in 5 infants in the grade III group, and all were classified as having a spastic bilateral CP of a diplegic type. 4 of these infants had associated PVL grade 1, and 1 associated lesions in the basal ganglia. Infants without CP had a significantly higher DQ compared with infants in whom CP developed (p=.003).

CP developed in 37 of 76 surviving infants (48.7%) with a grade IV hemorrhage. Spastic unilateral CP developed in 27 infants (35.5%). Spastic diplegia developed in 8 infants (10.5%). 3 infants had bilateral parenchymal hemorrhages, 2 infants showed associated contralateral c-PVL grade 3, and a hemiplegia with associated spastic diplegia developed in the latter 2 infants. Infants without CP had a significantly higher DQ than infants in whom CP developed (p=.001; Table II)

3 infants had cerebral visual impairment and were legally blind (4%), and all 3 had a grade IV hemorrhage. Epilepsy developed in one infant with a grade III hemorrhage (1.4%) and 8 infants with a grade IV hemorrhage (11%; p=.025). This was associated with cerebral palsy in all the children except 1.

Table 2: Neurodevelopmental outcomes for grade of hemorrhage

	Grade III **n = 68** (1 no DQ)	**Grade IV** **n = 76** (3 no DQ)
DQ>85 + no CP, n (%), CA	59 (86)	34 (45)
DQ>85, n (%), CA	61 (91)	58 (79)
DQ mean (SD), CA	99 (11)	95 (13)
DQ mean (SD), chronological age	86 (10)	84 (12)
DQ mean (SD), no CP (CA / chronological age)	100 (10) / 87 (10)	99 (10) / 89 (9)
DQ mean (SD), + CP (CA / chronological age)	85 (12) / 75 (8)	89 (13) / 80 (12)
CP, n (%)	5 (7.4)	37 (48.7)
GMFCS level (n)		
I	1	7
II	3	20
III	1	5
IV	0	5
Epilepsy, n (%)	1 (1.4)	8 (11)
Cerebral visual impairment, n (%)	0	3 (4)

CA, corrected age; CP, cerebral palsy; DQ, developmental quotient; GMFCS, Gross Motor Function Classification System.

Effect of Severity of the Hemorrhage on Outcome

There was no significant difference in DQ in both groups for the uncorrected DQ (p=.258). Infants with a grade III hemorrhage, however, had a significantly higher corrected DQ than infants in the grade IV-group. (p=.021)

The proportion of infants in whom developed CP was significantly higher in the grade IV hemorrhage group than in the grade III-group (p<.001). In Figure 2, the grade III and grade IV groups are compared, for total DQ, the influence of PHVD, and CP.

There was no significant difference between the grade III group and grade IV group in the severity of CP, according to the GMFCS (p=.841), but GMFCS grade IV was only seen in the grade IV hemorrhage group.

Outcome Grade III and IV hemorrhage, and relation with PHVD and CP

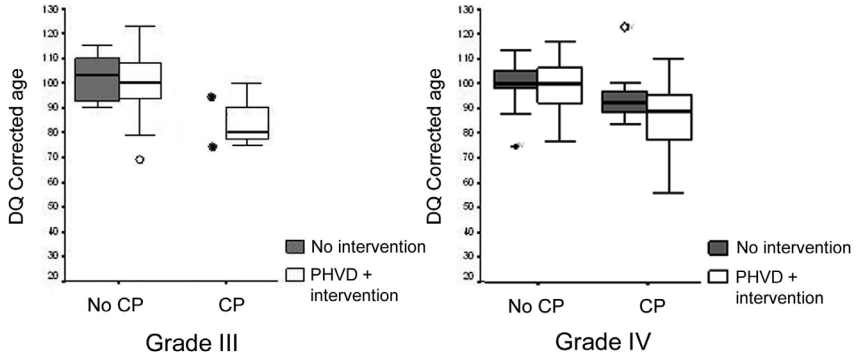

Figure 2: Comparison of the grade III (left) and grade IV (right) hemorrhage groups, of the effect of PHVD (requiring intervention) and CP on total DQ. The proportion of infants in whom CP developed was significantly higher in infants with a grade IV hemorrhage than in infants with a grade III hemorrhage (p<.001).

Effect of PHVD on Outcome

Of the infants in the grade III-group with intervention for PHVD, 5 of 52 (data of one child is unknown; 9.6%) had a DQ < 85 compared with 1 of 15 infants (6.7%) without intervention for PHVD, which was not significant (p=.725). In the grade IV group, there was a significant difference (p=.004) in outcome between infants with intervention for PHVD and infants without intervention for PHVD. 13 of the 40 infants (33.3%) with intervention for PHVD had a poor outcome, compared with 2 of 36 (5.6%) without PHVD.

Effect of Timing of PHVD Intervention

Data were available for 74 of the 93 infants with PHVD. Infants with PHVD who were treated early for their PHVD, before reaching the 97th centile + 4 mm line of Levene, had a significantly higher DQ than infants treated later, when they exceeded the 97th centile + 4 mm line (p=.029). Of the known data of 74 infants, 35/37 (94.6%) treated below the 97th centile + 4 mm line had a DQ>85 compared to 26/37 (70.3%) of the infants treated after reaching the 97th centile + 4 mm line (p=.017).

No significant difference was noted between low- and high-threshold therapy of PHVD for later development of CP. Of the 74 infants CP developed in 10 of 37 (27%) in the low-threshold group, compared with 11 of 37 infants (29.7%) in the high-threshold group (p=.752).

Effect of VP Shunt Requirement on Neurodevelopmental Outcome

26 of the surviving infants (18%) required a VP shunt, 11 of the 68 surviving infants with a grade III IVH (16.2%) and 15 (19.7%) of the 76 surviving infants with a grade IV IVH. The overall rate of CP in the children with IH and a VP shunt was 46.2% (12/26), and all those 12 infants had a grade IV IVH.

Data about early versus late treatment were available for 22 of 26 infants in this group. 6 infants (27.2%) who were treated early needed a VP shunt, compared with 16 infants (72.7%) treated late, once the 97th centile + 4mm line of Levene was reached (p<.001).

DISCUSSION

We report the evolution and short-term neurodevelopmental outcome of preterm infants with grade III and IV hemorrhage, classified according to Papile [3], using a threshold for therapy of associated PHVD. The DQs of the surviving infants with grade III or grade IV hemorrhage were better than reported previously: 59 infants (86%) with a grade III IVH had a normal outcome (DQ>85, CA, without CP) as did 34 infants (45%) in the grade IV-group.

PHVD developed in significantly more infants in the grade III group than infants in the grade IV group. This can partly be explained by the larger amount of intraventricular blood, which usually involves both ventricles, in infants with a grade III hemorrhage. Also, more infants with a grade IV hemorrhage died before PHVD could develop, because PHVD usually develops within 10 to 20 days after the onset of the hemorrhage.

21% of the infants with a grade III hemorrhage who required any form of intervention eventually needed a VP shunt. 38% of infants with a grade IV

hemorrhage who needed any form of intervention needed a VP shunt, compared with 37% in a recent study. [25]

The percentage of infants with CP was high (80%) in the shunted grade IV group, compared with none in infants needing a shunt in the grade III group. This suggests that parenchymal involvement in itself is the main determinant for later motor outcome. Increased intracranial pressure and subsequent need for intervention and VP shunt placement may have a further adverse effect on the developing brain.

When comparing our outcome with the recent literature, several issues need to be addressed. Studies of outcome are difficult to compare due to heterogeneity of the severity of the lesions in the surviving infants. Also, it is not always possible to know how many of the infants had a grade III or grade IV hemorrhage or how many had associated cystic periventricular leukomalacia, which is a known risk factor for adverse neurological sequelae.

The incidence of 2.6% in this study for grade III hemorrhage was similar to the 3% in the EPIPAGE study. [26] The incidence of 3.2% for grade IV hemorrhage in infants with a GA ≤ 34 weeks was slightly lower than the 4 % reported in infants with a birthweight < 1500 grams [25] and similar to the 3% in the EPIPAGE study [26], but our mean GA was higher than in these 2 studies.

It is also important to compare our mortality rate (grade III, 28%; grade IV, 37%), which was partly related to withdrawal of intensive care treatment, with that of other studies. This information is not always available because many studies only report data for the children who survived and in whom PHVD or IH developed. The data from the EPIPAGE study [26,27] and those of Fugati et al, [28,29] however, show a higher mortality rate both for infants with a grade III hemorrhage and for infants with a grade IV hemorrhage. The mortality rate was especially high in Futagi's study [29], 49% of the infants with a grade III hemorrhage and 59% of infants with a grade IV hemorrhage, compared with our cohort, but our population consisted of infants with a higher GA and birthweight. The mortality rate of our infants with a GA ≤ 32 weeks was however much lower than the overall Dutch mortality rates (28% versus 39% grade III and 37% versus 66% grade IV; data provided by The Netherlands Perinatal Registry).

Our *long-term outcome* was better than reported previously. [28,30] Futagi et al [28] showed lower DQs in their infants with a grade III and grade IV hemorrhage compared with the infants in our study. They compared the outcome of different treatment policies of these infants (surgical, medical, and no intervention). The proportion of CP in their study was 52% in the surgically treated group and 20% were mentally retarded, compared with 36% and 23%, respectively, in our study. Resch et al [30] investigated the outcome of infants with an IVH/PVH. Only 15% were found to have a normal development at 1 year of age corrected for prematurity. Of the infants with a grade III IVH/PVH, 37% had a poor outcome, and this figure increased to 77% in infants with a grade IV hemorrhage.

Another important issue is the GA range of the study population. A limitation of our study could be that intensive care in the Netherlands is almost exclusively restricted to infants with a GA ≥ 25 weeks, which could be a factor explaining our more favorable outcome. However, this is a very large group of infants from a single NICU, with a specific treatment policy that did not change during the study period. Recent data by Persson et al [14] showed mental retardation in 67% of their cohort and CP in 88%. In this study, however, only preterm infants ≤ 32 weeks GA and IH requiring insertion of a VP shunt were included. Of our subgroup of preterm infants meeting the same criteria, CP developed in only 50%. A difference in mortality of their infants with a grade III and IV hemorrhage might be an important factor to explain possible differences in outcome, but unfortunately this information is not available. Ment et al [5] report a high percentage (55%) of infants with ventriculomegaly having a very low IQ. 45% of this group of infants had CP. Infants with a combination of ventriculomegaly and parenchymal involvement had the poorest outcome. This agrees with our study, because we also show that infants with intraparenchymal lesion (IPL) and PHVD scored significantly lower on developmental outcome than infants with IPL without PHVD and CP developed significantly more often in them than in the infants with IPL but without PHVD. A small proportion of our infants in the grade III group had associated PVL grade 1 and contralateral c-PVL was found in a few infants in the grade IV group. These additional changes in the white matter should not be overlooked because they may explain the adverse outcome

in these infants.

There was no significant difference in the neurodevelopmental outcome of infants with grade III hemorrhage who survived with or without intervention for PHVD (p=.725). Infants in whom intervention was started before they crossed the p97+4 mm line had a better DQ at 2 years CA than infants who were treated once this line was crossed. Because this is an observational study, we one can only speculate about the role of early intervention. Early intervention of PHVD may help to prevent the development of IH, its cerebral complications, and subsequent adverse sequelae, as has been reported previously [8] and this study supports earlier findings.

We thank 'The Netherlands Perinatal Registry' for providing the data of all Dutch NICUs.

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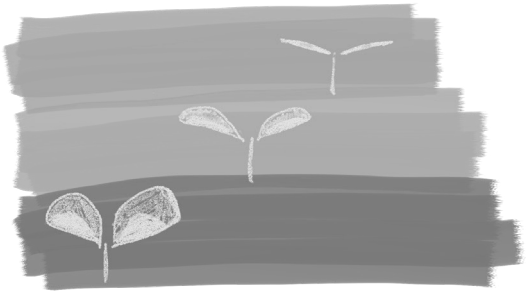
6

Cognitive and Neurological Outcome of Preterm Infants at the age of 5-8 years with Post-Haemorrhagic Ventricular Dilatation requiring Neurosurgical Intervention



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ABSTRACT

Aim: To evaluate neurodevelopmental and cognitive outcomes among preterm infants with severe IVH (grade III or IV), requiring neurosurgical intervention for their associated post-haemorrhagic ventricular dilatation.

Methods: Between 1999 and 2004, 32 preterm infants with a gestational age (GA) between 26 and 35 weeks were admitted to a level three neonatal intensive care unit with post-haemorrhagic ventricular dilatation (PHVD) requiring neurosurgical intervention, either a ventricular reservoir and/or a ventriculo-peritoneal shunt (VP shunt). All 32 infants were seen in the follow-up clinic and had standardized cognitive, behavioural and neurological assessments between 5 and 8 years of age. For the 23 infants with a GA < 30 weeks, matched controls were available and their cognitive, behavioural and neurological outcome was compared with the IVH group.

Results: The majority (59.4%) had no impairments, consisting of cognitive problems, cerebral palsy (CP) or epilepsy. None of the children with a grade III and eight of the 15 children (53%) with a grade IV haemorrhage developed cerebral palsy (CP). More subtle motor problems assessed with the Movement-ABC score were seen in 39 % (n=9), six of whom had an IVH grade III and three with a grade IV haemorrhage; the mean IQ of all children was 93.4, and 29% of the children had an IQ < 85 (-1SD). Timing of intervention did not have a beneficial effect on neurodevelopmental outcome, but all infants were treated early, before signs of intracranial pressure or a rapid increase in head circumference occurred. With respect to cognition, no significant differences were found between the IVH group and the control group.

Conclusion: Overall, children with a severe haemorrhage had a more favourable outcome than reported previously. Whether this was due to earlier neurosurgical intervention is currently being investigated.

INTRODUCTION

Preterm infants with cystic periventricular leukomalacia (c-PVL) and severe intraventricular haemorrhages are known to be at risk of neurological sequelae. While the incidence of c-PVL was noted by several groups to be coming down, we and others have not been able to show a reduction in the incidence of a severe intraventricular haemorrhage (IVH). [1,2] The incidence of grade III and IV haemorrhage remained around 5-10% for infants < 30 weeks over the last fifteen years in our Neonatal Intensive Care Unit (NICU). [3]

Preterm infants with a large IVH are known to be at risk of developing post-haemorrhagic ventricular dilatation (PHVD) and this risk increases further with an increasing amount of blood in the ventricular system. [4]

The risk of adverse neurological sequelae increases to approximately 50% in infants with a severe haemorrhage. The outcome of the infant with an IVH mainly depends on the presence of associated parenchymal injury. Infants with an IVH complicated by a periventricular haemorrhagic infarction (PHVI) or cystic periventricular leukomalacia (c-PVL) are most at risk of developing neurological sequelae, including cognitive impairment and cerebral palsy. [1,5]

However, as a result of improvements in care and maybe also because of earlier and more effective intervention, PHVD is not necessarily associated with an unfavourable outcome. Preterm infants who develop progressive PHVD in the absence of associated parenchymal lesions may have a normal neurodevelopmental outcome. In a recent retrospective cohort study [6] short-term neurodevelopmental outcome of preterm infants with grade III or IV haemorrhage was better than reported previously. The short term outcome of infants with a grade III haemorrhage was the same for infants who did or did not require intervention for PHVD. [6]

The aim of this study was to evaluate long term neurodevelopmental and cognitive outcome in preterm born infants who developed a severe IVH, grade III or IV according to Papile [7] and associated post-haemorrhagic ventricular dilatation. Only those who required neurosurgical intervention, a ventricular reservoir with or without subsequent placement of a permanent ventriculo-

peritoneal shunt (VP-shunt), were eligible for this study. We were also interested in the potentially beneficial effect of early intervention. Furthermore, we matched the IVH group with a GA < 30 weeks with a control group to compare cognitive and neurological outcome.

METHODS AND PATIENTS

Patients

Between 1999 and 2004, 1785 preterm infants with a gestational age (GA) between 25 and 35 weeks were admitted to the level three NICU of the Wilhelmina Children's Hospital. Abnormalities on cranial ultrasound (cUS) were classified as reported previously. IVH was classified according to Papile et al. [7] A total of 97 (5.4%) developed a severe IVH, 35 a grade III and 62 a grade IV haemorrhage. Mortality of these 97 was 27.8% (n=27). Of the 70 surviving infants, 34 required neurosurgical intervention following the development of PHVD, either a ventricular reservoir or a VP shunt. Clinical characteristics (i.e. gender, GA, BW and Apgar score at 1 and 5 minutes) are summarized in Table 1. Two infants showed associated c-PVL and were therefore excluded from further analysis.

All preterm infants below 32 weeks GA are routinely seen in our follow-up clinic till at least 24 months corrected age. Only preterm infants with a GA below 30 weeks are seen again by the neonatologist, physiotherapist and psychologist at 5,5 years uncorrected age. For the 23 infants with a GA below 30 weeks, we were therefore able to find controls in our database and these were matched for GA, birth weight, and gender. All infants above 30 wks gestation who were treated for their PHVD were also seen on a regular basis till 5,5 years of age. Children were assessed for their motor performance (Movement-ABC), cognition (Wechsler Preschool and Primary Scale of Intelligence, third edition, Dutch edition, WPPSI-III-NL) and behavior (Child Behavior Checklist (CBCL) and Teacher Report Form (TRF) at the age of 5-8 years.

PHVD

The ventricular width was measured according to the criteria of Levene [8] and PHVD was defined as a measurement of the ventricular width >p97. Once the development of PHVD had been established, cUS was performed every other day and sometimes even daily following insertion of a reservoir to decide which amount of fluid should be removed. Regular cUS examinations were performed until stabilisation of the PHVD occurred.

Intervention in progressive PHVD

Intervention for PHVD started with performing lumbar punctures (LPs) in infants who showed a rapid progression of the ventricular width, with a measurement exceeding the 97th centile of Levene and increasing towards the p97+4 mm line. This change in ventricular width tends to be associated with a change in anterior horn width (>6 mm), leading to a change in ventricular shape: the so-called 'ballooning'. With the LP, the aim was to withdraw 10 ml/kg liquor. Some infants were first treated after exceeding the 97th +4mm line (late intervention) because of an unexpected rapid increase of the dilatation or because infants were referred from other tertiary NICUs, where it was not possible to perform neurosurgical procedures, such as insertion of a reservoir or a VP-shunt. If stabilization of PHVD had not been achieved over the next 5-10 days despite daily LPs, or when LPs were not successful, because of a lack of communication, a ventricular reservoir was inserted by the paediatric neurosurgeon to allow further control of the PHVD through daily or twice daily punctures from the reservoir. Cerebrospinal fluid (CSF) was removed at a controlled speed (1 ml/min) from the reservoir. This treatment is in our unit often combined with administration of Isosorbide (8 g/kg/day orally in six doses), an osmotic diuretic that is considered to reduce the production of CSF. [9]

This treatment regimen was the routine regimen during the entire study period, and the majority of the medical staff involved in treating these infants remained the same during this period.

Motor outcome

The standardized Movement-ABC test [10,11] was used to test fine and gross motor function, including static and dynamic balance. A score is given for each of the parts of the test, resulting in a total motor score. Scores below the p5 indicate definite motor problems and scores between p5 and p15 a borderline motor function. Measurements were performed by two experienced examiners, a physical therapist and a neonatologist, who were trained in the administration of the Movement-ABC. The Movement-ABC is specifically developed for children with motor impairment without mental retardation or any known physical disorder such as cerebral palsy (CP). [11]

CP was defined according to criteria reported in the literature. [12] The severity of CP was classified according to the Gross Motor Function Classification System (GMFCS). [13-15] This is a functional, 5-level classification system for CP based on self initiated movement with particular emphasis on sitting and walking.

Cognitive outcome

Cognition was assessed in children below 8 years with the Wechsler Preschool and Primary Scale of Intelligence, third edition, Dutch version (WPPSI-III-NL) [16] or with the "Revisie Amsterdamse Kinder Intelligentietest" (RAKIT), a Dutch intelligence test. [17,18] Children with hearing or language problems were tested with a Dutch nonverbal intelligence test, the Snijders Oomen Nonverbal Intelligence Test 2 1/2 -7 - Revised (SON-R 2 ½ -7) [19]. Concurrent validity of the SON-R 2½-7 IQ's with the WPPSI-III-NL IQ's is 0.51. Eight-year olds were tested with the WISC-III-NL[20], concurrent validity of the WISC-III with the WPPSI-III is 0.80 [21].

All tests have a mean of 100 and SD of 15. The Full Scale Intelligence Quotient (FSIQ), the Verbal Intelligence Quotient (VIQ) and the Performance Intelligence Quotient (PIQ) were analysed and compared with the matched controls for those < 30 wks gestation. Cognitive delay was defined by a test result more than 1SD below the norm (IQ<85).

Behavioural outcome

Behaviour was assessed by behavioural questionnaires. Parents completed the Child Behaviour Checklist (CBCL) and teachers the Teacher Report Form (TRF). [22]

The CBCL consists of a total problem scale, an internalizing problem scale and an externalizing problem scale. The internalizing problem scale consists of the subscales: emotionally reactive behaviour, anxious depressed, somatic complaints, withdrawn behaviour and sleep problems. The externalizing problem scale consists of the scales attention problems and aggressive behaviour. The TRF has the same subscales, except for sleep problems. Mean T score is 50, T scores >60 are subclinical and T scores >63 are classified as clinical.

Statistics

Statistical analysis was performed using the Mann Whitney test, the $\chi 2$ test for comparison of proportions and the analysis of variance for comparison of means.

Statistical analyses were performed by using SPSS software for Windows, version 15 (SPSS, Chicago, IL). Statistical significance was set at a p value of .05.

Since all tests have a mean of 100 en SD of 15, there was no need to compute a Z-score.

RESULTS

Figure 1 shows a flow chart of the initial study population. Of the 34 neonates, 17 had an IVH grade III and 17 an IVH grade IV according to the classification of Papile. [7] Two infants with an IVH grade IV were excluded because of associated c-PVL. Of the remaining 32 infants, no significant differences between infants with an IVH grade III and IV were found with respect to gender, GA, BW or Apgar score. (Table 1) LPs were performed in 29/32 infants (91 %) and 31/32 (97%) infants subsequently needed insertion of a ventricular reservoir (one infant required direct insertion of a VP shunt). In total 12/32 (37.5 %) infants needed a

VP shunt. Revision of the VP shunt was required in 3 infants. Two infants had one revision because of a drain dysfunction, both at the age of 6 months. One infant needed two revisions because of a drain dysfunction, the first revision 3 weeks after placement of the drain and the second time after 4.5 years.

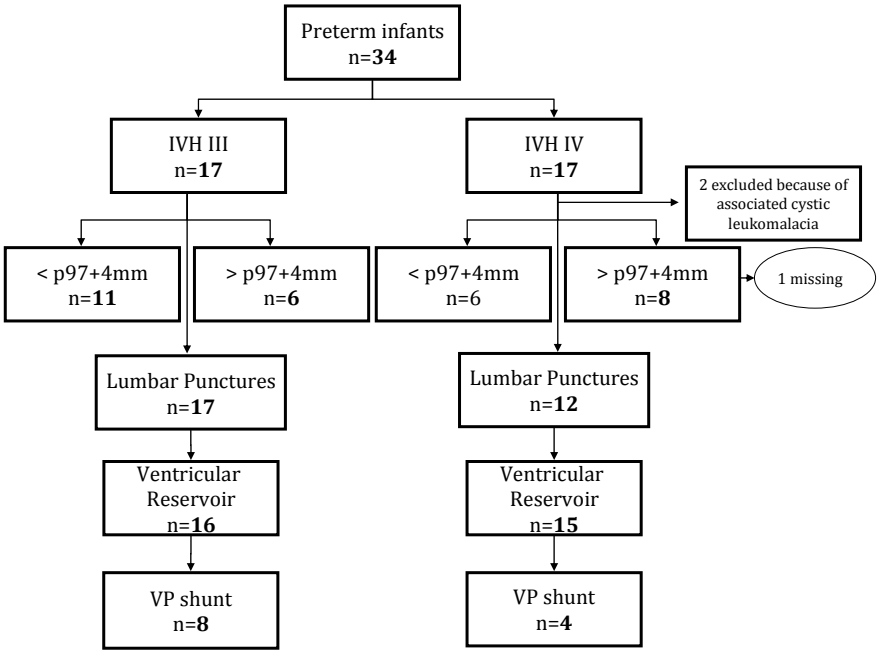

Figure 1: Study population

Table 1: Clinical characteristics of the study population

	Grade III n=17	**Grade IV n=15**
Male / Female	10/7	6/9*
Gestational age, weeks (mean ± SD)	28.9 ± 2.7	29.7 ± 2.6*
Birth weight, g (mean ± SD)	1308 ± 517	1370 ± 397*
Apgar score at 1 minute, median (range)	6 (1-10)	8 (5-10)*
Apgar score at 5 minute, median (range)	6 (1-9)	8 (5-10)*

***** No significant difference

The median age of the children when last seen was 5.7 years (range: 4 – 8 years). Three children were older than 6 years.

Matched controls were found in our database for the 23 infants with a GA below 30 weeks. There was a small discrepancy in respect to gender, because one twin-boy was matched with his twin-sister. The IVH group was compared with the control group on: administration of antenatal steroids, days of mechanical ventilation, occurrence of a patent ductus arteriosus, necrotizing enterocolitis, sepsis and chronic lung disease and the administration of surfactant and hydrocortisone. Antenatal steroids were significantly more often administered to the control group, more infants in the IVH group needed surfactant and mechanical ventilation for more than 7 days. (Table 2)

Table 2: Clinical characteristics of the study population <30 wks and control group

	IVH n=23	**Controls n=23**	**p**
Male / female	13 / 10	12 / 11	NS
Gestational age, weeks (mean ± SD)	27.9 ± 1.5	27.7 ± 1.2	NS
Birth weight, g (mean ± SD)	1099 ± 240	1110 ± 242	NS
Apgar 1 min	5	6	NS
Apgar 5 min	7	8	NS
Antenatal steroids	14/20 ^	22/23	.015
Mechanical ventilation	21/23	19/23	NS
Mechanical ventilation > 7 days	16/23	9/23	.038
Surfactant	18/23	11/23	.032
Patent Ductus Arteriosis	7/23	9/23	NS
Necrotizing Enterocolitis	2/23	2/23	NS
Sepsis	9/23	14/23	NS
Chronic Lung Disease	9/23	8/23	NS
Hydrocortisone	8/23	4/23	NS

^ data of 3 missing

Multiple impairments

Of the 32 children, 19 (59.4%) had no major impairments, including cognitive problems, CP or epilepsy. A significant difference was seen between both IVH groups: 14/17, (82%) children with an IVH grade III compared to 5/15 (33%) children with an IVH grade IV had no impairments (p=.015). A combination

of impairments was seen in two (6.3%) children, both following an IVH grade IV. One child had a combination of three impairments (epilepsy, CP, learning disabilities) and one child had a combination of two impairments (CP and learning disabilities).

Gross Motor Function Classification Scale (GMFCS) / CP

Eight of the 32 children developed CP (25%). None of the 17 children with a grade III haemorrhage developed CP, compared to 8/15 (53%) with a grade IV haemorrhage. All children had a unilateral spastic cerebral palsy (USCP). On the GMFCS, five children scored a level I, two a level II, one child a level III.

Movement ABC

23/24 children without CP were tested using the movement-ABC (1 missing), 9/23 (39%) performed below the p5 on the total motor score, and thus had definite motor problems; six had an IVH grade III. Another six children (26%) performed below the p15, all six had an IVH grade III, and 8/23 (34.8%) performed above the p15, four had an IVH grade IV.

The 18 children of the IVH group (GA<30 wks, without CP) and their controls (1 missing) were tested by the movement-ABC. The control group performed significantly better on motor outcome compared with the IVH group. (p=.006). No child in the control group performed below p5, in comparison with 8/18 (44%) in the IVH-group. Of the controls, 12/17 (70.6%) performed >p15, compared to 6/18 (33,3%) in the IVH-group (p=.053).

Cognition (Table 3)

Twenty-one of the 32 children were tested with the WPPSI-III-NL, five children with the RAKIT, three with SON-R and two with the WISC-III. One child could not perform any test because of the severity of her handicap (level III on the GMFCS). In total 9/31 (29%, 1 missing) children had an IQ < 85, 4/17 with a grade III and 5/14 with a grade IV hemorrhage. (p=.457).

Children with an IVH grade III and a VP shunt had a mean IQ of 90 (SD 19), which was lower than those without a VP shunt (IQ = 101,SD 9; p=.147). In the IVH-IV group, children with a VP shunt had a mean IQ of 90.2 (SD 13), compared

to 91.1(SD19; p=.938) in those without. The seven (1 missing) children with CP had a mean IQ of 87 (SD 17); four of them had an IQ ≥85 (57%), which was not significantly different from children without CP, who had a mean IQ of 95 (p=.229).

Table 3: Cognition

Group	N	IQ, mean (SD)	IQ > 85, n (%)
IVH III & IV	32	93 (16) ^	22 (71) ^
IVH III	17	96 (15)	13 (76.5)
IVH IV	15	91 (10) ^	9 (64.3) ^
IVH III <p97+4mm	11	99 (17)	9 (82)
IVH III >p97+4mm	6	90 (10)	4 (66.6)
IVH IV <p97+4mm	6	95 (22) ^	3 (60) ^
IVH IV >p97+4mm	8	89 (15)	6 (75)
IVH < 30wk	23	92 (17)	15 (65.2)
Controls	23	98 (15)	17 (74)

^ 1 child could not be tested

For the children tested with a Wechsler test (WPPSI-III or WISC-III), the total IQ score could be subdivided in a verbal IQ score, a performal IQ score and a score for production speed. (Table 4) The better achievement of the controls on performal tasks and production speed did not reach significance.

Table 4: Mean IQ-scores on subscales from children tested with a Wechsler intelligence test

	IVH (n=23)	IVH <30 wks (n=16)	Controls (n=24)
Verbal scale	97 (SD 13)	94 (SD 13)	96 (SD 13)
Performal scale	94 (SD 16)	93 (SD 15)	103 (SD 14)
Production speed	87 (SD 22)	85 (SD 24)	93 (SD 14)

Behavioural outcome (Table 5)

More than 80% of the parents and the teachers completed the CBCL and TRF respectively.

In the IVH-group, the IVH-group <30 wks and the control group more (subclinical) T scores were reported on the teacher report than on the parent report. There were no significant differences between the IVH-group <30 wks and the controls on mean T score on the total scale, the internalizing scale and the externalizing scale.

Table 5: Behavioural Outcome CBCL and TRF

Behavioural outcome	**Mean T score and number of parents with scores in the (sub)clinical range on CBCL**					
	IVH (n=26)		**IVH < 30 wks (n=20)**		**Controls < 30 wks (n=23)**	
	Mean T score (SD)	N (%) in (sub) clinical range	Mean T score (SD)	N (%) in (sub) clinical range	Mean T score (SD)	N (%) in (sub) clinical range
Total scale	48,2 (8,4)	3 (12%)	46,9 (8,3)	2 (10%)	44,3 (7,8)	1 (4%)
Internalizing problem scale	49,2 (8,9)	5 (19%)	48,2 (8,4)	3 (15%)	49,2 (9,2)	5 (21%)
Externalizing problem scale	46,8 (9,4)	2 (8%)	45,1 (9,5)	1 (5%)	43,7 (7,5)	0
Behavioural outcome	**Mean T score and number of teachers with (sub)clinical scores on TRF**					
	IVH (n=25)		**IVH < 30 wks (n=19)**		**Controls < 30 wks (n=22)**	
	Mean T score (SD)	N (%) in (sub) clinical range	Mean T score (SD)	N (%) in (sub) clinical range	Mean T score (SD)	N (%) in (sub) clinical range
Total scale	54,7 (8,7)	6 (24%)	53,9 (9,0)	4 (21%)	50,9 (9,8)	4 (18%)
Internalizing problem scale	53,2 (10,8)	4 (16%)	52,2 (11,7)	3 (16%)	52,4 (11,4)	7 (32%)
Externalizing problem scale	54,3 (6,7)	3 (12%)	54,1 (7,0)	2 (11%)	49,7 (7,7)	2 (9%)

Effect of timing of PHVD- intervention

Data were available for 31 of the 32 children for this part of the analysis. (Table 3)

No significant differences were found in cognitive outcome between children treated early for their PHVD (before crossing the 97th centile + 4mm line of Levene) and children who were treated after they exceeded the 97th + 4mm line, neither in the grade III-IVH nor in the grade IV-IVH group.

Of the children receiving early intervention, 4/17 children developed CP, compared to 3/14 children who received late intervention (data of 1 child is missing) (p=.211).

Of the children (without CP) treated before they crossed the +4mm line, 4/13 (30.8%) performed below the p5 on the total Movement-ABC score (3 children had an IVH grade III) and 5/10 (3 children had an IVH grade III) who were treated late performed below p5 (50%, data of 1 child is missing). (p=.472).

DISCUSSION

In this study the neurodevelopmental and cognitive outcomes were evaluated among preterm infants who developed a severe IVH (grade III or IV) during the neonatal period and required neurosurgical intervention, either a ventricular reservoir and/or a VP shunt. The majority (59.4%) had no impairments in the form of cognitive problems, CP or epilepsy. Twenty-five percent developed CP and a further 39 percent of this population had a Movement-ABC score below the p 5. While the mean IQ of this total population was 93.4, 29% of the children had an IQ < 85 (-1SD). No significant differences were found between the IVH group and control group with respect to cognition, despite the fact that the IVH-group had a more complicated neonatal course compared with the control group.

It was of interest to see that CP was not seen in any of the children with a grade III IVH. This could maybe be explained by starting intervention early before the VI crossed the p97+4 mm line. Prolonged periods of raised intracranial

pressure with periventricular oedema and distortion of the developing axonal pathways with an adverse effect on subsequent myelination will thus be avoided. In the absence of obvious parenchymal involvement one would not expect CP to develop. Others have however shown that about a 25-57% of their patients did develop CP, with a greater risk when a shunt was required. [23] A Movement-ABC score below the p5 was however present in a third of our children with a grade III haemorrhage. CP was seen in just over half of the infants with a grade IV haemorrhage. They developed USCP, and the GMFCS level tended to be mild (level I-II) in all but one of the children.

We were unable to show significant differences with regard to timing of intervention. Since the number of patients in our study was limited, and we could not increase our sample size, we calculated that the power of our study to detect 15 points (1 SD) difference in IQ was 0.75.

Infants treated early did have a slightly better outcome, but no significant differences were found between infants treated early or late (once the P97+4mm was crossed). This could possibly be due to the fact that all infants were treated before the onset of any clinical symptoms of raised intracranial pressure occurred, such as a full fontanelle, apnea or a rapid increase in head circumference.

The effect of timing of intervention on neurodevelopmental outcome is an important, and still unanswered, question. The ELVIS (Early versus Late Ventricular Intervention Study; trial number ISRCTN43171322) trial is ongoing to assess the potential beneficial role of early intervention.

The percentage of children with behavioural problems in the (sub)clinical range, reported by parents (CBCL) seems to be relatively low (12%) in comparison with other studies and in comparison with the American norms, but is comparable with the 13% of the total group of preterm infants with a GA <30 wks in our hospital (n=307) (unpublished results).

Reijneveld et al. [24] compared children at 5 years of age born below 32 weeks and/or with a birth weight below 1500g (n=431) with a large national sample (n=6007): 22.1% of the preterm born infants had a clinical or subclinical score on the total scale of the CBCL in this study versus 15.0% in the general Dutch population. In the study of Roze et al. [25] the CBCL was administered

to 17 parents of preterm infants who were <37 weeks' gestation and who had a periventricular haemorrhagic infarction. Mean age was 8.7 years (range 4.4-12.5 years). 37 % of the children had a score in the clinical or subclinical range, compared to 9% in our IVH grade IV group (n=11). A possible explanation for the lower scores in our study could be the fact that we used the (newer) version of the CBCL for children of 1,5-5 years. In this version the subscales 'social problems' and 'thought problems' are not one of the subscales as it is in the version for 4-18 years. Odds ratios were relatively high for these scales in the study of Reijneveld et al. Comparable studies with the version 1,5-5 years are not yet available.

Scores are comparable with our scores in the IVH and control group, with an internalizing problem score of 15%- 20% on CBCL and TRF and externalizing problem percentage of 5%-10% on CBCL and in TRF. The study group is too small to conclude that the effect of prematurity on behaviour is higher than the influence of the presence of IVH or PHVD on behaviour in preterm infants. Further research is recommended.

A limitation of this study is the use of different intelligence tests. All tests have a mean IQ of 100 and SD of 15, but there are significant differences in mean IQ between children tested with the RAKIT or with the WPPSI. Between 2005 and 2007, 196 children born below 30 weeks and/or 1000 grams were tested with the RAKIT and the mean IQ of this group was 103. Between 2008 and 2010, 143 preterm born infants were tested with the WPPSI and the mean IQ of this group was 98. This difference of 5 IQ points is significant ($p < .05$) (unpublished results). In this population no significant differences were found between the RAKIT and the WPPSI. There is no significant effect on results measurable in this study, because only a small number of children were tested with the RAKIT (n=5). For the analyses with the control group we only compared children assessed by the same intelligence tests as their match in the IVH group.

There are striking differences between our results and previous data in the literature. In the study of Persson et al. [26] who studied 14 children with a GA< 32 wks with infantile hydrocephalus (shunt for PHVD), 58% of the children had an IQ < 70 compared to only 1/7 of our children (GA<32 wks and a shunt).

CP was seen in 88% of the 14 children with a GA< 32 wks, compared to 20% of the children with CP in our subgroup of preterm infants < 32 wks, only 1 child with a GA < 32 wks and a shunt had CP. Their treatment policy of PHVD may have been different from our policy. Timing of intervention is not clearly stated and neither is their mortality rate. It is possible that the GA range of their study population was different with more infants with a GA below 25 wks. During the study period, intensive care in the Netherlands was almost exclusively restricted to infants with a GA of 25 weeks or above, which could be a factor explaining our more favorable outcome. The policy regarding withdrawal of intensive care in very preterm infants with a severe haemorrhage may also be different, even though we have previously shown that our mortality rate (27.8%) was not different from other studies.[6]

Sherlock et al [23] examined the relationship between the severity of IVH and neurodevelopmental outcome in school-aged children born as ELBW or very preterm (< 28 weeks). They concluded that children with a grade IV IVH had a significantly worse neurodevelopmental outcome, with all children with a grade IV haemorrhage having CP and an IQ < -1SD. When we look at our population specific for the ELBW or very preterm infants (n=5), 3/5 have CP and only 1/5 had an IQ < 85. It is not clear whether the infants in their study developed PHVD and how or when the PHVD was treated.

Our results are similar to the results of Roze et al. [25] They also reported that preterm infants who had developed CP following a parenchymal haemorrhage and were seen again at school age had mostly limited functional impairment and the majority (57%) was still able to attend mainstream education. This is in agreement with our results; the GMFCS level of our children with CP had level I or II, and none of the children were in level IV-V.

Adams-Chapman et al [27] examined the neurodevelopmental outcome of Extremely Low Birth Weight (ELBW) infants with PHVD requiring shunt insertion. ELBW infants are at risk for adverse neurocognitive outcome. ELBW infants with PHVD requiring shunt insertion are at greater risk for an adverse outcome compared to those without a severe IVH and without an IVH needing insertion of a shunt. In this cohort high percentages of their infants with a grade III IVH/shunt

and IV IVH/shunt had CP, a PDI<70 and/or a MDI<70. Of the 8 ELBW infants in our cohort, three have no impairments, two have CP, and three have an IQ<85, but >70. We have only 4 shunt dependent infants meeting the same criteria of a BW< 1000g, three infants with a Grade III IVH. Of these 4, one has CP and 2 children have a DQ between 70 and 85.

CONCLUSION

The majority of the children in our population had no impairments, consisting of cognitive problems, cerebral palsy or epilepsy. CP was not seen in any of the infants with a grade III haemorrhage. Overall, our children with an IVH grade III or IV haemorrhage had a more favourable outcome than reported previously. Whether this was due to earlier neurosurgical intervention is currently being investigated in a prospective randomized trial.

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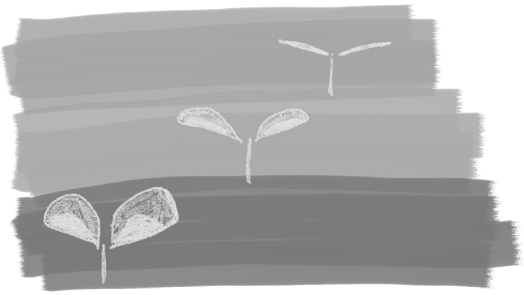
7

Intracranial haemorrhage in full-term newborns:

a hospital-based cohort study



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ABSTRACT

Introduction: In recent years intracranial hemorrhage (ICH) with parenchymal involvement has been diagnosed more often in full-term neonates due to improved neuroimaging techniques. The aim of this study is to describe clinical and neuroimaging data in the neonatal period and relate imaging findings to outcome in a hospital-based population admitted to a level 3 Neonatal Intensive Care Unit (NICU).

Methods: From our neuroimaging database, we retrospectively retrieved records and images of 53 term infants (1991-2008) in whom an imaging diagnosis of ICH with parenchymal involvement was made. Clinical data, including mode of delivery, clinical manifestations, neurological symptoms, extent and site of the hemorrhage, neurosurgical intervention and neurodevelopmental outcomes, were recorded.

Results: Seventeen of the 53 term infants had infratentorial ICH, 20 had supratentorial ICH, and 16 had a combination of the two. Seizures were the most common presenting symptom (71.7%), another ten infants (18.9%) presented with apneic seizures, and five infants had no clinical signs but were admitted to our NICU because of perinatal asphyxia (n=2), respiratory distress (n=2) and development of posthemorrhagic ventricular dilatation (n=1). Continuous amplitude-integrated electroencephalography recordings were performed in all infants. Clinical or subclinical seizures were seen in 48/53 (90.6%) infants; all received anti-epileptic drugs. Thirteen of all 53 (24.5%) infants died. Lowest mortality rate was seen in infants with supratentorial ICH (10%). Three infants with a midline shift required craniotomy, six infants needed a subcutaneous reservoir due to outflow obstruction, and three subsequently required a ventriculoperitoneal shunt. The group with poor outcome (death or developmental quotient (DQ) <85) had a significantly lower 5-min Apgar score (p=.006).

Follow-up data were available for 37/40 survivors aged at least 15 months. Patients were assessed with the Griffiths Mental Developmental Scales, and the mean DQ of all survivors was 97 (SD=12). Six infants (17%) had a DQ below

85 (2 of them had cerebral palsy). Three infants developed CP (8.6%); one had cerebellar ataxia, and two had hemiplegia.

Conclusions: ICH with parenchymal involvement carries a risk of adverse neurologic sequelae with a mortality of 24.5% and development of cerebral palsy in 8.6%. The high mortality rate could partly be explained by associated perinatal asphyxia. Infants with a supratentorial ICH had a lower, although not significant, mortality rate compared with infants with infratentorial ICH and infants with a combination of supratentorial and infratentorial ICH. In spite of often large intraparenchymal lesions, 30 of the 34 survivors without cerebral palsy (88.2%) had a normal neurodevelopmental outcome at 15 months.

Keywords: Intracranial Hemorrhage - Intraparenchymal hemorrhage - Subdural Hemorrhage - Full-term newborns

INTRODUCTION

Neonatal intracranial hemorrhage (ICH) has five major clinical types: subdural hemorrhage (SDH), primary subarachnoid hemorrhage (SAH), cerebellar hemorrhage, intraventricular hemorrhage (IVH), and intraparenchymal hemorrhage. SDH and intraparenchymal hemorrhage are more often found in the term infant, while SAH, IVH and cerebellar hemorrhages are more common in the preterm infant.[1]

ICH, including SDH (with or without parenchymal involvement), used to be a common cause of neonatal death following a traumatic delivery, but the incidence has decreased with improved obstetric care. In recent years, SDH has been recognized more often mainly because neuro-imaging is now also performed routinely in infants not presenting with clinical symptoms.[1] ICH in the term infant usually presents with nonspecific neurological signs and symptoms. Signs can be general and may not point directly to the brain as the source of the problem. [2]

ICH in the newborn is frequently associated with a prolonged or precipitous delivery, vaginal breech delivery, instrumental delivery, useof forceps or ventouse extraction, and primiparity or extreme multiparity. [2-6] Hemorrhage may be due to rupture of veins in the subdural space, with bleeding from the venous sinus or from hemorrhage within the cerebellum. [2] Accumulation of blood in the posterior fossa can cause neurologic symptoms that manifest within the first few days after delivery, such as a tense or bulging fontanelle, increasing head circumference, apneas, bradycardia, and/or seizures. [3] The true incidence of intracranial hemorrhage is probably higher than reported because only a fraction of the infants with ICH present with clinical symptoms.[1]

The aim of this study was to describe precipitating factors, presenting symptoms, neuroimaging data, and neurodevelopmental outcome of infants in whom an imaging diagnosis [computed tomography (CT) or magnetic resonance imaging (MRI)] of ICH was made.

METHODS AND PATIENTS

Patients

The study was approved by the local ethical committee. Between October 1991 and November 2008, 53 neonates with a gestational age (GA) of 37 weeks or more were admitted to the level 3 neonatal intensive care unit (NICU) of a hospital with a diagnosis of ICH associated with parenchymal involvement. All records and images of infants in whom an imaging diagnosis of an ICH was made were retrieved from a neuroimaging database. Clinical data, including mode of delivery, clinical manifestations, neurological symptoms, treatment, neurosurgical intervention, and neurodevelopmental outcomes were recorded. Infants were only eligible when SDH or SAH was diagnosed in the presence of associated parenchymal injury. Neurological development was assessed in all surviving patients at approximately 24 months of age.

Neuroimaging

Cranial ultrasound was performed within the first 6 h after admission and repeated at least two times a week until discharge.

Ultrasound findings were confirmed by CT and/or MRI. CT was only performed on the day of admission when a shift of the midline was noted with cranial ultrasound and neurosurgical intervention was considered. MRI was the preferred neuroimaging technique and was performed within a week of delivery to obtain detailed information about parenchymal involvement.

MRI was performed on a 1.5-Tesla Philips system (Intera or Achieva 1.5 T; Philips, Healthcare, Best, The Netherlands). Sagittal T1-weighted images (TR: 450-550 ms; TE: 15-30 ms; slice thickness = 5 mm), axial inversion recovery (IR) scan (TR: 2,500-3,000 ms; TE = 30 ms; slice thickness: 2 or 5 mm) and axial T2-weighted images (TR: 3,000-3,150 ms; TE: 150 ms; slice thickness: 2-5 mm) were acquired. During the last 4 years phase contrast sagittal (PCA) images have been added to the protocol. When indicated, magnetic resonance venography (MRV) was performed with flow velocities of 30 and 15 cm/s. Phase contrast sagittal images became available in 2003 but were used routinely starting in 2006,

and three-dimensial (3D) MRV became available in 2008. Since 1995, diffusion weighted (DW) MRI has been performed using an interweaved DW acquisition with an echo planar imaging factor of 41, a TR/TE of 4,000/148ms, a field of view of 210mm x 210mm, a slice thickness of 4 mm, a slice gap of 0.5 mm, and *b* factors of 0 and 1,000 s/mm^2. After completion of imaging, the trace apparent diffusion coefficient map was calculated to avoid confusion with T_2 effects.

ICH was divided into three categories based on the site of hemorrhage; supratentorial, infratentorial or a combination of the two sites. Every lobe (frontal, temporal, parietal, and occipital) of every case was described in detail. The presence of a midline shift was recorded.

Amplitude-Integrated Electroencephalography

Continuous one-channel or two-channel amplitude-Integrated Electroencephalography (aEEG) recordings were routinely used in all infants admitted with neurological problems or perinatal asphyxia (such as Apgar score at 5 minutes < 5, pH<7.10, multi organ failure, or clinical seizures) to assess the background pattern and to aid in the detection of (sub)clinical seizures.

Anti-epileptic medication protocol

Phenobarbital is the first choice for anti-epileptic drug (AED). From 1992 to 1998, lidocaine was used as rescue treatment when other anti-convulsive drugs (phenobarbital, phenytoin, and midazolam) had failed.[4] Lidocaine is administered following a strict protocol. From 1998 onwards, we have been using a strict AED protocol: phenobarbital first, followed by midazolam and lidocaine.

Assessment of Neurodevelopmental Outcome

The surviving infants were seen in the follow-up clinic at regular intervals. Assessment of outcome was based on clinical examination at discharge and follow- up using the Griffiths Mental Developmental Scale (GMDS) at a mean age of 20 months.

The GMDS provides a subscale and general developmental age and quotient equivalents (mean = 100; SD = 15) of raw scores. Five domains of functioning are

tested: locomotor, personal-social, hearing and speech, eye-hand coordination, and performance. The GMDS shows continuity validity with time and across cultures.[5,6] A DQ of >85 at 2 years of age is considered to be within the reference range. The infants were assessed by developmental pediatricians / neonatologists using the GMDS.

Statistics

Statistical analysis was performed using the Mann-Whitney or Kruskal-Wallis test, the $\chi 2$ test for comparison of proportions and the analysis of variance for comparison of means.

Statistical analyses were performed by using SPSS software for Windows, version 15 (SPSS, Chicago, IL). Statistical significance was set at $p = .05$.

RESULTS

Clinical characteristics

Between October 1991 and November 2008, 53 full-term neonates (30 male neonates and 23 female neonates) with ICH and associated parenchymal involvement were admitted to our level 3 NICU. All infants had both intra-axial hemorrhage (intraparenchymal and intraventricular) and extra-axial hemorrhage (subdural and subarachnoid). Associated SDH was present in 50/53 infants (94.3%), SAH was present in 8/53 (15.1%), and associated IVH was present in 12/53 infants (22.6%). A combination of SAH and SDH was present in 6/53 infants (11.3%); from among these six infants, three (5.7%) had an IVH as well.

The clinical characteristics of the infants, divided into three groups (supratentorial, infratentorial and supratentorial plus infratentorial), are summarized in Table 1. Clinical presentation occurred in 47.2% on the first day after birth (n=25) and in 26.4% on the second day (n=14), eight infants showed signs between 3 and 5 days, and one infant first presented with severe ventricular dilatation at 30 days. Seizures were the most common presenting symptom (71.7%); a further ten infants (18.9%) presented with apneic seizures, and five

infants had no clinical signs but were admitted to our NICU because of perinatal asphyxia (n=2), respiratory distress (n=2) and development of posthemorrhagic ventricular dilatation (n=1).

Table 1: Clinical characteristics of the study population

	Supratentorial (n= 20)	**Infratentorial (n= 17)**	**Supratentorial + infratentorial (n= 16)**	**p-value**
Male / Female	9 / 11	11 / 6	10 / 6	.411
Gestational age, (weeks) [mean ± SD]	38 ± 1	40 ± 1.2	39 ± 1.3	.005
Birth weight, (g) [mean ± SD]	3,229 ± 719	3,437 ± 539	3,130 ± 594	.378
Apgar score at 1 min [median (range)]	8 (0-10)	6 (0-10)	7 (1-9)	.046
	10 (4-10)	6 (0-10)	8 (1-10)	.033
Day of clinical presentation [median (range)]	2 (1-4)	1 (1-5)	1 (1-30)	.096
Day of MRI /CT [median (range)]	1 (1-9)	2 (1-14)	1 (1-26)	.77
Mortality [*n* (%)]	2 (10)	6 (35.3)	5 (31.3)	.160

Infants with poor outcome (death or a DQ of <85) had a significantly lower Apgar score at 5 minutes (p=.006). All were born at term (>37 wks), with a mean birth weight of 3,265 grams (SD = 630), 8 infants (15.1%) had a birth weight of ≥ p95, and 12 infants (22.6%) had a birth weight below p10, according to The Dutch Perinatal Registry Birth Weight centiles (http://www.perinatreg.nl/referentiecurven).

Thrombocytopenia (<150 x 10^9 /L^{-1}) was present in 11/50 (22%; data for three infants were not available). Thrombocytopenia was significantly more common in infants who died than in survivors (6/13 versus 5/37; p=.023). Thrombocytopenia was due to neonatal alloimmune thrombocytopenic purpura in one infant.

Among 9 of 53 infants, clotting time (activated partial thromboplastin time and thrombin time) was not available. Of the remaining 44 infants, 12 (27.3%) infants had prolonged clotting time; 5 of 32 survivors (missing data for eight) had prolonged clotting time versus 7 of 12 infants who died (missing dat for one; p=.008). One of the survivors had haemophilia A (factor VIII).

Mode of delivery

Thirty-six of the 53 mothers (67.9%) were nulliparous. (Table 2) Uncomplicated spontaneous vaginal delivery was the mode of delivery in 14/53 (26.4%). In 10/20 (50%) infants with a supratentorial ICH compared to 2/17 (11.8%) infants with an infratentorial ICH and 2/16 (12.5%) infants with a supra- and infratentorial ICH, an uncomplicated spontaneous vaginal delivery was the mode of delivery (p=.010). Twelve infants (22.6%) were delivered with ventouse extraction; 7/17 (41.2%) infants with an infratentorial ICH compared to 3/20 (15%) infants with a supratentorial ICH and 2/16 infants (12.5%) with a supratentorial and infratentorial ICH (p=.174). Vaginal breech delivery was the mode of delivery in 11/56 (25%), in 3/17 (17.6%) infants with infratentorial ICH, and in 8/16 (50 %) infants with a supratentorial and infratentorial ICH (p=.132).

Of the five infants delivered by Caesarean section (CS), four were delivered by emergency CS, and one was delivered by elective CS because of breech presentation.

Table 2: Delivery

Delivery	Supratentorial (n)	Infratentorial (n)	Supratentorial + infratentorial (n)	Total (n)
Breech		3	8	11
Vaginal	10	2	2	14
Ventouse	3	7	2	12
Ventouse followed by Caesarean section	1	2	1	4
Precipitous	1	1		2
Forceps / breech		1		1
Ventouse + forceps followed by Caesarean section		1		1
Caesarean section	4 (1 elective)		1	5
Ventouse + forceps			1	1
Forceps			1	1
prolonged	1			1
Total	**20**	**17**	**16**	**53**

Clinical findings

Thirty-three (62.3%) infants required intubation and ventilation: 31 infants were intubated due to respiratory insufficiency, and two infants were intubated and ventilated prior to neurosurgical intervention.

aEEG recordings were obtained in all infants. Clinical or subclinical seizures were the presenting symptom in 48/53 (90.6%) infants, and different AEDs were administered to all. Phenobarbital was administered to 46 infants, 1 infant received lidocaine, and 1 infant showed seizures before admission and needed no medication after admission. Of these 48 infants, 18 were treated with phenobarbital monotherapy, 12 infants needed two different AEDs, and 18 infants needed three or more AEDs. Of the 13 infants who died, 1 infant had status epilepticus, 7 infants had an isoelectric recording, 4 infants had a burst-suppression background pattern with epileptic activity, and 1 infant a discontinuous background pattern without sleep-wake cycling. In all but four infants, a standard electroencephalogram was performed as well to confirm the aEEG diagnosis.

Mortality

Intensive care was withdrawn in 13 of the 53 infants (24.5%) because of a combination of neuroimaging findings and neurophysiologic data, consisting mostly of a severely abnormal aEEG result, including a very suppressed background pattern with seizures that persisted despite administration of different AEDs. Infants with a supratentorial ICH had a lower, although not significant, mortality rate compared with infants with infratentorial ICH and infants with both supratentorial and infratentorial ICH; 2/20 (10%) infants with supratentorial ICH, 6/17 (35.3%) infants with infratentorial ICH and 5/16 (31.3%) infants with ICH involving both the supra- and infratentorial region died.

Postmortem examination

In 10/13 infants, parental permission for autopsy was obtained. In four infants, infratentorial SDH was associated with a tentorial tear. Three infants had parenchymal hemorrhage associated with extensive ischemic lesions, one

infant had a massive ICH, one infant had a massive hemorrhage in the temporal lobe combined with parenchymal infarction, and one infant had temporal parietal hemorrhage associated with parenchymal cysts and histological findings compatible with hypoxic ischemia following neonatal alloimmune thrombocytopenia.

Imaging findings

All infants were examined with cranial ultrasound. MRI or CT was performed in all but four infants, who were too unstable to be transported to the CT or MR unit. Twelve infants had CT only, 12 infants first had CT followed by MRI, and 24 infants had MRI only. Two of the four infants who did not have MRI or CT had postmortem examination.

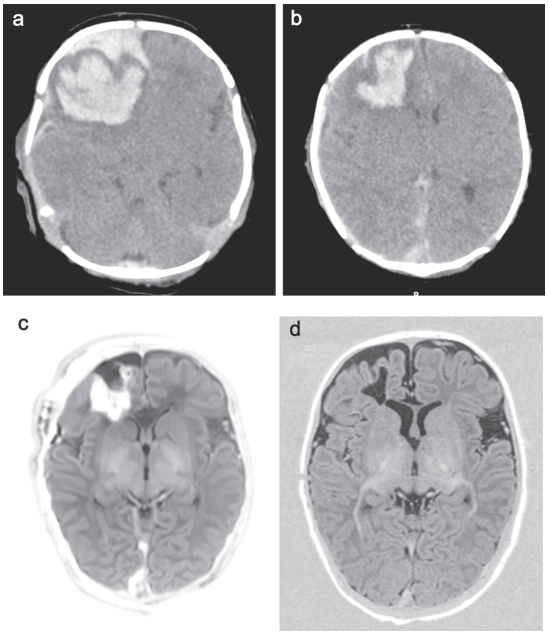

Figure 1: CT performed on day 2 **(a, b)**, showing a large intraparenchymal and SDH in the right frontal lobe, causing a shift in midline. MRI and IR axial view obtained on day 8 following craniotomy **(c)** showing resolution of the midline shift and reduction of subdural and intraparenchymal hematoma. A repeat MRI, IR axial view at 3 months **(d)** shows a small area of cavitation and mild atrophy of the right frontal lobe. Outcome was well within the normal range at 2 years of age.

The frontal lobe was predominantly affected in 11 infants; this was associated with a midline shift in 7 infants and required surgical intervention in 3 infants. (Fig 1) Delivery was uncomplicated in 7/11 infants (63.6%). The temporal lobe was primarily involved in ten infants. Both frontal and temporal parenchymal hemorrhages can be associated with cerebral sinovenous thrombosis (CSVT). Only 4/21 infants with frontal or temporal parenchymal hemorrhage, possibly associated with a CSVT, were studied with a PCA, but none had 3D MRV. A possible CSVT of the superior sagital sinus was suspected on PCA in one child with a large frontal parenchymal hemorrhage.

The occipital lobe was more often involved in infants with both supratentorial and infratentorial hemorrhage (75%), compared with 40% of the infants with supratentorial hemorrhage. (Fig 2)

Follow-up MRI was performed in 30/40 survivors between 6 weeks and 10 years.

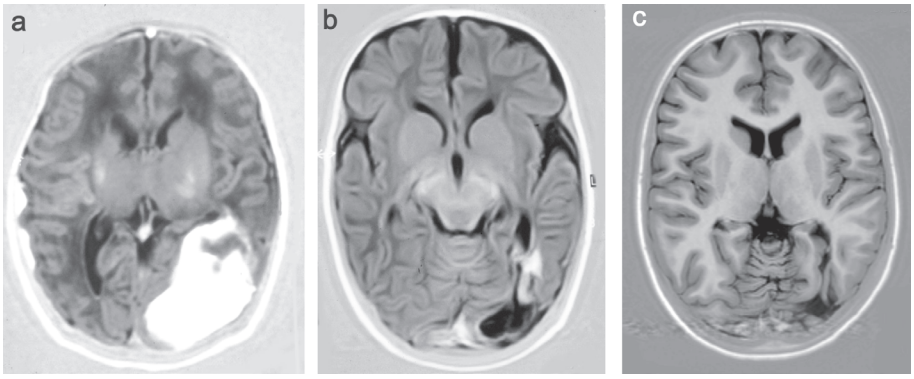

Figure 2: MRI and IR axial view obtained on day 8, at 3 months, and at 11 years. A large parieto-occipital hemorrhage is seen in the neonatal period **(a)**. The hemorrhage has almost completely resolved by 3 months, resulting in a small cavity **(b)**, which is still present at 11 years **(c)**. Outcome is within the normal range.

Surgical intervention

Twenty-one infants (39.6%) showed an associated midline shift. In only three infants was this considered severe enough to require neurosurgical intervention (all three had supratentorial ICH). These infants had craniotomy to reduce intracranial pressure. Of the 21 infants, 12 (57.1%) had supratentorial ICH. In the infratentorial ICH group 5/17 (29.4%) showed a midline shift of the cerebellum. Of the infants with supratentorial and infratentorial ICH, four (25%) had a midline shift, of which one infant had both a supratentorial midline shift and a midline shift of the cerebellum.

Sixteen (30.2%) infants developed hydrocephalus due to outflow obstruction following supratentorial hemorrhage in 3/20, infratentorial hemorrhage in 7/17, and combined supratentorial and infratentorial hemorrhage in 6/16. Nine infants were treated with isosorbide, an osmotic diuretic that is considered to reduce the production of cerebrospinal fluid. [7] Six infants had insertion of a subcutaneous ventricular reservoir to control ventricular size and intraventricular pressure, which was increased due to the outflow obstruction; one infant had an external ventricular drain. Three infants subsequently needed a ventriculo-peritoneal drain, in two infants, revision of the ventriculo-peritoneal drain was necessary, and one infant needed multiple revisions.

Outcome

Of the 40 surviving infants, 37 were seen in the follow-up clinic at a mean age of 20 months (range, 15-29 months of age; 24 infants were between 18 and 26 months of age); one infant was lost to follow-up and two infants were still too young. The mean DQ was 97 (SD = 12). Infants with infratentorial ICH had a mean DQ of 99 (SD = 12), those with supratentorial ICH had a mean DQ of 96 (SD = 11), and those with a supratentorial and infratentorial ICH had a mean DQ of 96 (SD = 14), which was not significantly different. Of these 37 infants, 31 (83.8%) had a DQ > 85. No significant difference in outcome - whether or not a midline shift was present - was found. Infants needing neurosurgical intervention, either craniotomy or reservoir, had a mean DQ of 96 (SD = 13). No significant difference was found on whether or not the infant needed neurosurgery.

Of the 12 infants with a birth weight below p10, seven had a poor outcome (four infants died, and three had a DQ of <85), and three infants had a DQ of >85 (missing data for one, and one was too young). Six of the eight infants with a birth weight of ≥p95 had a DQ of >85, and one infant died.

Involvement of a single lobe was seen in 9 of the 20 infants with supratentorial ICH. No significant difference in outcome was seen on whether or not there was involvement of one, two, or three lobes. The infants in which the frontal lobe was predominantly affected had a mean DQ of 99 (SD = 8.3) and one infant had a DQ of <85 (missing data for two).

One infant with supratentorial ICH developed postneonatal epilepsy. Two infants - one with infratentorial ICH and one with supratentorial and infratentorial ICH - had visual impairment. One infant with supratentorial and infratentorial ICH had infantile esotropia. Three infants developed cerebral palsy (CP); one infant developed cerebellar ataxia following a severe cerebellar hemorrhage (Fig 3) (never achieved independent walking), and two infants developed a hemiplegia following severe supratentorial hemorrhage, one needed craniotomy, and one scored low on all five domains of the GMDS.

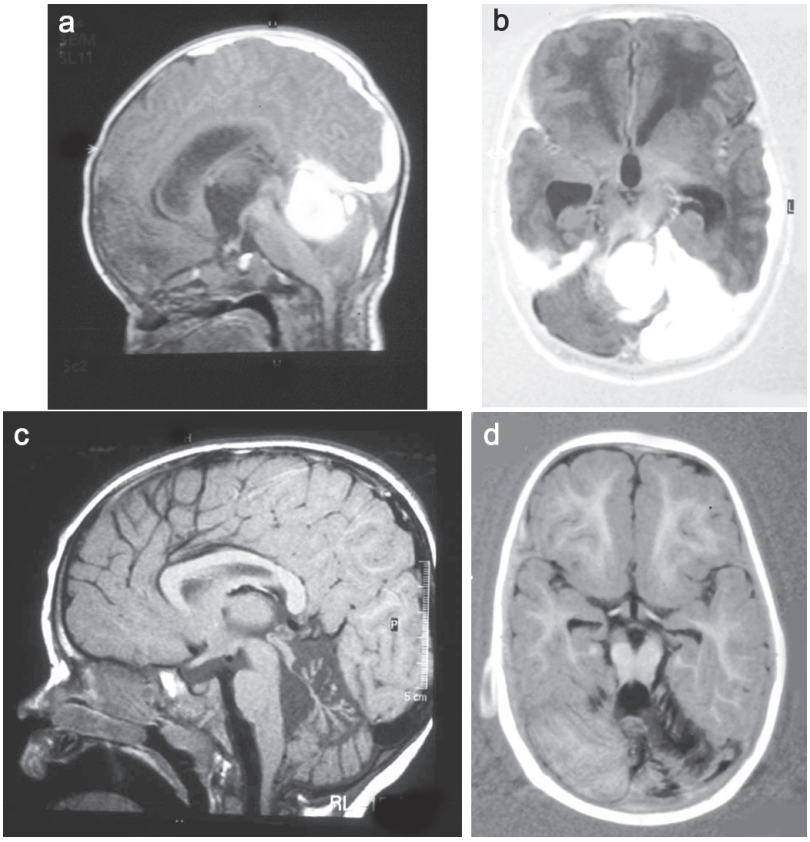

Figure 3: MRI, T1-weighted spinecho, midsagittal view **(a)**, and IR, axial view **(b)**, both obtained on day 10; T1-weighted SE, midsagittal view **(c)** and IR, axial view, obtained at 18 months of age **(c,d)**. A large infratentorial haemorrhage involving the left cerebellar hemisphere and the fourth ventricle is seen. There is also a supratentorial SDH **(a,b)**. Follow-up MRI shows severe atrophy of the vermis and the left cerebellar hemisphere **(c,d)**. The child developed severe ataxia and also has growth hormone deficiency.

DISCUSSION

We report neonatal and follow-up data of 53 full-term infants with ICH with associated parenchymal involvement admitted to a level 3 NICU over a period of 17 years. This is a large hospital-based cohort of infants with symptomatic ICH. Most studies [1,8-10] described asymptomatic infants with SDH or small series of symptomatic ICH. [11-14] The study of Rooks et al [9] shows a high incidence of ICH in asymptomatic infants.

In our study the mortality rate was high (24.5%), but the neurodevelopmental outcome among the survivors, with known outcome, was within the normal range in the majority of the children (83.8%). The high mortality rate could partly be explained by associated perinatal asphyxia, since the group with a poor outcome (death or a DQ of <85) had a significantly lower Apgar score at 5 min (p=.006). Apgar scores at 1 min were less than 7 in 46.2% of the infants, and Apgar scores at 5 min were less than 7 in 28.8% of the infants. Infants with poor outcome had a significantly lower Apgar score at 5 min, which could be due to associated perinatal asphyxia.

The most important finding in the report by Towner et al. [15] is that forceps assistance, ventouse extraction, and CS were all associated with an increased risk for ICH. Benedetti [16] stated that if an attempt for operative vaginal delivery fails, the risk of injury is increased no matter which method of delivery is chosen. In the study of Whitbey et al [1], those delivered by forceps after attempted ventouse delivery were more likely to have SDH compared to those delivered by any other method of delivery. The common risk factor for ICH is therefore complicated labor. [15,17] This is similar to the results in our population where 38% of the deliveries were assisted ventouse or forceps deliveries or CS following a failed attempt for instrumental vaginal delivery. Fifteen infants (27%) in our population were delivered by elective CS (n=1) or were uncomplicated vaginal deliveries (n=14); all these infants had supratentorial ICH. Huang and Robertson [12] also reported five infants who had spontaneous parenchymal hemorrhage after a vaginal delivery. The series of Looney et al. [8] and Whitby et al. [1] did not report any infants with an ICH after delivery through CS. In our group, however, five

infants with supratentorial ICH were delivered by CS; four infants were delivered via emergency CS because of fetal distress.

Several risk factors have been reported in term newborns with ICH, but only a few studies have demonstrated a relationship between the proposed risk factors and ICH, and these comprise only a small number of cases. [18] Thrombocytopenia is the most common condition associated with ICH. [19]. In our population 11 infants (22%) had a platelet count of less than 150 x 10^9 /L^{-1} on admission (data of three infants are missing), with 8% of the infants having a platelet count <70 x 10^9 /L^{-1}. Jhawar et al [19] described a high prevalence (30.8%) of infants with a platelet count <70 x 10^9 /L^{-1}, and they concluded that thrombocytopenia is the most important predictor of ICH and is also associated with the most severe type of hemorrhage, in agreement with our findings. Infants who died had significantly more often a thrombocytopenia. [19] It is therefore recommended that a coagulation profile be obtained from all infants suspected to have ICH. Since this is a retrospective study, we have limited data about the associated coagulopathy of our infants.

The mean birth weight in our group was on the 40th percentile; however, 9 infants (17%) had a birth weight above the 90 th percentile, and 12 infants (22.6%) had a birth weight below the 10th percentile. Infants with a birth weight of <10th percentile were more at risk for an adverse outcome. We did not have reliable head circumference data on our patients because caput succedaneum was often present following a ventouse extraction. This measurement was therefore not included in the analysis.

Nulliparous women are more likely to deliver with ventouse or forceps assistance and therefore are at increased risk. [17,20] In our cohort, 36 (67.9%) of the mothers were nulliparous and only one woman an extreme multiparous, an associated factor previously mentioned by others. [21]

While the strength of this study is that it spans a period of almost 20 years, this also led to a major limitation of this study, with a change in imaging sequences over the years. While we were initially only able to perform T1 and T2 sequences in these newborn infants, diffusion-weighted imaging became available in the mid-1990s; MRV (initially phase contrast parasagittal scans and later 3D-MRV)

became available some 4 years ago, enabling us to diagnose CSVT in some of these children, while this could only be assumed in those born in the 1990s (Fig 4). Infants with a confirmed CSVT with unilateral thalamic hemorrhage were reported previously. [22] We consider this subgroup of infants as a different group – often displaying a later onset of symptoms and mostly born after an uncomplicated vaginal delivery, but with signs of infection and/or dehydration - and therefore did not include them in the present study. [23] It is well possible that our infants with temporal lobe hemorrhage did indeed have a sinovenous thrombosis, but we were unable to prove this due to the lack of MRV in most of these infants. It has recently been suggested that infants with temporal lobe hemorrhage tend to present with apneic spells. [24,25] In our group, 11 infants had involvement of the temporal lobe, and 6/11 (54.5%) presented with apneic seizures. (Fig 4) Slaughter et al. [13] described the surprisingly good outcome of infants with hemorrhagic infarct in the temporal lobe. As there was only one infant with a single temporal hemorrhage in our population, we cannot draw the same conclusion. Most of our infants also had involvement of either the parietal lobe and/or the occipital lobe. However, our conclusion for this whole population is the same: despite often impressive imaging abnormalities and clinical presentation, infants with ICH tend to have better early outcome than expected. Clinical follow-up needs to be continued to school age, as these infants are likely to be at risk for cognitive or behavioral problems at school age.

CONCLUSION

ICH with parenchymal involvement carries a risk of adverse neurologic sequelae with a mortality of 24.5% and a development of CP in 8.6%. The high mortality rate could partly be explained by associated perinatal asphyxia. Infants with supratentorial ICH had a lower, although not significant, mortality rate compared with infants with infratentorial ICH and infants with combined supratentorial and infratentorial ICH. In spite of often large intraparenchymal lesions, 88.2% of the survivors without CP had a normal early neurodevelopmental outcome.

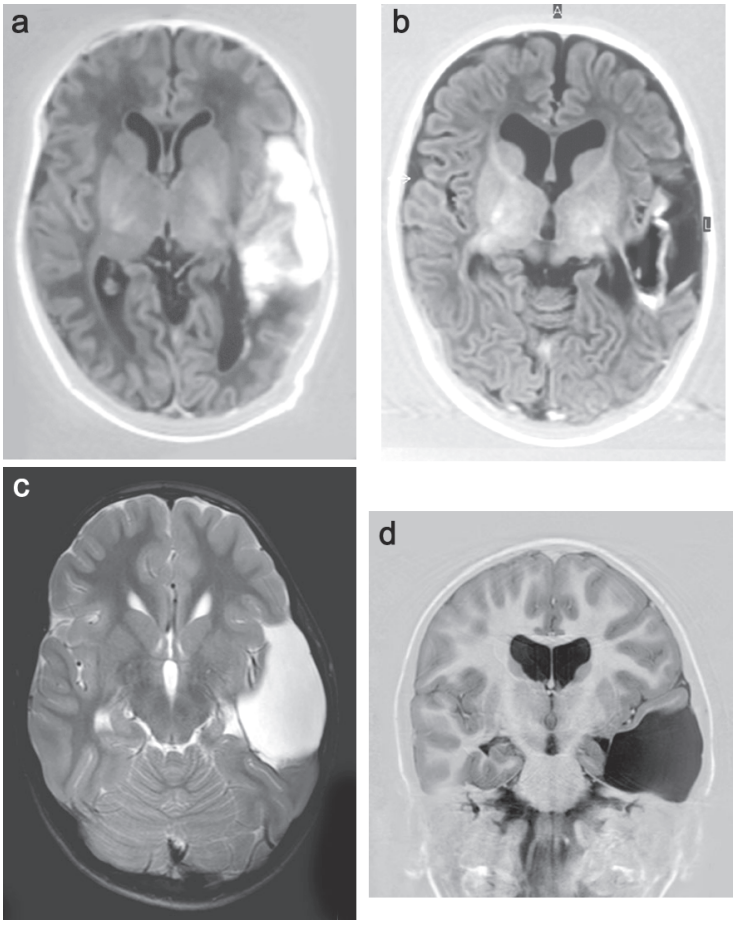

Figure 4: MRI, IR **(a,b)**, and T2 spin echo **(c)** axial views obtained on day 10, at 3 months and at 7 years and coronal IR **(d)** obtained at 7 years. A large hemorrhage in the temporal lobe is seen in the neonatal period **(a)** with cystic evolution at 3 months **(b)**. End stage of the lesion showing complete destruction of the left temporal lobe can be appreciated at 7 years **(c,d)**. Outcome is complicated by behavioral problems (tics and hyperactivity).

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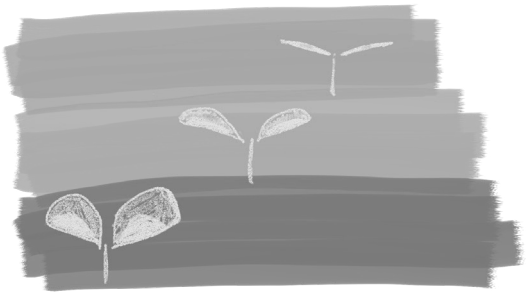
8

Summary & Future directions



In this thesis we have described the treatment and subsequent outcome of preterm infants with a severe intraventricular haemorrhage (IVH) who subsequently developed post haemorrhagic ventricular dilatation (PHVD) and the treatment and outcome of term infants who suffered from an intracranial haemorrhage (ICH).

As a result of improvements in neonatal care during the last decades and maybe also because of earlier and more effective intervention, PHVD is no longer invariably associated with an unfavourable outcome. Preterm infants who develop rapidly progressive PHVD in the absence of associated parenchymal lesions may even have a normal outcome at school age.

SUMMARY

In *chapter 2*, we have described the results of a European survey about the diagnosis and treatment of PHVD. We obtained a positive response in 86.5% of the neonatologists from 17 different European countries. This questionnaire offers insight into the variety of different perspectives regarding the diagnosis and treatment of PHVD among European centres with a special interest in neonatal neurology. From this survey, it can be concluded that there are considerable differences in the diagnostic and therapeutic approaches to the preterm infant with PHVD.

In *chapter 3*, we retrospectively studied the incidence of infections of subcutaneous reservoirs in preterm infants. The number of infants with an infection of the reservoir decreased considerably over the two 6-year periods. Subcutaneous reservoirs appeared to be a safe and effective method to ensure controlled CSF removal in preterm infants with PHVD. In experienced hands, the incidence of an infection or major complications remains < 5%, which we consider within acceptable limits.

In *chapter 4*, we described a pilot study which involved implementing nurses' performance of ventricular punctures. This practice innovation was successfully adopted by nurses and physicians. The successful change in policy means that punctures are now performed on schedule and nurses have more control in planning periods of rest for the infants in their care.

In *chapter 5*, we evaluated the natural evolution of GMH-IVH, the need for intervention for PHVD, and neurodevelopmental outcome at 24 months corrected age in 214 preterm infants (≤ 34 weeks GA). Forty-four percent had a grade III intraventricular hemorrhage and 56% infants a grade IV hemorrhage. The short-term neurodevelopmental outcome of preterm infants with a grade III or IV hemorrhage was better than reported previously. [1,2] If was of interest to find that there was no significant difference in DQ at 24 months corrected age between infants who did or did not need intervention. Requiring intervention for PHVD only had a negative effect on DQ in infants with a grade IV hemorrhage. Infants with cerebral palsy had significantly lower DQs, irrespective of the severity of IVH.

As this was an observational study, we could only speculate about the positive role of early intervention. Infants in whom intervention was started before they crossed the p97+4 mm line had a better DQ at 2 years corrected age than infants who were treated once this line was crossed.

In *chapter 6*, we evaluated the neurodevelopmental and cognitive outcome in preterm infants at school age, who had a severe IVH (grade III or IV) and required neurosurgical intervention, either a subcutaneous reservoir and/or a VP shunt. The majority (59.4%) had no neuroimpairments in the form of learning disabilities, CP or epilepsy. Thirty-nine percent of this population had definite motor problems; the mean IQ of the total population was 93.4, 29% of the children had an IQ < 85 (-1SD). Children in the grade IV group were more at risk to develop CP, irrespective of timing of intervention. This was as expected, as there was involvement of the brain parenchyma. None of the children with a grade III hemorrhage developed CP. This is different from other studies. We

speculate that this is due to early intervention, avoiding prolonged periods of raised intracranial pressure with periventricular oedema and distortion of the developing axonal pathways and disturbance of the myelination process.

In *chapter 7*, we reported neonatal and follow-up data of 53 full-term infants with ICH with associated parenchymal involvement admitted to a level 3 NICU over a period of 17 years. This is a large hospital-based cohort of infants with symptomatic ICH. ICH with parenchymal involvement carries a risk of adverse neurological sequelae with a mortality of 24.5% and a development of CP in 8.6%. The high mortality rate could partly be explained by associated perinatal asphyxia. Infants with supratentorial ICH tended to have a lower mortality rate compared with infants with infratentorial ICH and infants with combined supratentorial and infratentorial ICH. In spite of often large intraparenchymal lesions, 88.2% of the survivors without CP had a normal early neurodevelopmental outcome.

FUTURE DIRECTIONS

In contrast to a reported decrease in incidence of c-PVL [3], there is no fall in the incidence of IVH grade III and IV. Both remain at a constant level over time and infants who suffer from an IVH grade III and IV are at risk of adverse neurological sequelae.[4] It is clear that we need interventions to decrease this incidence. Postnatal administration of phenobarbitone cannot be recommended as prophylaxis to prevent IVH in preterm infants and is associated with an increased need for mechanical ventilation.[5] Approximately 80% of IVH occurs by 72 h after birth but a considerable proportion of IVH is visible on the first scan performed within a few hours after birth. [6] This means that interventions to prevent IVH should ideally be commenced prior to, or immediately after birth. PHVD is common in preterm infants who suffer a large IVH and is associated with an increased risk of an adverse neurological outcome. We should aim for an optimal management of PHVD both with regard to timing of intervention and the best method. [7]

There are still opportunities to improve care for infants in the neonatal period, especially for those who are at risk of haemorrhagic brain injury:

1. Delayed cord clamping has been reported to be associated with a decreased incidence of IVH [8-10] The data of the RCT by Mercer et al. [8] indicates that a brief delay in cord-clamping time, 30 to 45 seconds, accompanied by lowering the infant to hasten the placental transfusion offers protection from IVH. This is a simple intervention that could easily be implemented in daily practice.

2. Evaluation for the need of a six hour period of lying flat.
To prevent hypotension, bradycardia, nausea and vomiting, infants in our hospital have to lie flat for six hours after a puncture from the subcutaneous reservoir. These six hours are not based on any evidence. Infants lie flat for 6-18 hours a day, depending on the frequency of punctures. This is inconvenient for both infants and parents. It could be of benefit to the patient, and parents, to shorten this period. The length of this period should be studied, by scanning the infant every hour (to judge the refilling of the ventricle) combined with a tool to measure the comfort of the infant (e.g. the skin conductance algesimeter; SCA, or Comfort Scale). [11-13]

3. The introduction of an '*IVH prevention bundle*' may be a useful preventive strategy to reduce severe IVH. The IVH prevention bundle could include the following: head of the isolette/cot at 15 degrees, head in the midline during the first 72 hours, avoid a head down position, avoid rapid flushes of fluid and medication and maintain temperature greater than 36.5 degrees C. A prospective study is needed to confirm preliminary observations. [14]

4. Measurement of near infrared spectroscopy (NIRS) during PHVD management. Increased intracranial pressure may reduce cerebral perfusion and cause ischaemia during a critical period. In daily clinical practice cerebral oxygenation can be monitored continuously, non-invasively and at the bed side

using NIRS. The NIRS-monitored regional cerebral oxygen saturation has also shown to be an estimator of cerebral tissue perfusion. This could be of additional value in infants with conditions such as PHVD that may disturb cerebral perfusion. In future research NIRS may prove to be valuable in detecting impending cerebral ischemia, and thereby a guide of the appropriate therapy of infants with PHVD. NIRS can detect clinically important changes in cerebral perfusion during CSF removal [15] and may be helpful in the optimal treatment and timing of treatment of infants with PHVD.

5. Ultrasound guided reservoir placement

Surgical insertion of a ventricular reservoir could be optimized by using cranial ultrasound during the procedure. This way the reservoir can be placed in the perfect position and this may help to avoid re-placement and unnecessary penetration of brain tissue outside the region of interest.

6. Timing of intervention for PHVD

The optimal timing of intervention in infants who develop PHVD is still an unsolved issue. There is no evidence based consensus about the timing of intervention. Currently, the prospective randomized ELVIS trial (Early versus Late Ventricular Intervention Study, ISRCTN43171322) is ongoing to assess the potential beneficial role of early intervention (i.e. intervention after the VI crosses the p97 line according to Levene) over late intervention (i.e. after the VI exceeds the p97+4mm line). Outcome of this ELVIS trial could give insight in the optimal treatment of infants with PHVD in the future.

Final conclusion: Promising results are reported in this thesis about short and long-term outcome of preterm infants who did develop PHVD. Especially for the preterm infants with a grade III haemorrhage. However, care of infants with an intracranial haemorrhage can be improved further, with regard to prevention and timing of intervention.

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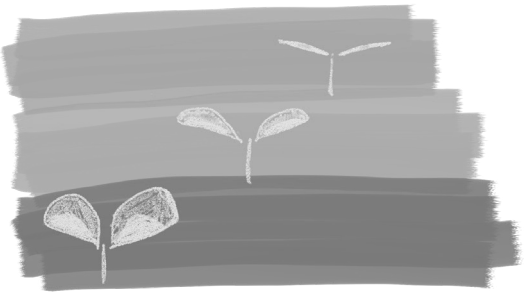
Nederlandse samenvatting & toekomst perspectieven



In dit proefschrift is de behandeling en uitkomst beschreven van prematuur geboren kinderen met een grote hersenbloeding die ten gevolge daarvan verwijding van de hersenkamers ontwikkelden (post haemorrhagische ventrikel dilatatie, PHVD). Tevens is de behandeling en uitkomst bestudeerd van a terme geboren neonaten met een intracraniële bloeding.

Als gevolg van verbeteringen in de neonatale zorg en mogelijk ook als gevolg van een vroege en meer effectieve behandeling, is het bestaan van een PHVD niet langer geassocieerd met een slechte uitkomst. Kinderen die een PHVD ontwikkelen, zonder schade van de witte stof in de hersenen kunnen een normale ontwikkeling hebben op school leeftijd.

SAMENVATTING

In *hoofdstuk 2* zijn de resultaten beschreven van een Europese enquête over de diagnose en behandeling van PHVD. Er was een respons van 86.5% van neonatologen uit 17 verschillende Europese landen. De uitkomsten van de enquête geven inzicht in de perspectieven ten aanzien van de diagnose en behandeling van PHVD in de Europese centra die gespecialiseerd zijn in de neonatale neurologie. Concluderend kan er gesteld worden dat er aanzienlijke verschillen zijn tussen de verschillende Europese centra in de diagnostiek en behandeling van prematuren met een PHVD.

In *hoofdstuk 3* is het optreden van infecties bij prematuren met een subcutaan ventrikel reservoir bestudeerd. Er was een aanzienlijke toename van het aantal kinderen met een ventrikel reservoir in de periode 1998-2003 ten opzichte van 1992-1997. Liquor afname via een subcutaan ventrikel reservoir blijkt een veilige en effectieve methode te zijn. Als de ventrikel punctie door ervaren mensen gedaan wordt blijft het optreden van infecties of andere ernstige complicaties binnen een acceptabele grens van < 5%.

In *hoofdstuk 4* wordt de pilot studie "ventrikelpuncties door verpleegkundigen" beschreven. Deze innovatie werd succesvol ingevoerd en geaccepteerd door verpleegkundigen en artsen. Deze succesvolle beleidsverandering heeft tot gevolg dat de ventrikelpuncties nu op tijd uitgevoerd worden en dat verpleegkundigen meer controle hebben over het plannen van rustperiodes voor de neonaat.

In *hoofdstuk 5* is van 214 prematuren (zwangerschapsduur korter dan 34 weken) het verloop van de bloedingen, de noodzaak tot PHVD-interventie en neurologische ontwikkeling op een gecorrigeerde leeftijd van 2 jaar, geëvalueerd. Vierenveertig procent had een graad III bloeding (ernstige bloeding waarbij de hersenkamer voor meer dan 50% met bloed is gevuld en daarbij een acute verwijding van de hersenkamer optreedt) en 56% een graad IV bloeding (ernstige bloeding met uitbreiding in de periventriculaire witte stof). De neurologische ontwikkeling op korte termijn van prematuren met een graad III en IV bloeding is beter dan eerder gerapporteerd. Opmerkelijk was dat er geen aanzienlijke verschillen waren qua ontwikkelingsquotiënt (DQ) op 2 jarige leeftijd, tussen kinderen die geen interventie voor hun PHVD nodig hadden en de groep die wel een interventie nodig had. De noodzaak tot een interventie had alleen een negatief effect op de kinderen met een graad IV bloeding. Kinderen met een cerebrale parese (CP) hadden een significant lager ontwikkelingsquotiënt, onafhankelijk van de ernst van de bloeding.

Omdat dit een observationele studie was konden we alleen maar speculeren over de positieve invloed van de vroege interventie. Kinderen waar de interventie vroeg was gestart (voordat de p97+4mm lijn volgens de curve van Levene, was gepasseerd), hadden een beter DQ op 2-jarige leeftijd dan de kinderen die laat behandeld werden.

In *hoofdstuk 6* werd de neuromotorische en cognitieve uitkomst van prematuren op schoolleeftijd geëvalueerd. Het ging hierbij om prematuren met een graad III of graad IV bloeding en een PHVD, waarvoor neurochirurgische interventie noodzakelijk was; een ventrikel reservoir en/of een ventriculoperitoneale shunt

(VP shunt). De meerderheid (59.4%) had geen ontwikkelingsproblemen zoals leerproblemen, cerebrale parese of epilepsie. Bij 39% van de kinderen werden motorische problemen geconstateerd; het gemiddelde intelligentie quotiënt (IQ) van de gehele groep was 93.4, en 29% had een IQ<85 (-1SD). Kinderen in de graad IV-IVH groep hadden een grotere kans op cerebrale parese, onafhankelijk van het tijdstip van behandelen. Dit was volgens verwachting omdat bij een graad IV bloeding ook het hersenparenchym is aangedaan. In tegenstelling tot andere studies ontwikkelde geen van de kinderen met een graad III bloeding cerebrale parese. We speculeren dat dit het resultaat is van een vroegtijdige behandeling, zodat langdurige periodes van verhoogde intracraniële druk met periventriculair oedeem, verdringing van de motorische banen en verstoring van het myelinisatie proces voorkomen worden.

In *hoofdstuk 7* werden de neonatale en follow-up gegevens van 53 a terme neonaten met een intracraniële bloeding (ICH) en daarbij geassocieerde parenchymale betrokkenheid over een periode van 17 jaar gerapporteerd. Al deze neonaten waren opgenomen op een neonatale intensive care unit. Dit is een groot cohort van neonaten met symptomatische ICH. ICH met schade aan het parenchym geeft een groot risico op slechte neurologische restverschijnselen met een mortaliteit van 24.5% en ontwikkeling van CP bij 8.6% van de kinderen. De hoge mortaliteit kan deels verklaard worden door de geassocieerde perinatale asfyxie. Neonaten met een supratentoriale ICH hadden een lagere mortaliteit vergeleken met neonaten met een infratentoriale of met neonaten met een gecombineerde infratentoriale en supratentoriale ICH. Ondanks de vaak grote intrapenchymale schade had 88.2% van de overlevende kinderen zonder CP een normale neurologische ontwikkeling.

TOEKOMST PERSPECTIEVEN

In tegenstelling tot de gerapporteerde dalende incidentie van cysteuze periventriculaire leukomalacie (cPVL; ernstige witte stof schade in de hersenen) daalt de incidentie van ernstige intracraniële bloedingen (IVH graad III en IV) niet. De incidentie van zowel graad III als graad IV bloedingen blijven op een constant niveau. Neonaten met deze grote bloedingen lopen risico op een slechte neurologische uitkomst. Postnatale toediening van fenobarbital kan niet aanbevolen worden ter voorkoming van IVH bij prematuren en is geassocieerd met een verhoogde noodzaak tot mechanische ventilatie. Ongeveer 80% van de bloedingen ontstaan binnen 72 uur na geboorte, maar een aanzienlijk deel is al zichtbaar op de 1e schedelecho, enkele uren na geboorte. Dit houdt in dat de interventies om IVH te voorkomen moeten beginnen voor de geboorte of direct erna. PHVD komt regelmatig voor bij prematuren met een grote bloeding en is geassocieerd met een nadelige neurologische ontwikkeling. We moeten streven naar een optimale behandeling van PHVD, zowel met betrekking tot de timing als de optimale methode van behandelen.

Er zijn nog steeds kansen om de neonatale zorg te verbeteren, vooral voor die neonaten die een vergrote kans hebben op een Intracraniële bloeding:

1. *Het uitstellen van het afklemmen van de navelstreng* is als interventie geassocieerd met een lagere incidentie van IVH. De data van de RCT van Mercer et al. geven aan dat het uitstellen van het afklemmen van de navelstreng met 30 tot 45 seconden en het laag houden van de neonaat om de placentaire transfusie te bespoedigen, bescherming biedt tegen het ontstaan van IVH. Dit is een eenvoudige interventie die eenvoudig ingevoerd kan worden in de dagelijkse praktijk.

2. *Evaluatie van de platte bedrust van 6 uur*.

Om daling van de hypotensie, bradycardie, misselijkheid en braken te voorkomen, moeten neonaten op onze afdeling 6 uur in een platte houding

liggen na een punctie uit een ventrikel reservoir. Deze tijdsduur is niet gebaseerd op enig wetenschappelijk bewijs. Neonaten moeten nu 6 tot 18 uur per dag plat liggen, afhankelijk van de frequentie van puncteren. Dit is ongemakkelijk voor zowel kind als ouders. Het kan een voordeel zijn voor kind en ouders om deze periode te verkorten. De lengte van deze 6 uurs periode zou bestudeerd moeten worden. De vulling van de hersenkamers kan beoordeeld worden door elk uur een echo van het hoofd te maken. Tevens kan het comfort van het kind elk uur bepaald worden met behulp van de Comfort Scale (een pijnmeetinstrument) of de pijnmonitor.

3. De introductie van een '*IVH-preventie bundel'* kan een waardevolle preventieve strategie zijn in het optreden van ernstige IVH. De IVH preventie bundle kan het volgende inhouden: hoogte van hoofdeind van de couveuse of bed maximaal op 15 °, het hoofd gedurende de 1e 72 uur zo veel mogelijk in de 'midline', voorkomen dat het hoofd naar beneden ligt, voorkomen van snel flushen van infusie- of medicatie vloeistoffen en de lichaamstemperatuur stabiel > 36.5 °C. Een prospectieve studie moet de voorlopige resultaten bevestigen.

4. Meting van nabij infrarood spectroscopie (NIRS) tijdens PHVD behandeling. Verhoogde intracraniële druk kan de cerebrale perfusie verminderen en ischemie veroorzaken in een kritieke periode. In de dagelijkse praktijk kan de zuurstofvoorziening in de hersenen continue, aan het bed en non-invasief door middel van NIRS gemeten worden. De regionale cerebrale zuurstof verzadiging blijkt ook een schatting te zijn van de cerebrale weefsel perfusie. Dit kan van toegevoegde waarde zijn in de behandeling van neonaten met bijvoorbeeld PHVD, een situatie die van invloed kan zijn op de cerebrale perfusie. In de toekomst kan NIRS van waarde zijn voor het opsporen van dreigende ischemie en daarbij een leidraad zijn in de juiste behandeling van kinderen met een PHVD. NIRS kan belangrijk zijn in het signaleren van klinische veranderingen van de cerebrale perfusie gedurende liquor afname en kan van belang zijn voor het optimaal behandelen van neonaten met een PHVD.

5. Plaatsen van een ventrikel reservoir onder echo geleiding

Chirurgisch plaatsen van een ventrikel reservoir kan geoptimaliseerd worden door het gebruik van schedelechografie gedurende de procedure. Op deze manier kan het reservoir geplaatst worden op de optimale plaats en kan herplaatsen en onnodig schade van hersenweefsel buiten het aangedane gebied voorkomen worden.

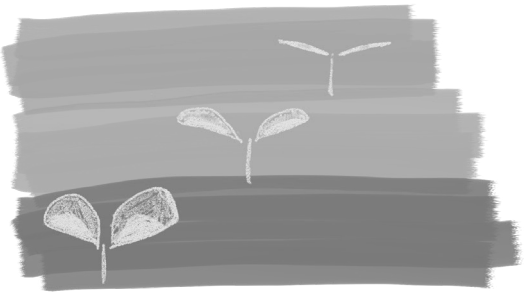
6. Timing van de PHVD behandeling

De optimale timing van de behandeling van PHVD is nog steeds onduidelijk. Er is geen wetenschappelijk bewijs over de optimale timing van het starten van de behandeling. Op dit moment loopt de prospectieve gerandomiseerde ELVIS trial (Early versus Late Ventricular Intervention Study, ISRCTN43171322) om het potentiële voordeel aan te tonen van een vroege behandeling (voor overschrijding van de p97 + 4mm lijn volgens de curve van Levene) versus een late behandeling (na overschrijding p97 + 4mm lijn). De resultaten van deze ELVIS trial zullen van belang zijn om duidelijkheid te krijgen over de optimale behandeling van neonaten met een PHVD in de toekomst.

Eindconclusie

In dit proefschrift zijn veelbelovende resultaten gepresenteerd over de korte- en lange termijn uitkomsten van neonaten met een PHVD. Vooral voor neonaten met een graad III bloeding. De behandeling van deze neonaten kan nog verder geoptimaliseerd worden met betrekking tot preventie en timing.

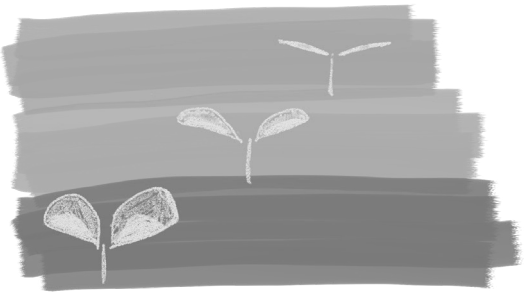
Abbreviations



ABBREVIATIONS

AHW	anterior horn width
BW	birth weight
CBCL	child behaviour checklist
CP	cerebral palsy
CSF	cerebrospinal fluid
CT	computed tomography
cUS	cranial ultrasound
c-PVL	cystic periventricular leukomalacia
DRIFT	drainage, irrigation, and fibrinolytic therapy
DQ	developmental quotient
EVD	external ventricular drain
FSIQ	full scale intelligence quotient
GA	gestational age
GMFCS	gross motor function classification system
GMH-IVH	germinal matrix intraventricular haemorrhage
ICH	intracranial haemorrhage
IQ	intelligence quotient
LP	lumbar puncture
MDI	mental developmental index
MRI	magnetic resonance imaging
PHVD	post haemorrhagic ventricular dilation
PIQ	performance intelligence quotient
SAH	subarachnoid haemorrhage
SDH	subdural haemorrhage
TOD	thalamo-occipital distance
TRF	teacher report form
USCP	unilateral spastic cerebral palsy
VAD	ventricular access device
VI	ventricular index
VIQ	verbal intelligence quotient
Vpshunt	ventriculoperitoneal shunt
WPPSI	Wechsler preschool and primary scale of intelligence

List of publications



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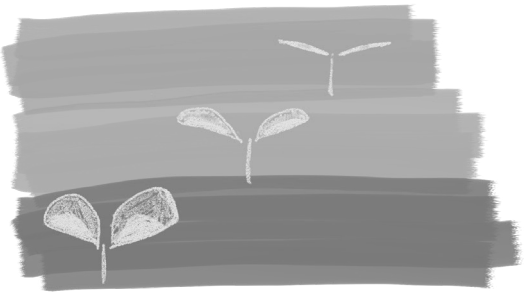

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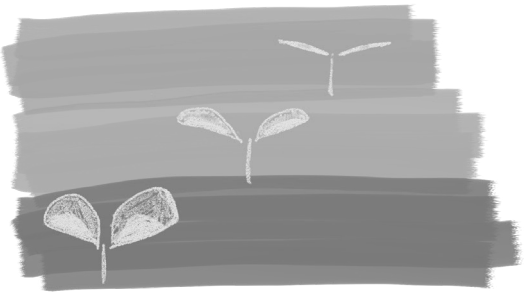

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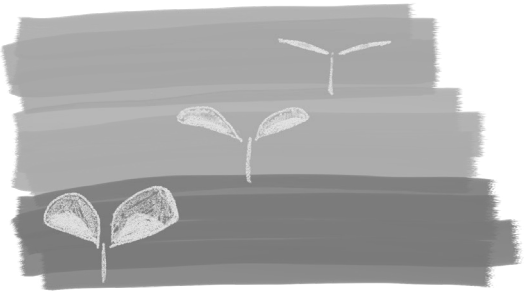
Mieke

Curriculum vitae



CURRICULUM VITAE

Mieke Brouwer is geboren in Winschoten op 18 november 1962. Na enkele omzwervingen door Nederland, behaalde zij in 1982 haar VWO diploma aan de Samenwerkingsschool te Waddinxveen. In 1982 begon ze in het Bleulandziekenhuis in Gouda aan de Inservice opleiding tot A-verpleegkundige. Hierna deed zij de brede basis IC-opleiding in hetzelfde ziekenhuis. In 1988 maakte ze de overstap naar het Wilhelmina Kinder Ziekenhuis te Utrecht om de opleiding tot neonatologie verpleegkundige te volgen. Op deze afdeling is zij van 1990-1992 teamleidster geweest, na het volgen van een management opleiding.

In 2000 startte zij met de studie Algemene Gezondheidswetenschappen, richting Verplegingswetenschap aan de Universiteit van Utrecht. De studie werd in 2004 afgerond. Vanaf april 2005 begon ze aan het promotietraject, onder begeleiding van Prof. dr. LS de Vries en dr. F Groenendaal, wat geleid heeft tot dit proefschrift. In deze periode is zij lid geweest van de Medisch Ethische Toetsingscommissie van het UMCU. Tevens was zij gedurende 2 jaar lid van de scientific committee van de ESPNIC. Nu is zij nog lid van de Landelijke Pijnwerkgroep NICU's, waar zij 1 van de 10 NICU's vertegenwoordigt.
Mieke heeft 2 kinderen