Aus der Klinik für Neonatologie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

NEUROENDOSCOPIC LAVAGE FOR THE TREATMENT OF POSTHEMORRHAGIC NEONATAL HYDROCEPHALUS

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von
Charlotte d'Arcangues
aus Arcangues, Frankreich

Datum der Promotion: 18.12.2020

VORWORT

Durch meine wissenschaftlichen Arbeit, hatte ich Anteil an folgenden Publikationen:

« d'Arcangues C, Schulz M, Bührer C, Thome U, Krause M, Thomale UW. Extended Experience with Neuroendoscopic Lavage for Posthemorrhagic Hydrocephalus in Neonates. World Neurosurg. 2018 May 2 »

Ich habe eine retrospektive wissenschaftliche Arbeit in der Abteilung für Neonatologie und Pädiatrische Neurochirurgie der Charité-Universität Berlin durchgeführt um alle Patienten, die eine neuroendoscopische Lavage zur Behandlung eines posthämorrhagischen Hydrocephalus zwischen August 2010 und Mai 2016 durchgeführt haben, zu identifizieren. Diese Daten von 45 Patienten stammen aus den medizinischen Akten der Patienten (handgeschrieben und Datenbank) und sind von mir aufgezeichnet und statistisch ausgewertet.

Um die statistische Aussagekraft der Studie zu erhöhen, wurden 11 Patienten aus dem Leipziger Pädiatrischen Neurochirurgischen Zentrum mit einbezogen. Dies war die Arbeit von Wissenschaftlern aus Leipzig.

Als co-erste Autorin veröffentliche ich Teile davon (Text und Abbildung) in meiner Doktorarbeit.

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LIST OF ABBREVIATIONS

BPD: Bronchopulmonary Dysplasia
BSID-II: Bayley Scales of Infant Development, second edition
BW: Birth Weight
CNS: Cerebral Nervous System
CRIB: Clinical Risk Index for Babies
CRP: C-reactive protein
CSF: Cerebrospinal Fluid
DRIFT: Drainage, Irrigation and Fibrinolytic Therapy
EVD: External Ventricular Drainage
GA: Gestational Age
GMFCS: Gross Motor Function Classification System
IL6: Interleukin-6
IVH: Intraventricular Hemorrhage
MDI: Mental Development Index
NB: Newborn
NEL: Neuroendoscopic Lavage
NICU: neonatal intensive care unit
NO: Nitric Oxide
PH: Pulmonary Hypertension
PDA: Patent Ductus Arteriosus
PVHI: Periventricular Hemorrhagic Infarction
ROP: Retinopathy of Prematurity
RR: Rickham Reservoir
SPC: Social Pediatric Center
TTTS: Twin-to-twin Transfusion syndrome
UapH: Umbilical Artery pH
VSGS: Ventriculo Sub-galeal shunt
VP shunt: Ventriculo-peritoneal Shunt

ABSTRACT IN ENGLISH

OBJECTIVE:

Neuroendoscopic lavage (NEL) was introduced to achieve the removal of intraventricular hematoma and to allow the treatment of elevated intracranial pressure in a less invasive and more controlled setting. This study analyses complications and results of NEL in the pediatric neurosurgical center of Charité University Medicine Berlin.

METHODS:

Retrospective research was done on all patients who underwent an NEL for treatment of posthemorrhagic hydrocephalus between August 2010 and May 2016 with a minimum follow-up period of 12 months. Efficacy of blood removal, as assessed by cerebral ultrasound, and postoperative complications were analyzed. Shunt placement rate and subsequent shunt revisions were recorded. At two years corrected age, evidence of cognitive disability, cerebral palsy and antiepileptic treatment were examined.

RESULTS:

Forty-five patients (29 male) underwent NEL at a median age of 22 days (5 - 58 days), at a postmenstrual median age of 31 + 2 weeks (26 + 1 - 52 + 3 weeks), and at a median weight of 1605 g (734 - 4360 g). After NEL procedure there was a significant reduction of intraventricular hematoma grades ($p < 0.01$). A second NEL procedure was performed on 8 patients, 2 patients developed an infection of the cerebral nervous system, and in 3 patients a new intracranial hematoma was documented by cranial ultrasound after the procedure. Median follow-up was 34 months after NEL procedure (12 – 80 months); one patient died, and 27 patients (60%) required permanent ventriculo-peritoneal shunts (VP shunt). There was no significant correlation between the need for VP shunts after NEL and the gestational age ($p = 0.05$), birth weight ($p = 0.29$), age at NEL ($p = 0.17$), or weight at NEL ($p = 0.29$). Revision-free shunt survival was 67% at 12 months and 55.5% at 24 months. At 24 months corrected age, the Mental Development Index (MDI) was greater than 70 in 11 patients (44%) and the median MDI was 80 (49 - 151); 14/33 patients (42%) walked without limitations at home and outdoors; and 8/37 patients (22%) were in need of antiepileptic medication.

CONCLUSIONS:

NEL is confirmed to be a safe and effective operative technique to significantly lower the amount of intraventricular hematoma in posthemorrhagic hydrocephalus of neonates. NEL avoided VP shunt placement in 40% of cases and may have also decreased the frequency of subsequent VP shunt revisions. Nevertheless, more neurodevelopmental outcome data is required to more thoroughly assess the value of NEL.

ABSTRACT IN GERMAN

EINLEITUNG:

Die neuroendoskopische Lavage (NEL) ermöglicht intraventrikuläre Blutungen weniger invasiv und besser gesteuert zu beseitigen und einen erhöhten intrakraniellen Druck zu behandeln. Diese Arbeit analysiert Komplikationen und Ergebnisse der NEL in der pädiatrischen neurochirurgischen Abteilung der Charité Universitätsmedizin Berlin.

METHODE:

Es wurde eine retrospektive Studie aller Patienten durchgeführt, die zwischen August 2010 und Mai 2016 eine NEL zur Behandlung eines posthämorrhagischen Hydrocephalus erhielten. Der Nachbeobachtungszeit betrug mindestens 12 Monate. Die Beseitigung von Blut und Blutabbauprodukten und postoperative Komplikationen wurden durch zerebralen Ultraschall beurteilt. Mittelfristig wurden die Notwendigkeit einer Shuntimplantation und einer nachfolgender Shuntrevision erfasst. Bei einem korrigierten Alter von 2 Jahren wurden die kognitive Leistung, das Vorliegen einer Zerebralparese, sowie die Einnahme antiepileptischer Medikamente beurteilt.

ERGEBNISSE:

Bei fünfundvierzig Patienten (29 männliche Patienten) wurde eine NEL in einem medianen Alter von 22 Tagen (5 – 58 Tagen) und korrigiert 31 + 2 Schwangerschaftswochen (26 +1 - 52 + 3 Schwangerschaftswochen) sowie einem medianen Gewicht von 1605 g (734 - 4360 g) durchgeführt. Die NEL führte zu einer signifikanten Reduktion des intraventrikulären Blutes und der Blutabbauprodukte ($p < 0.01$). Eine zweite NEL war bei 8 Patienten notwendig; 2 Patienten entwickelten eine Infektion des zerebralen Nervensystems; bei 3 Patienten wurde nach dem Eingriff eine erneute intrakranielle Blutung durch kranialen Ultraschall dokumentiert. Der mediane Nachbeobachtungszeitraum betrug 34 Monate (12 – 80 Monate); ein Patient verstarb; und 27 Patienten (60%) benötigten ventrikulo-peritoneale Shunts (VP-Shunt). Es bestand keine signifikante Korrelation zwischen der Notwendigkeit eines VP-Shunts nach NEL und dem Gestationssalter ($p = 0.05$), dem Geburtsgewicht ($p = 0.29$) sowie dem Alter ($p = 0.17$) und dem Gewicht zum Zeitpunkt des Eingriffes ($p = 0.29$). 67% der Patienten in den ersten 12 Monaten und 55.5% der Patienten in den ersten 24 Monaten benötigten nach Shuntanlage keine Shunt Revision. Bei einem korrigierten Alter von 2 Jahren war der Mental Development Index (MDI) bei 11 Patienten (44%) größer als 70 und der mediane MDI war 80 (49 - 151); 14/33 Patienten (42%) waren in der Lage zu Hause und im Freien ohne Einschränkungen zu gehen; und 8/37 Patienten (22%) hatten antiepileptische Therapie.

ZUSAMMENFASSUNG :

Es wurde bestätigt, dass die neuroendoskopische Lavage eine sichere und effiziente Operationstechnik zur Reduktion von intraventrikulären Blut und Blutabbauprodukten beim posthämorrhagischen Hydrocephalus von Neugeborenen ist. NEL vermied eine Shuntimplantation bei 40% der Neugeborenen und konnte bei Shuntimplantation die Häufigkeit nachfolgender Shuntrevisionen verringern. Dennoch sind mehr neurologische Entwicklungsdaten erforderlich, um den Wert von NEL genauer zu untersuchen.

INTRODUCTION

The main causes of morbidity and mortality of premature newborns (NB) are respiratory, neurological, digestive and infectious diseases (62). Neurological complications mainly result from ischemic and hemorrhagic damage. Most intraventricular hemorrhages (IVH) occur in premature infants with low birth weight (BW) and low gestational age (GA). The highest rates of severe IVH (grades III or IV) are observed in infants with a gestational age < 30 weeks and a birth weight < 1500g (64, 65, 66, 67, 68, 71, 73, 74, 78, 96, 98).

IVH characteristically initiates in the periventricular germinal matrix (47). The germinal matrix, located at the head of the caudate nucleus and underneath the ventricular ependyma, is a highly vascular collection of glial and neuronal precursor cells. This periventricular region is particularly vulnerable to hemorrhage in premature infants, predominantly in the first 48 hours of life. When a hemorrhage in the germinal matrix is substantial, the ependyma breaks, and the cerebral ventricle fills with blood. Thus, IVH is typically a progression of a germinal matrix hemorrhage. A grade IV or periventricular hemorrhagic infarction (PVHI) results from congestion to the brain tissue around the ventricles when a large IVH has occurred. The anatomical distribution and histological features of these hemorrhages suggest that they result from venous infarction, with venous drainage of the periventricular tissues being obstructed by the germinal layer hemorrhages (48, 50, 51, 54, 55).

The majority of infants with IVH are asymptomatic and diagnosis is based on screening cranial ultrasound (49, 52, 53). Some infants manifest with subtle abnormalities in the level of consciousness, movement, tone, respiration, and eye movement; and uncommonly, there is a catastrophic deterioration presenting with stupor, coma, decerebrate posturing, generalized tonic seizure, epilepsy, or a drop in hemoglobin.

During the neonatal period, many pre- and postnatal factors may result in IVH and these factors need to be therapeutically managed. Pathogenesis of IVH is multifactorial and is primarily ascribed to: 1) inherent fragility of the germinal matrix vasculature, which might be worsened by an inflammatory injury to the blood brain barrier ; 2) platelet and coagulation disorders and hemostatic failure ; and 3) disturbances in the cerebral blood flow.

Disruption of cerebral blood flow can result from : a) fluctuations caused by hypoxia, hypercapnia, severe acidosis, or rapid infusion of $NaHCO_3$, asynchrony between infants breathing and ventilator settings, severe respiratory distress syndrome, patent ductus arteriosis (PDA), and twin-to-twin transfusion syndrome (TTTS) ; b) high cerebral venous pressure due to pneumothorax, high ventilator pressure, and prolonged vaginal delivery; and c) abnormal blood pressure from hypotension, hypertension, sepsis and dehydration. Hence, the rapid stabilization of normal cerebral blood flow on the first day of life is a potential strategy for preventing IVH in premature infants (48, 60, 63, 64, 65, 67, 68, 69, 70, 71, 72, 73, 76, 77, 81, 82, 99).

IVH in premature and newborn babies poses a significant risk of impaired neurological development for the affected child, not only because of primary damage at the parenchymal site of hemorrhage but also because of potential secondary damage caused by the developing hydrocephalus and detrimental effects of intraventricular blood degradation products (1, 15, 19, 28, 59, 93). There is also further risk associated with medical and surgical treatment of this condition, which becomes relevant in determining the clinical course for the patient. Up to 7 - 9% of children with a gestational age < 30 weeks will be affected with higher grades III - IV IVH. Of these, up to 50% will develop a disturbed cerebrospinal fluid (CSF) circulation resulting in increased intracranial pressure, which necessitates a therapeutic intervention (1, 30).

CSF is produced by the ependymal cells in the choroid plexus, found at the inferior horn of the lateral ventricles. From the lateral ventricles it flows through the foramina of Monro to the third ventricle, and then into the fourth ventricle via the cerebral aqueduct of Sylvius. CSF exits the fourth ventricle through the foramina of Magendie and Luschka to the subarachnoid space surrounding the spinal cord and the brain, from where it is absorbed by the arachnoid granulations. Posthemorrhagic hydrocephalus results from progressive accumulation of CSF, due to reduced reabsorption and blockage of flow caused by small blood clots and the subsequent chronic arachnoiditis (Annex 1 and 2).

Treating posthemorrhagic hydrocephalus is challenging due to the low body weight of premature babies and because of the high load of blood degradation products at the time of the first intervention. Both factors can contribute to high rates of complications associated with surgical treatment (1, 24, 31, 37, 102, 103). Currently several types of neurosurgical intervention are practiced around the world (2, 4, 19, 23, 24, 25, 30, 36, 56).

At present, the primary damage at the parenchymal site caused by the hemorrhage cannot be reversed. Consequently, treatment has been directed to counteracting the secondary adverse effects of CSF circulation disturbances, to reduce intracranial pressure and the burden of intraventricular blood components. The high quantity of intraventricular blood degradation products, combined with the fragility of premature babies, mandates temporary initial treatment efforts. Indeed, shunt insertion in very premature infants after ventricular hemorrhage is associated with elevated rates of shunt failure, shunt infection, and shunt obstruction (28, 34, 44). Temporary initial treatment efforts consist of CSF diversion either by repeated punctures of an implanted reservoir, by continuous CSF diversion through an external ventricular drainage (EVD), or by subgaleal shunt (3, 25, 26, 32, 33, 35, 36, 37, 38, 43, 45, 46). At the time of shunt insertion, a body weight of more than 2kg and normal CSF cell count and protein levels are required. Studies tend to recommend early intervention; however, they do not specify the best time point (8, 27, 38). Whitelaw demonstrated in a meta-analysis that there was no benefit in performing repeated lumbar punctures and that there was even a significant risk of infection (41). Studies have not established any benefit derived from diuretic therapy, though they point out the existence of adverse effects such as metabolic disorders (nephrocalcinosis) and increased neurologic morbidity (39, 40, 42).

In addition to alleviating increased intracranial pressure by initial temporary CSF diversion, removal of the intraventricular hematoma has also been reported by drainage, irrigation and fibrinolytic therapy (DRIFT). Furthermore, a better neurodevelopmental outcome for this therapeutic approach after 2 years was demonstrated compared to standard therapy in a randomized controlled setting, despite a higher rate of secondary intraventricular hemorrhages (1, 17, 18, 20). The practice of neuroendoscopic lavage (NEL) was introduced to achieve the removal of intraventricular hematomas in a less invasive and more controlled setting and to allow the treatment of elevated intracranial pressure (1, 2, 4).

This thesis analyses pre- and postnatal characteristics, radiological and clinical results of neurosurgical interventions, and the neurological outcome of two-year-old children. These children were neonates who had severe hydrocephalus post-IVH over a long observation period between 2010 and 2016 at the pediatric neurosurgical center of Charité University Medicine Berlin.

MATERIALS AND METHODOLOGY

PATIENTS

A retrospective search of operations performed at the Division of Pediatric Neurosurgery, Charité University, Berlin was done to identify all patients who underwent an NEL for treatment of posthemorrhagic hydrocephalus. Only patients in whom the initial hemorrhagic event occurred either antenatally or postnatally within the neonatal period (until 28 days after due term) were included. For all patients, a minimum period of 12 months clinical follow-up was required, between August 2010 and May 2016. Operation records, patient files, and radiological images were reviewed. The protocol for this project was approved by the local ethics committee, approval number: EA2/107/16 (1).

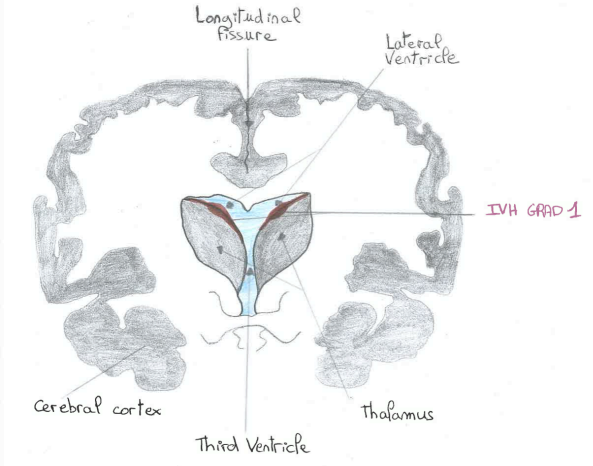
CLINICAL COURSE

All premature children were routinely screened with serial ultrasound as part of the postnatal routine. If detected, IVHs were graded according to the radiological classification of Papile *et al.* (81): grade I, subependymal hemorrhage; grade II, IVH with a hematoma occupying < 50% of the ventricular volume; grade III, IVH with hematoma occupying > 50% of the ventricular volume; and grade IV, IVH with PVHI (Figure 1).

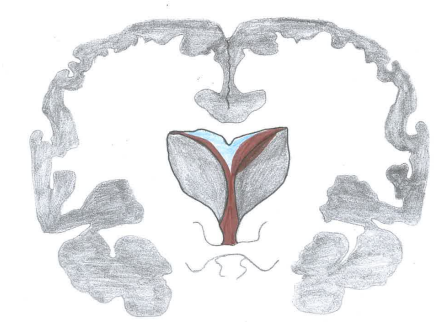
In case of IVH serial ultrasound exams, clinical examinations of the fontanel and serial measurements of head circumference were performed to assess for possible signs of a developing disturbed CSF circulation (1).

FIGURE 1: IVH, PAPILE'S CLASSIFICATION

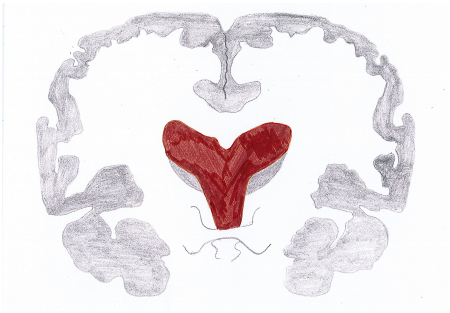
Grade I: the hemorrhage is localized to the germinal matrix.



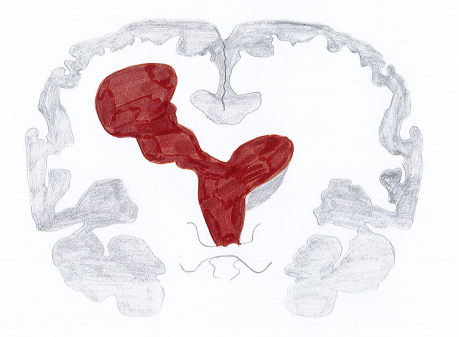
Grade II: the bleeding breaks into the ventricle but does not result in ventricular dilatation.



Grade III: IVH causes ventricular dilation and the clot spreads over half of the length of the ventricle.



Grade IV: IVH is accompanied by PVHI. This infarction is usually homolateral to the hemorrhage and follows the distribution of the medullary veins in the periventricular white matter. These intraparenchymal lesions are initially echodense but ultimately liquefy.



DATA COLLECTION

The data came from patients' handwritten and database medical files. The first survey was conducted on 34 patients with records from August 2010 to June 2015. In order to increase the power of the study, a second survey was conducted using medical records of 11 patients seen in Berlin from June 2015 to May 2016.

Neonatal data before IVH presentation

- Multiple gestation
- TTTS
- Antenatal steroids (betamethasone), administered as 2 injections of corticosteroid with a 24 hour interval
- Gestational age (GA)
- Apgar scores at 1, 5 and 10 minutes of life.
- Birth weight (BW)
- Gender
- Inpatient /outpatient birth status
- Umbilical artery pH (UaPH)
- Signs of neonatal infection, interleukin-6 (IL-6), C-reactive protein (CRP), administration of antibiotics
- Invasive and non-invasive ventilation
- Use of vasopressors (epinephrine, norepinephrine, dopamine)
- Indomethacin treatment
- Infusion of $NaHCO_3$

Diagnosis of IVH

- Age at time of bleeding
- Premature or full-term NB
- Right/left, grade
- PVHI

Comorbidity

- Clinical risk index for babies (CRIB; 80; Annex 3)

- Bronchopulmonary dysplasia (BPD) as defined by supplemental oxygen at 28 days of life (mild), 36 weeks postmenstrual age (moderate), or at discharge from the hospital (severe)
- Retinopathy of prematurity (ROP)
- Presence of PDA and treatments that have been carried out (anti-inflammatory non-steroidal treatment or surgery ligation)
- Lung bleeding
- Pulmonary hypertension (PH)
- Pneumothorax
- Gastrointestinal complications and laparotomy
- State of shock

Perioperative neurosurgery data of a) NEL of the ventricular system (with aspiration of solid hematoma) , b) second NEL and c) ventriculo-peritoneal shunt (VP Shunt) placement

- Anticonvulsant treatment
    - Pre-surgery: yes or no?
    - Post-surgery: treatment stopped or continuing? Started treatment?
    - Anticonvulsive treatment on hospital release

- Breathing assistance :
    - Pre-surgery: any, noninvasive or invasive?
    - Post-surgery: length of time of breathing assistance, invasive and then noninvasive

- Age and weight at time of intervention

- Perioperative management:
    - Where the intubation was carried out, in unit or in operating room?
    - Time spent in operating theatre
    - Duration of the intervention

- Post-surgery state of shock and catecholamine treatment
- Pain and extended analgesic treatment

- Post-surgery cerebral complications
    - Post-surgery brain hemorrhage
    - Subcutaneous CSF collection
    - Transcutaneous CSF fistula
    - Dislocation of the reservoir
    - Hygroma

- Post-surgery infection:
    - Time post-surgery
    - Positive blood cultures
    - Positive CSF cultures
    - Inflammatory parameters: CRP, IL-6
    - Antibiotic treatment
    - Neurosurgical follow-up

- Lowest post-surgical temperature
- Dysfunction of shunt
- Duration of hospitalization, date of first release from the hospital

Long-term post-surgery data

- Number of surgical procedures
- Rickham reservoir (RR) removal
- Evidence of cognitive disability, Bayley scale of infant development, second edition scores (BSID-II) at 2 years, corrected for age
- Cerebral palsy and attainment of independent walking; Gross Motor Function Classification System (GMFCS) score
- Antiepileptic treatment at 2 years corrected age

INDICATIONS FOR SURGERY

The decision to pursue a surgical treatment was always established through consultation between the neonatologist and the surgeons. The indications for intervention were a combination of: a) clinical signs of increased intracranial pressure, such as abnormal fontanel tension, vomiting, bradycardia, respiratory disturbances; b) accelerated head

growth (increased head circumference > 2mm per day averaged over a week); and c) radiologically documented ventricular dilatation (ventricular index > 97th percentile + 4 mm, anterior horn width > 97th percentile + 1 mm, thalamo-occipital distance > 97th percentile + 1 mm, and third ventricular width > 97th percentile + 1 mm; 1, 57; Figure 2).

FIGURE 2: RADIOLOGICALLY DOCUMENTED VENTRICULAR DILATATION

Fig. 2a: The ventricular index of Levene measures the distance from the falx to the border of the lateral ventricle in a coronal view taken in the plane of the 3rd ventricle. The width of the 3rd ventricle is also measured.

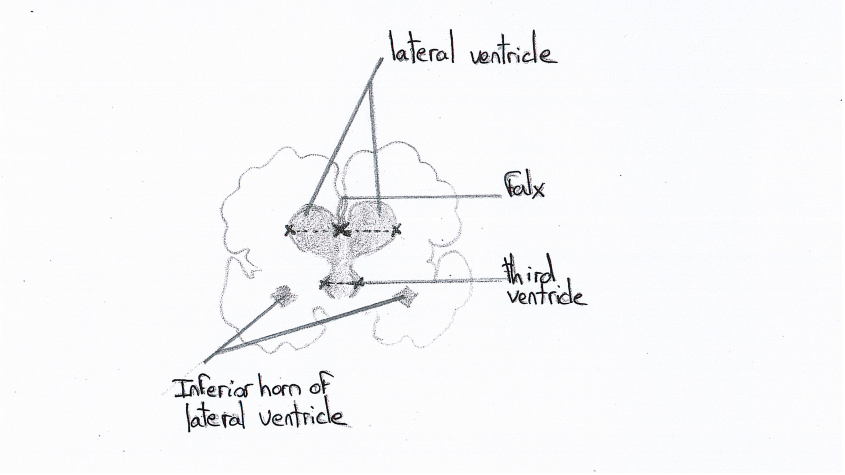


Fig. 2b: Measurement of the anterior horn width in an infant with bilateral posthemorrhagic hydrocephalus.

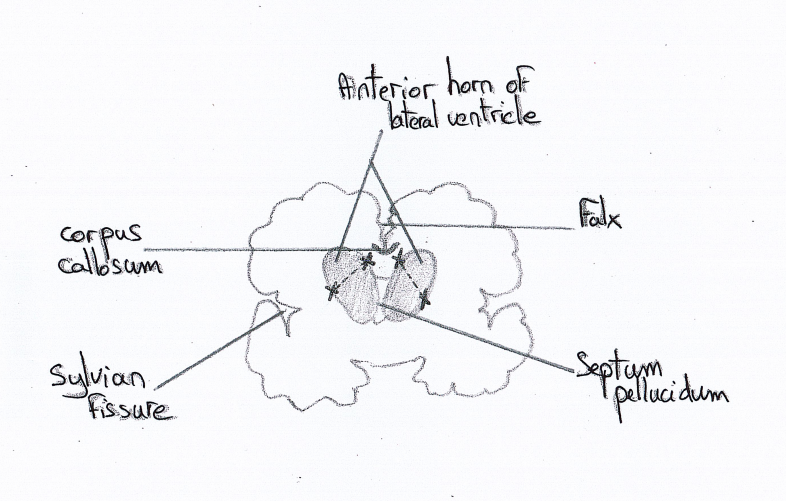
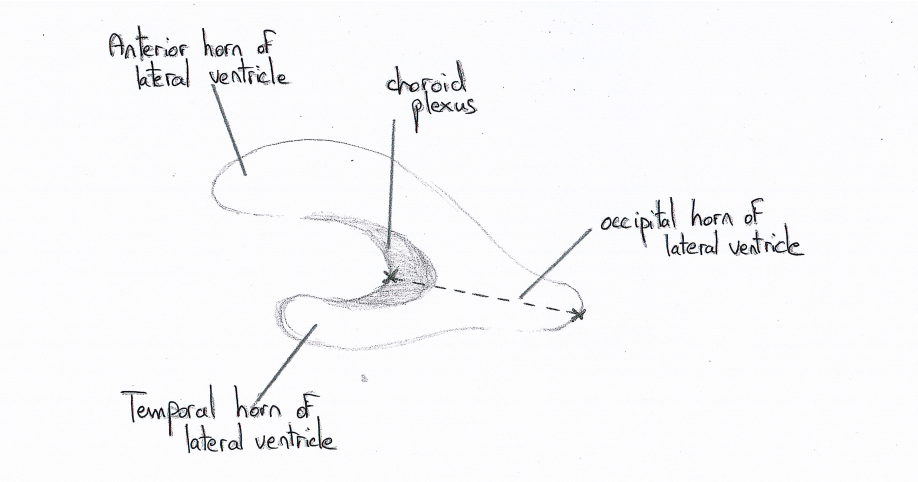


Fig. 2c: Measurement of the thalamo-occipital distance.



SURGICAL TREATMENT

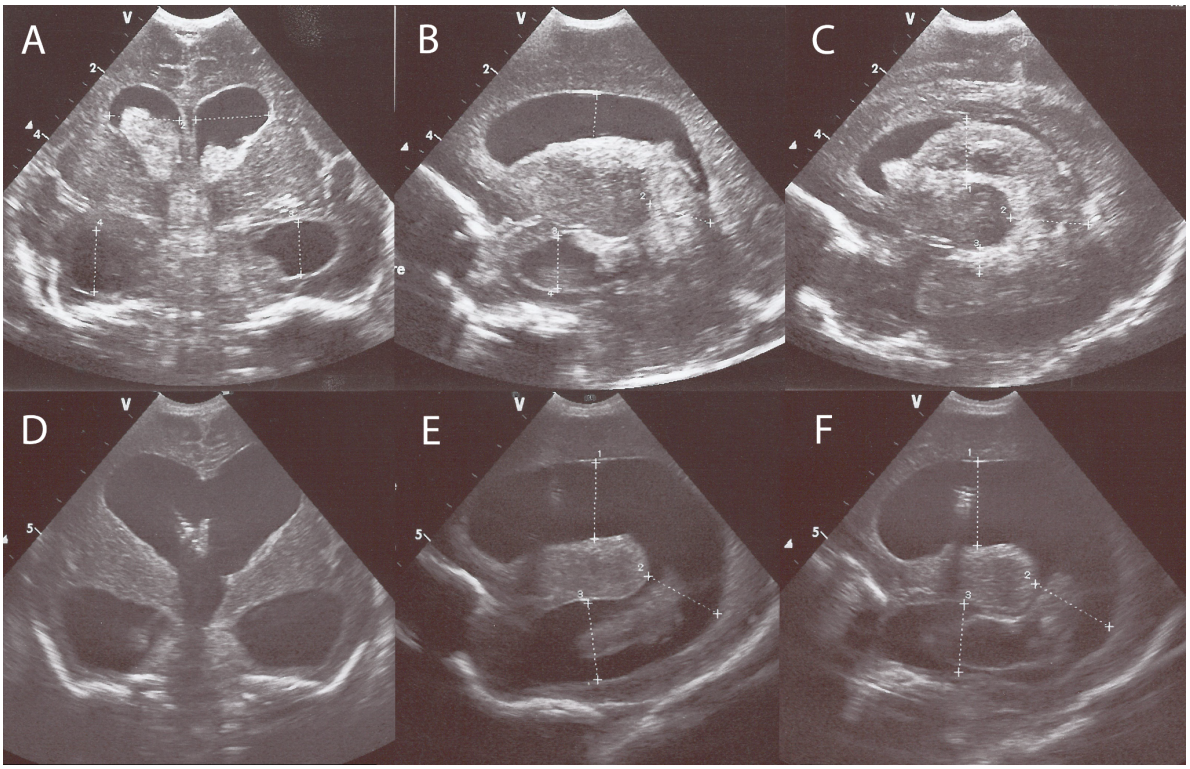
All reported patients underwent an NEL of the ventricular system with aspiration of solid hematoma, if present as described previously. Surgery was performed under general anesthetic with routine administration of prophylactic antibiotics. On the operating table the patients were placed supine with the head fixed in a vacuum mattress. Transfontanellar ultrasound was used to identify the lateral ventricle with the largest solid hematoma. After skin preparation, a frontal burr hole was made on the respective side and an endoscope (Minop, Aesculap, Germany or Paediscop, Stortz, Germany) was inserted into the lateral ventricle. Then, irrigation of the ventricular system with warmed balanced Ringer's solution (BBB, Germany) was initiated. When anatomical landmarks allowed orientation, an interventricular septostomy was performed to allow irrigation of the contralateral ventricle. Solid hematoma components were aspirated by bringing the endoscope's outflow opening proximal to the hematoma and applying controlled suction via a connected syringe. This allowed stepwise aspiration of solid hematoma until the interface with the cerebral parenchyma was reached. Both the lateral and the third ventricles were cleared. Irrigation ceased once all accessible parts of the hematoma were aspirated and the intraventricular fluid was clear. After removal of the endoscope a ventricular catheter connected to a subcutaneously positioned RR (Miethke, Potsdam, Germany) was usually

placed. The transcortical channel around the placed catheter was sealed with a gelatin sponge (Spongostan, Johnson & Johnson Medical, USA). The skin was then meticulously closed with subcutaneous and skin sutures.

Postoperatively all patients were transferred to a neonatal intensive care unit (NICU). Routine wound care with regular dressing changes was performed and cerebral ultrasounds were conducted every other day, as well as daily clinical exams and documentation of head circumference. If clinical signs of disturbed CSF circulation persisted, puncture of the implanted reservoir was initiated. Repeated puncture was performed until either CSF circulation normalized, or the patient reached a minimum weight of 2000g and a VP Shunt could be placed to allow permanent treatment of hydrocephalus. Placement of the shunt was usually made with ventricular access through the existing frontal transcortical channel. For all patients, gravitational-assisted valves were used (either adjustable proGAV or paediGAV, Miethke, Potsdam, Germany). Patients who showed a preoperatively elevated CSF protein concentration > 2g/L underwent a repeated NEL of the ventricular system with Ringer's solution to lessen the protein load and possibly minimize the risk of valve occlusion during VP shunt insertion (1; Figure 3).

FIGURE 3: PRE- AND POST NEUROENDOSCOPIC LAVAGE ULTRASOUND

There is solid hematoma in both lateral ventricles and the third ventricle (A-C). Postoperatively, no obvious hematoma can be seen in the third ventricle and the remaining hematoma in the lateral ventricles is greatly reduced in size. The remains are situated in the temporal horns and were left in place to minimize surgical trauma (D-F). The area of septostomy can be appreciated in panel (D). Postoperatively the dimensions of the lateral ventricles were progressive, necessitating temporary intermittent CSF diversion via the inserted ventricular catheter connected to a subcutaneously placed reservoir (E, F).



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RADIOLOGICAL EVALUATION

The pre- and the first postoperative ultrasound image after NEL were reviewed to quantify the amount of solid hematoma removed from the lateral ventricles. This amount was graded according the following categories: a) > 50% of the ventricular volume, b) 30 - 50% of the ventricular volume, c) 10 - 30% of the ventricular volume, d) < 10% of the ventricular volume, and e) no obvious intraventricular clot. The same grading was applied postoperatively to assess the size of the residual hematoma (1).

STATISTICS

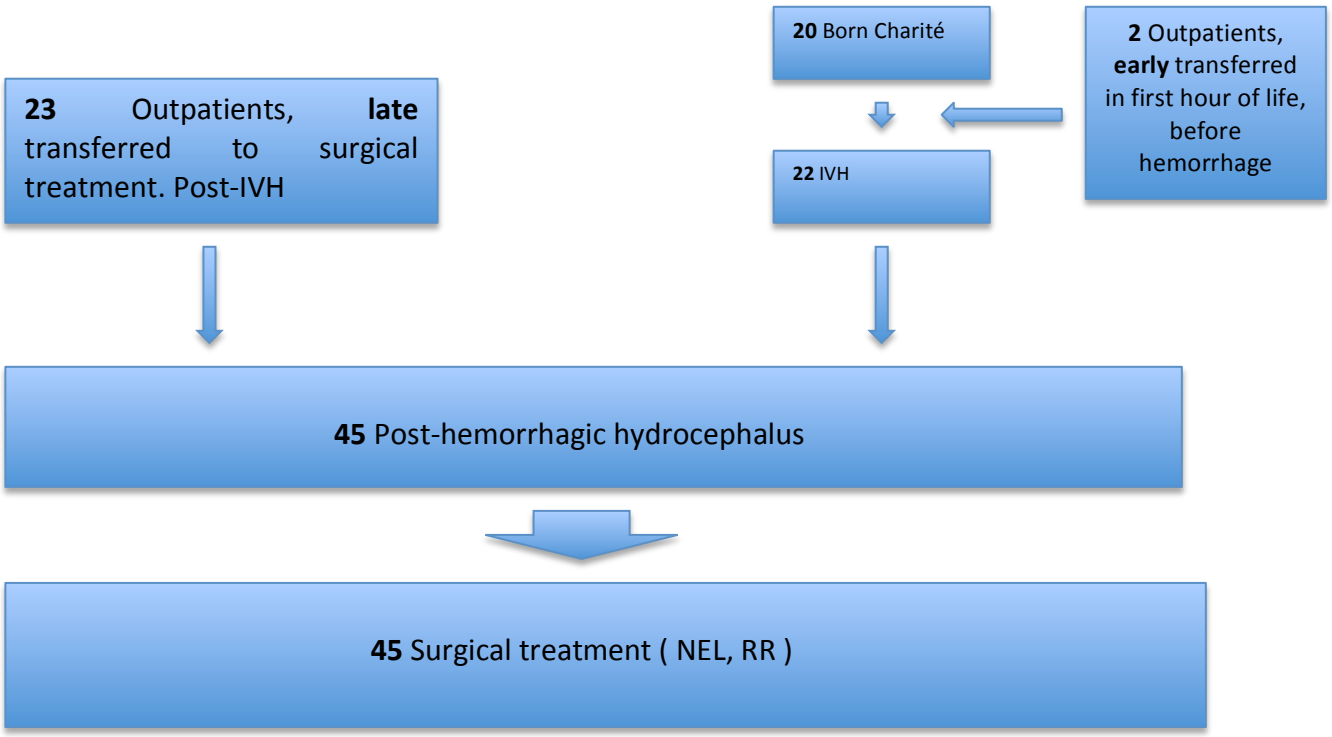
The data were expressed as a median with a range (minimum-maximum) noted in parentheses, or as a frequency with the percentage (%) noted in parentheses. The grading data of the proportion of intraventricular hematoma pre- and postoperatively were tested using the Wilcoxon matched pairs signed rank test, not assuming normal distribution. NEL and VP shunt survival data was analysed according to Kaplan-Meier estimates. The Wilcoxon-Man-Whitney U-test was used to examine quantitative, non-paired, non-parametrical pre- and postoperative data, and Chi-square analysis was used to examine categorical variable data. A p value of < 0.05 was considered to indicate statistical significance.

RESULTS

CHARACTERISTICS OF PATIENT COHORT

A total of 45 patients (16 female and 29 male) were found to have undergone an NEL at the Charité Universitätsmedizin Berlin during the period August 2010 - May 2016. Twenty patients were born at the neonatology unit at Charité, Berlin, while two were born as outpatients (outborn) and were transported to the hospital in the first moments of life before showing cerebral hemorrhage complications. Twenty-three patients were born as outpatients and were transported for neurosurgical care in the context of posthemorrhagic hydrocephalus (Figure 4).

FIGURE 4: FLOW CHART (1)



The median age of the patient group at birth was 27 weeks and 3 days GA (range, 23 weeks and 3 days - 41 weeks and 4 days) with a median weight of 1160g (range, 520 - 3370g). Thirty-two premature infants were born, before 32 weeks GA, of which twenty-four were under 28 weeks GA. Seven premature infants born between 32 weeks GA and 36 weeks and 6 days GA, and 6 full-term newborns were also included. Thirty premature infants were born with a weight < 1500 g, of whom eighteen wheighed < 1000 g, while fifteen had a weight > 1500 g. Only one premature baby exhibited a hypotrophic weight condition at birth. The sex ratio M / F of our population was 1.8. The median Apgar score at 1 minute was 5 (range, 1 - 9), at 10 minutes it was 8 (range, 3 - 10), and the median of the UapH was 7.30 (range, 6.83 - 7.42). The median postmenstrual age of the patients at the time of the NEL was 31 weeks and 2 days (range, 26 weeks and 1 day - 52 weeks and 3 days) and median age was 22 days (range, 5 - 58), with a median weight of 1605g (range, 734 - 4360; Table 1).

TABLE 1: CHARACTERISTICS OF PATIENT COHORT (1)

	All patients (n = 45)	Premature patients <32 weeks (n = 32)
GA at birth (weeks+days)	27 + 3 (range, 23+3 - 41+4)	26+4 (range, 23+3 - 31+1)
BW (g)	1160 (range, 520 - 3490)	912 (range, 520 - 1970)
Apgar 1min	5 (range, 1 - 9)	4 (range, 1 - 8)
Apgar 10min	8 (range, 3 - 10)	7 (range, 3 - 9)
UapH	7.30 (range, 6.83 – 7.42)	7.30 (range, 6.83 – 7.40)
Age at NEL (days)	22 (range, 5 - 58)	22 (range, 12 - 46)
Weight at NEL (g)	1605 (range, 734 - 4360)	1362 (range, 734 - 2575)

They were 9 sets of twins, of which 2 sets had TTTS, 1 set of triplets and 1 set of quadruplets. The number of antenatal betamethasone treatments for premature infants < 34 weeks GA was 13 complete (35%) and 3 incomplete (8%), while no antenatal betamethasone was administered in 17 cases (46%), and for 4 infants treatment was unknown (11%). Thirty-two patients (71%) received an antibiotic treatment at the birth because of a suspicion of maternal-fetal infection, of whom eighteen newborns (40%) received antibiotics due to signs of biological infection (CRP > 10mg/dl at day 2 - 4 and/or IL-6 > 100 ng/l at day 1). Twenty-eight patients (62%) needed invasive ventilation and 11 patients (24%) needed non-invasive ventilation. Sixteen patients received catecholamine treatment, of whom 7 received it before their IVH, 3 during their IVH, and 6 after their IVH. Treatment of metabolic acidosis with sodium bicarbonate was administered to 11 (24%) of the children. Five (16%) of the premature infants < 32 weeks GA were treated with indomethacin. Other peri- and postnatal diagnoses included: 11 cases of BPD (oxygen dependent at 36 weeks GA); 9 cases of ROP who needed laser treatment; 5 PDA cases, who received treatment with ibuprofen; and 3 PDAs that received treatment with ibuprofen and a surgical ligature. There were also 6 cases of lung bleeding, 8 cases of PH that received nitric oxide (NO) treatment, 4 cases of pneumothorax, and 3 laparotomies. IVHs were first documented by ultrasound at a median of 2 days (range, 0 - 9) after birth. Seven patients (16%) had prenatal intracerebral bleeding. The diagnosis of IVH was made in the first 72 hours of life in 59% of cases, and between the 4th and 7th day for 15% of patients. The latest diagnosis was made at day 9 (n = 1). For 4 children (8%), the age of IVH diagnosis was unknown. There were 3 NB (7%) with grade II, 18 NB (40%) with grade III, 23 NB (51%) with grade IV, and 1 NB (2%) with an unknown grade of IVH. The distribution of possible hemorrhages found in the lateral ventricles in all newborns was: no obvious hemorrhage (n = 1), grade I hemorrhage (n = 5), grade II hemorrhage (n = 18), grade III hemorrhage (n = 35), grade IV hemorrhage (n = 28), and unknown (n = 3; Table 2).

TABLE 2: CHARACTERISTICS OF PATIENT COHORT (2)

Parameter	Frequency
Multiple gestations and TTTS	9 Twins 2 TTTS 1 Triplet 1 Quadruplet
Antenatal betamethasone	13 Complete = 35% 3 Incomplete = 8% 17 no antenatal betamethasone = 46% 4 unknown = 11%
Infection	18 positive parameters of biological infection (CRP > 10 mg/dl at day 2 - 4 and/or IL6 > 100 ng/l at day 1) = 40% Il-6 100 - 1000 = 7 Il-6 > 1000 = 8 Il-6 unknown and CRP positive = 2 Il-6 negative and CRP positive =1 32 Antibiotic treatments = 71%
Ventilation	invasive 28 = 62% non-invasive 11 = 24%
Catecholamines	16 catecholamine treatments 7 before IVH 3 while IVH 6 after IVH
Treatment of metabolic acidosis with sodium bicarbonate	11 = 24%
Indomethacin	5 = 16%
Grade of IVH	Grade II, n = 3 (7%) Grade III, n = 18 (40%) Grade IV, n = 23 (51%) Unknown, n = 1 (2%)
Age at IVH	Prenatal intracerebral bleeding n = 7 (16%) at day 1, n = 7 (16%) at day 2, n=7 (16%) at day 3, n=12 (27%) at day 4, n=6 (13%) at day 5, n=1 (2%) at day 9, n=1 (2%) Unknown, n=4 (8%)
Peri- and postnatal events	11 BPD (Supplemental oxygen at 36 weeks GA) 9 ROP (laser treatment) 5 ibuprofen for PDA 3 ibuprofen + surgical closure for PDA 6 lung bleeding 8 NO treatment for PH 4 pneumothorax 3 laparotomies

At the end of the procedure, all patients received a RR as a temporary CSF diversion device. Fifteen patients (33%) required invasive ventilation before NEL surgery. The preoperative intubation was most of the time performed in the NICU (19 patients NICU and 11 in surgery). The median operative time was 70 minutes (range, 36 - 108), and the median time away from the NICU was 180 minutes (range, 120 - 235). The median postoperative temperature was 36 °C (range, 34.2 - 36.5).

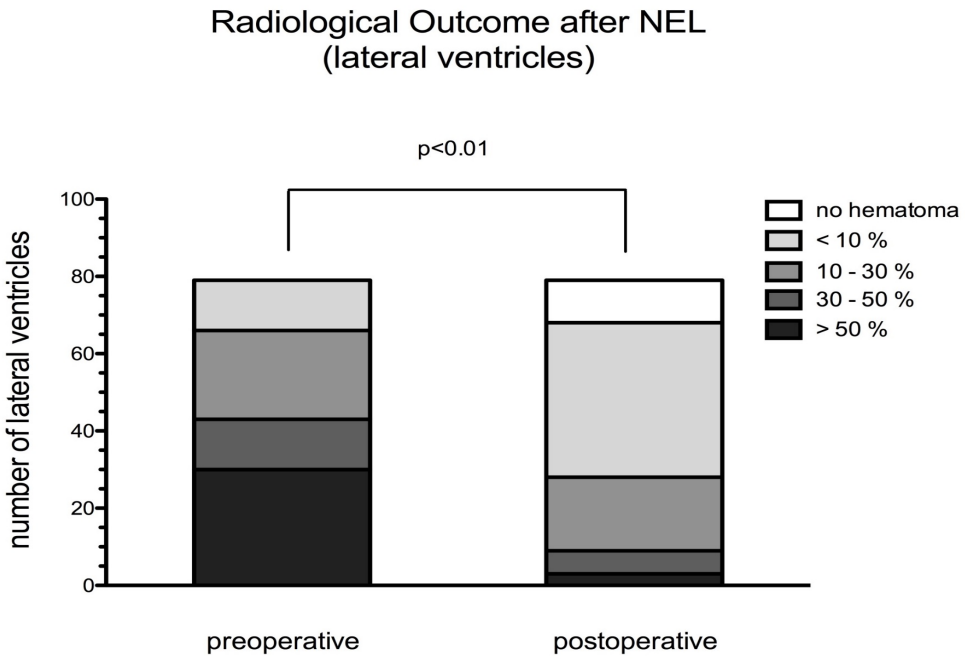
PRE- AND POSTOPERATIVE RADIOLOGICAL EVALUATION

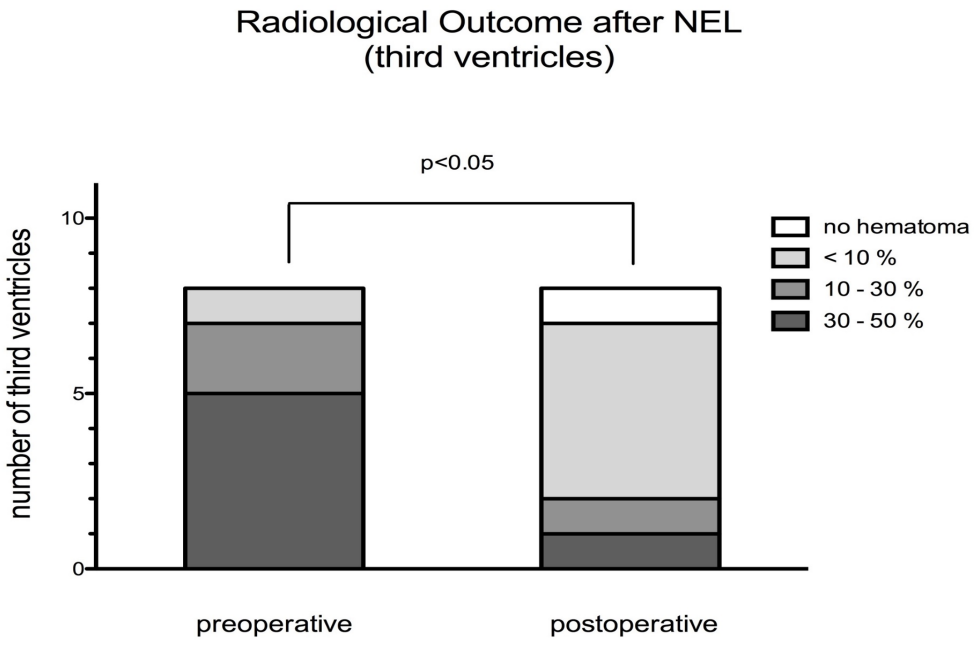
Before the NEL procedure, ultrasound demonstrated visible intraventricular solid hematoma in 79 lateral ventricles and 8 third ventricles. The size of the preoperative hematoma was estimated to occupy > 50% of the lateral ventricular volume in 30 ventricles, 30 - 50% of the ventricular volume in 13 ventricles, 10 - 30% of the ventricular volume in 23 ventricles, and < 10% of the ventricular volume in 13 ventricles. After the NEL procedure there was significant reduction in the distribution of hematoma grades; 3 lateral ventricles > 50% volume of hematoma, 6 lateral ventricles filled 30 - 50% with hematoma, 19 lateral ventricles with 10 - 30% of their volume as hematoma, 40 lateral ventricles contained < 10% hematoma, and 11 lateral ventricles showed no obvious residual hematoma ($p < 0.01$; Figure 5).

A solid hematoma was visible in 8 patients in the third ventricle before the NEL procedure, in 5 patients it was 30 - 50% of the third ventricular volume, in 2 patients 10 - 30% of the third ventricular volume, and for 1 patient it was < 10 % of the third ventricular volume. After NEL there was a significant reduction in the distribution of hematoma grades: 1 patient had a 30 - 50% volume of hematoma, 1 patient had a 10 - 30% volume of hematoma, 5 patients had < 10% volume of hematoma, and 1 patient had no obvious hematoma ($p < 0.05$; Figure 5).

FIGURE 5: RADIOLOGICAL OUTCOME AFTER NEL

Radiological results after NEL demonstrating a significant change in solid intraventricular hematoma volume for lateral (n = 79) and third (n = 8) ventricles. Numbers are depicted as a percentage distribution of patients between the respective grading.



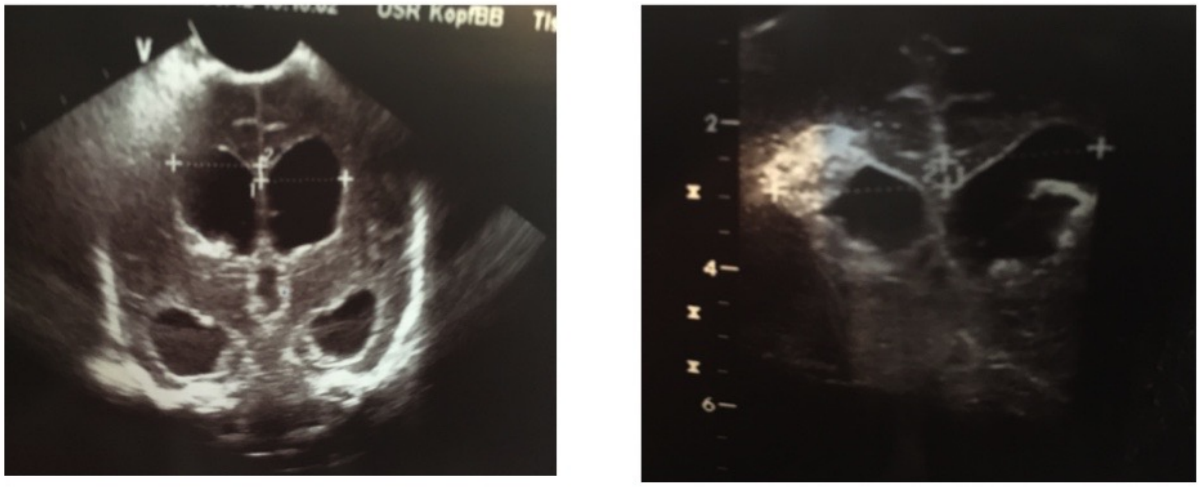


COMPLICATIONS AND REOPERATION

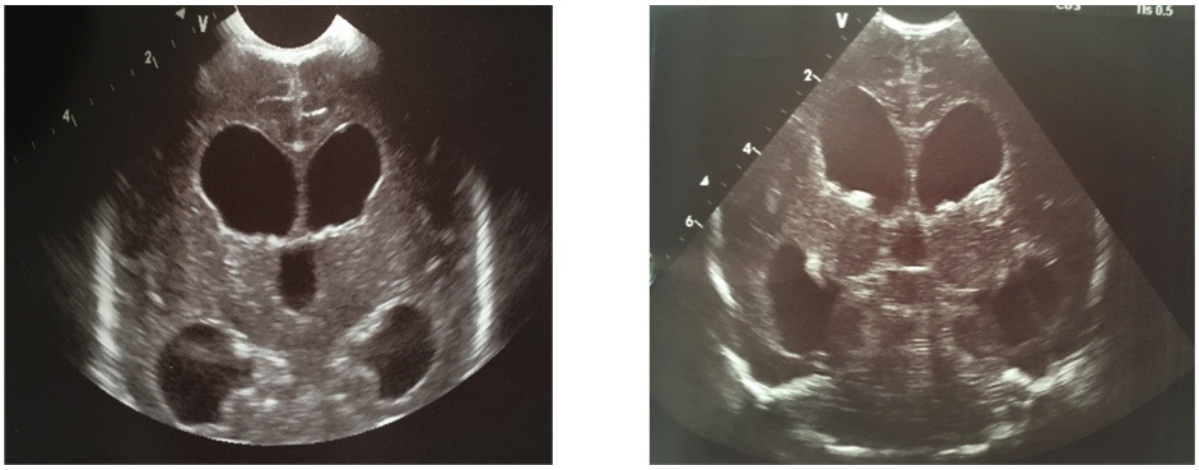
In three patients (6.7%) a new intracranial hematoma (1 intraventricular, 1 in the cortical channel, 1 subependymal) was documented by cranial ultrasound a few hours after the procedure. The age at which NEL was performed in these 3 patients was 16 days (26 weeks GA corrected age), 14 days (36 weeks GA corrected age) and 20 days (32 weeks GA corrected age), respectively. One of these 3 patients underwent a repeat of the NEL procedure (Figure 6).

FIGURE 6: NEW INTRACRANIAL HEMATOMAS POST-NEL

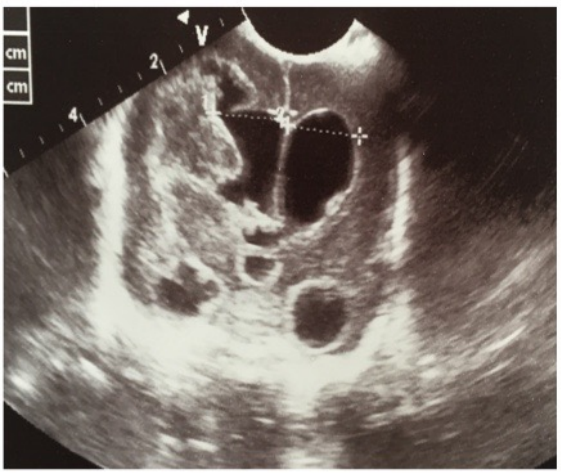
a) A new intracranial hematoma post-NEL in the cortical channel on the right ventricle

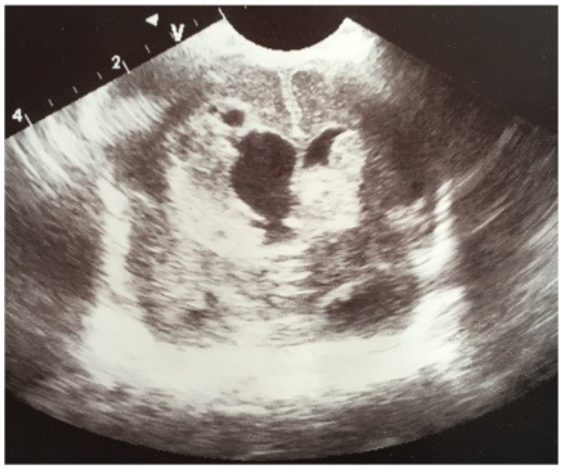


b) A new intracranial hematoma post-NEL subependymal on the left ventricle



c) A new intracranial hematoma post-NEL intraventricular on the left ventricle





A second NEL was performed for 8 of the 45 patients, due to clinical signs of progressive disturbed CSF circulation according to the afore-mentioned criteria and accessible residual intraventricular hematoma.

Two patients (4.5%) developed an infection of the CNS (cerebral nervous system), with positive CSF cultures 17 and 29 days after the NEL procedure. At that time, temporary CSF diversion via puncture of the RR had already been performed several times. One of these patients underwent a RR explant procedure. In 4 further patients (9%) an infection was considered due to clinical signs or laboratory markers, after a median time of 3 days (range, 3 - 4) after the NEL. Antibiotic therapy was given for a median time of 7 days (range, 6 - 12) after NEL, although prior CSF cultures remained negative.

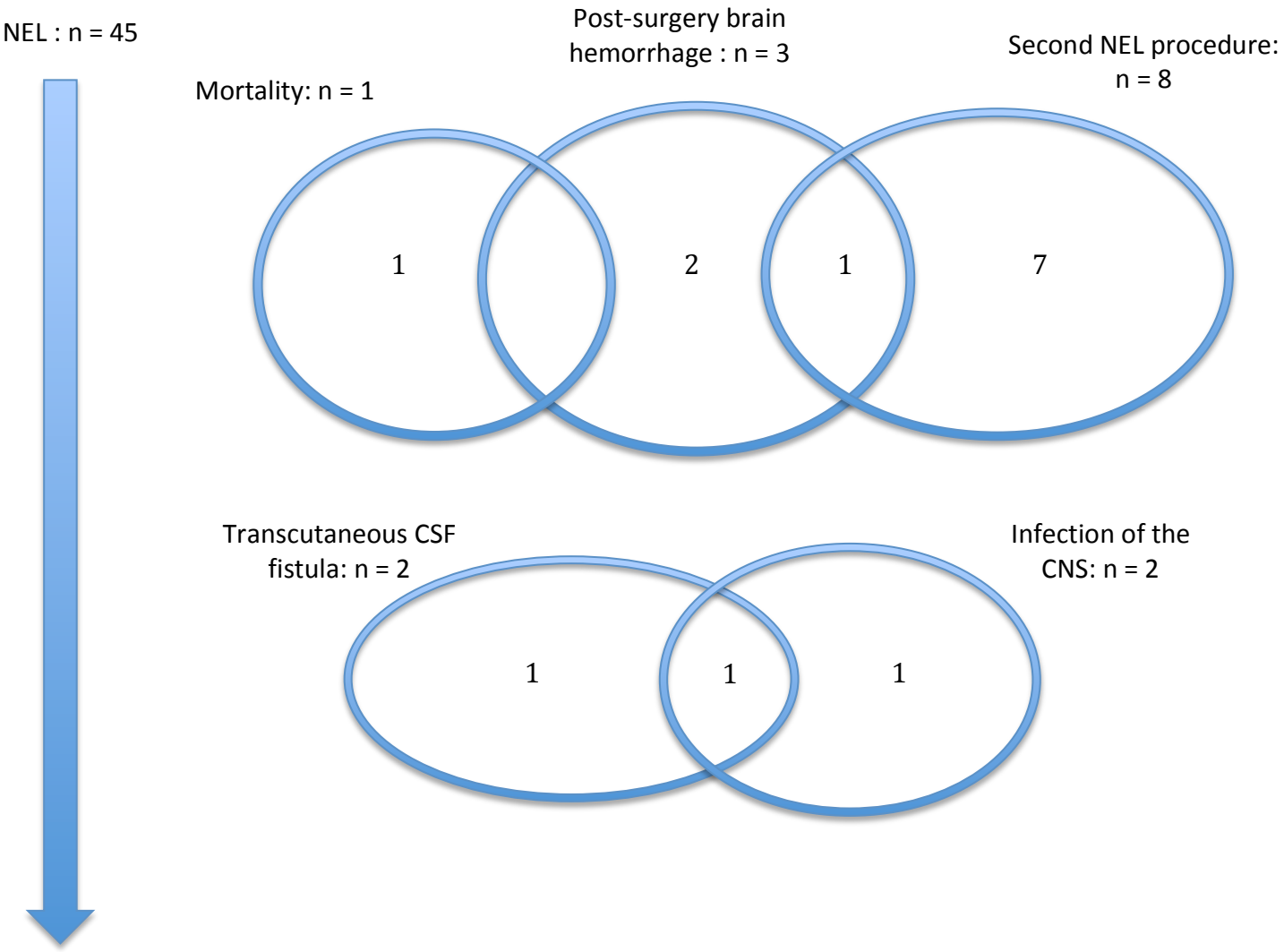
Two patients (4.5%) developed a subcutaneous CSF collection without the need for further intervention, and 2 patients (4.5%) developed a transcutaneous CSF fistula requiring additional suturing (Figure 7).

Twenty-three patients (51%) received antiepileptic treatment before the operation; treatment was stopped before NEL in 7 patients (15%) and after NEL in 6 patients (13%). Antiepileptic treatment was continued in the postoperative period in 10 patients (22%). Antiepileptic treatment was initiated in 8 patients (18%) after NEL.

Two patients (4.5%) developed an hygroma. One patient developed an epidural dislocation of the RR, and underwent surgical revision. The use of catecholamine was necessary in 3 patients (6.7%).

Twenty-eight patients (62%) did not have further complications post-surgery.

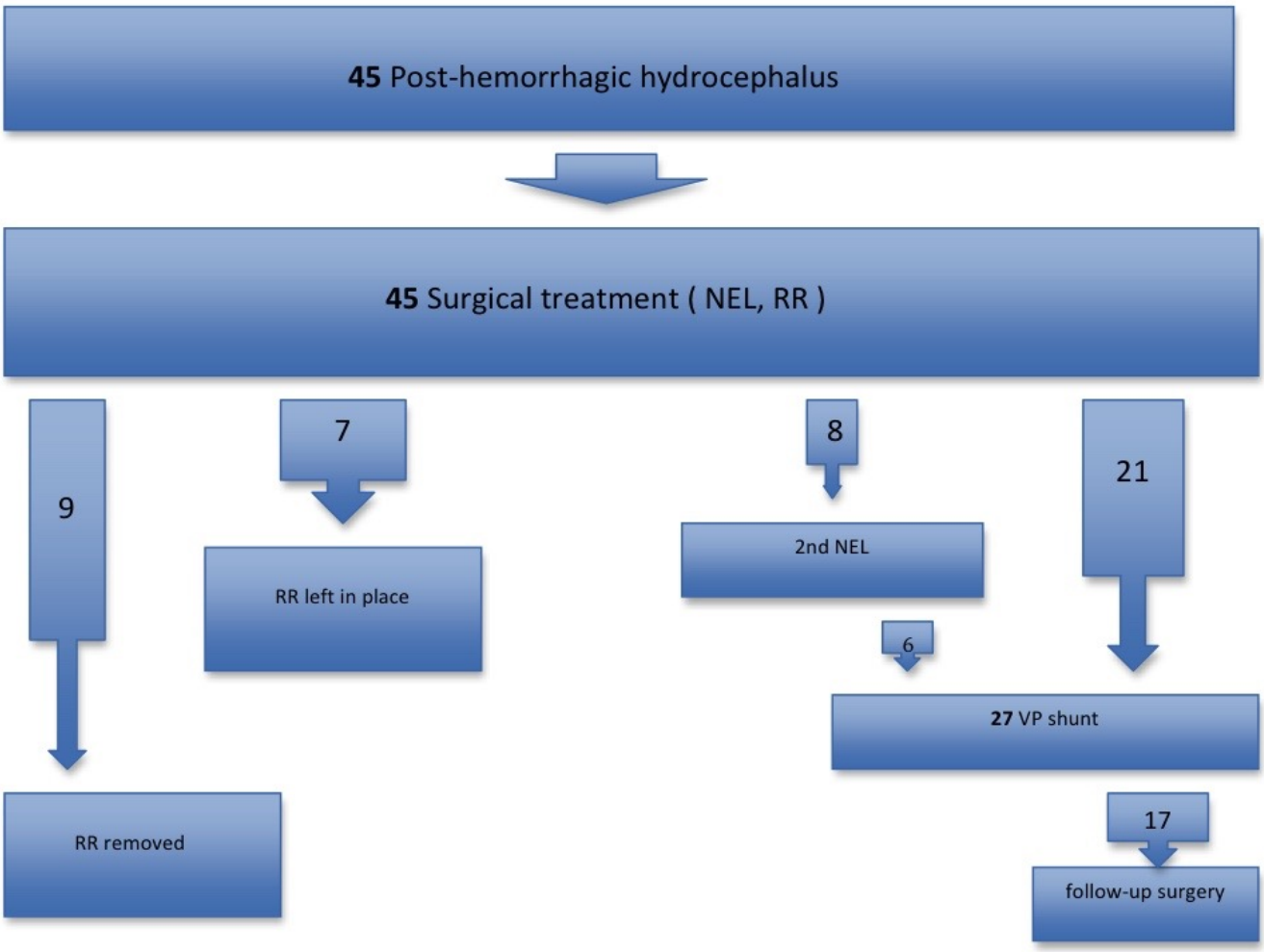
FIGURE 7: POSTOPERATIVE COMPLICATIONS



VP SHUNT INSERTION RATE AND FOLOW-UP

All patients were clinically followed for a median time of 2 years and 10 months (range, 1 year - 6 years and 8 months). Following the NEL procedure until May 2017, 9 patients had a RR removed, 7 of them did not have follow-up surgery, and for 8 patients a second lavage procedure was performed. Twenty-seven of the 45 patients (60%) required insertion of a permanent CSF diverting system by means of a VP shunt and for 17 patients follow-up surgery was performed (Figure 8).

FIGURE 8: FLOW CHART (2)



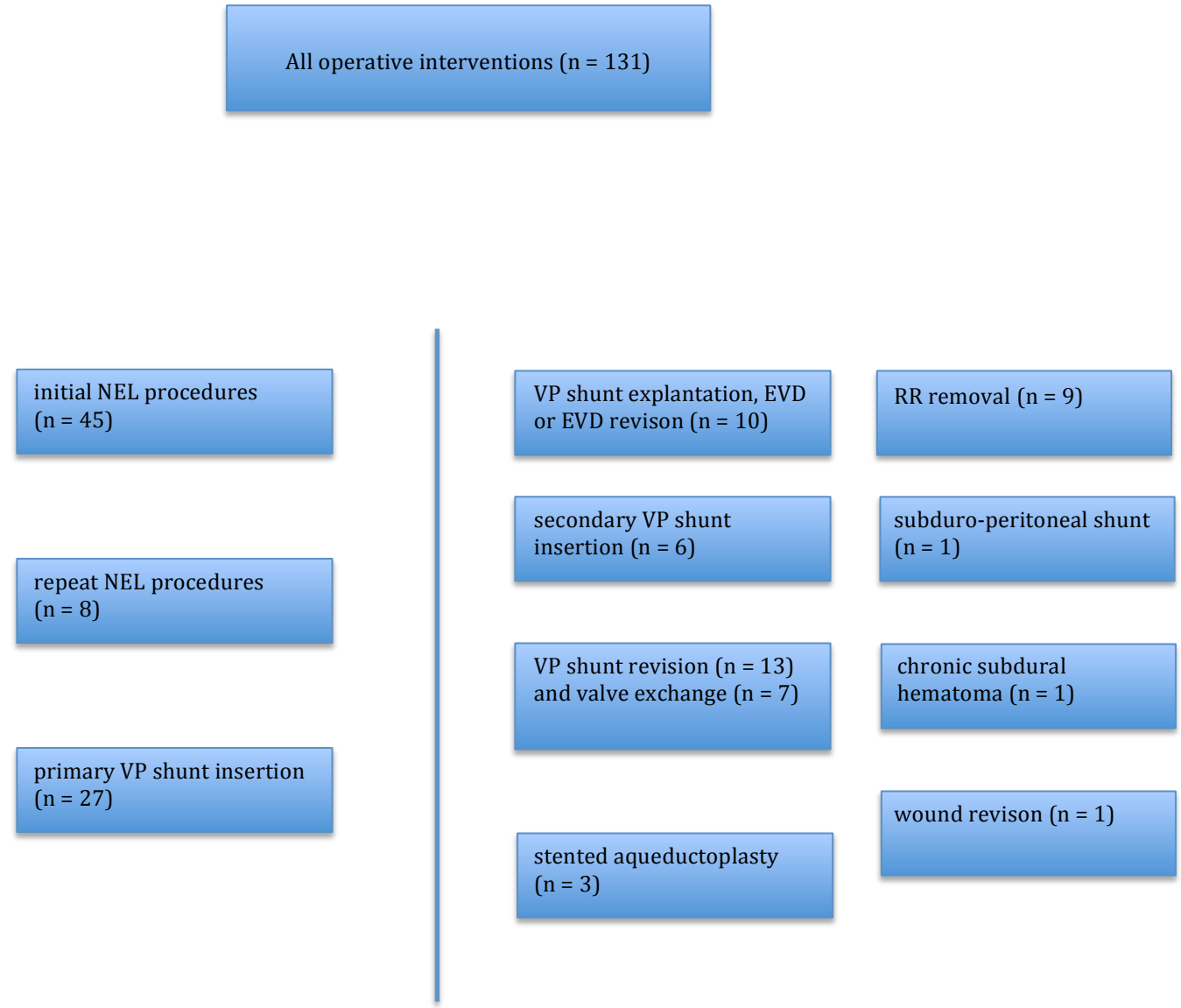
The median age of the patients at shunt insertion was 37 weeks and 4 days GA (range, 32 weeks and 4 days - 100 weeks and 5 days). The median weight of the patients at shunt insertion was 2900 g (range, 960 to 12900). There was no significant influence as to the timing of NEL after the initial hemorrhagic event between patients who later received a VP shunt (NEL after median of 24 days; range 5 - 58) and the patients who remained VP shunt free (NEL after a median of 20 days; range 9 - 78 days; p = 0.18). Furthermore, no significant difference could be demonstrated for these 2 groups with respect to GA and BW, GA and weight at NEL, and length of the NEL procedure and comorbidities. The number of days required on ventilation support during the postoperative period differed significantly between the 2 patient groups; there was a median of 4 days (range, 0 - 22) for children who received a shunt and a median of 2 days (range, 0 - 11) for children who remained shunt free *(*$p < 0.05$, Table 3).

TABLE 3: COMPARISON OF ASSOCIATED PARAMETERS IN RELATION TO PATIENTS' VP SHUNT STATUS

	VP Shunt (n = 27)	No VP Shunt (n = 18)	p value
GA at birth (weeks + days)	26 + 4 (range, 23 + 3 - 41 + 4)	30 + 3 (range, 23 + 6 - 41 + 2)	0.084
BW (grams)	930 (range, 520 - 3490)	1232 (range, 550 - 3460)	0.118
GA at NEL (weeks + days)	31 + 4 (range, 26 + 1 - 47 + 4)	33 + 3 (range, 27 + 0 - 46 + 4)	0.59
Age at NEL (in days)	24 (range, 5 - 58)	20 (range, 9 - 78)	0.178
Weight at NEL (grams)	1500 (range, 734 - 4360)	1560 (range, 950 - 4210)	0.297
Length of operation (min)	70 (range, 44 - 155)	70 (range, 36 - 213)	0.817
Comorbidities (≥ 2)	8 (30%)	4 (22%)	0.735
Duration of ventilation (days)	4 (range, 0 - 22)	2 (range, 0 - 11)	0.022

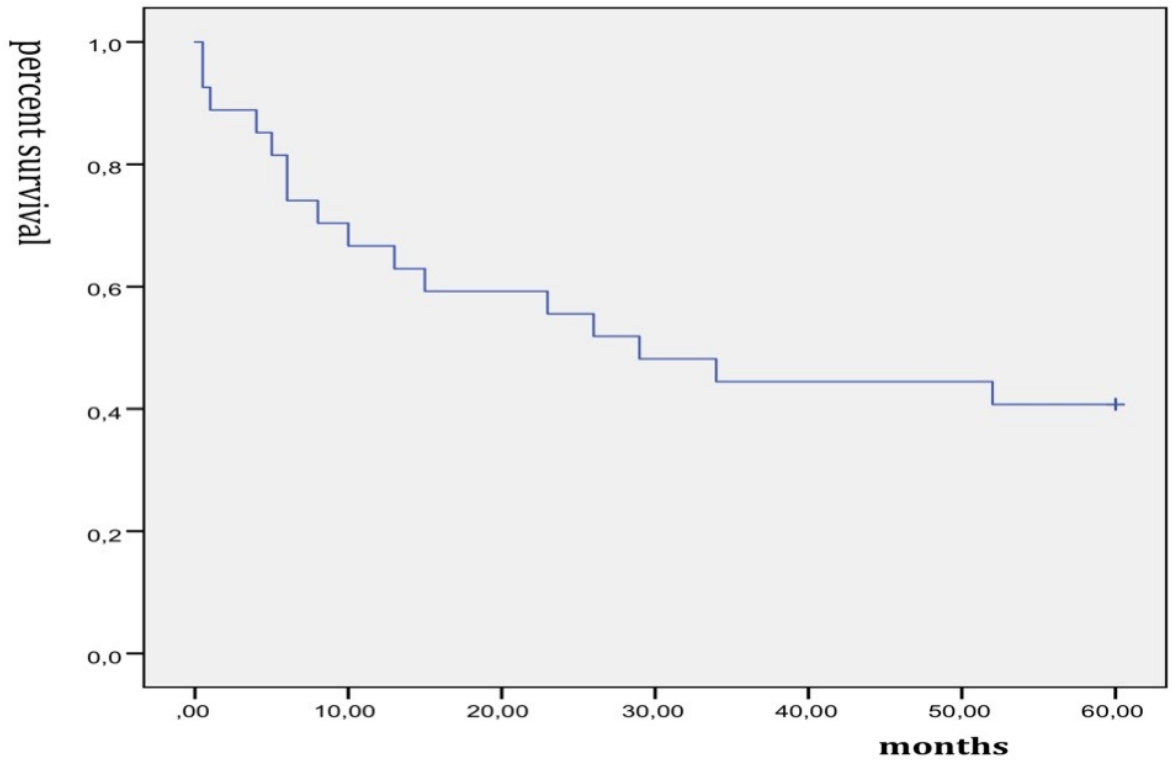
A total of 131 operative procedures were performed on the 45 patients during the whole observational period, including 45 primary NELs, 8 repeat NELs and 27 primary VP Shunt insertion procedures. The remaining 51 operative procedures, 1.1 (0 - 5) additional (unplanned) procedures per patient, consisted of 9 RR removals, 3 stented aqueductoplasties, 10 EVD placements or EVD revisions or VP shunt explantations, 6 secondary VP shunt placements, 13 VP shunt revisions, 7 valve exchanges, 1 posttraumatic chronic subdural hematoma evacuation in a patient with disturbed platelet function, 1 subduro-peritoneal shunt insertion, and 1 wound revision (Table 4). The total mean number of operations per patient for the whole observation period was 2.9 ± 1.8.

TABLE 4: ALL OPERATIVE INTERVENTIONS



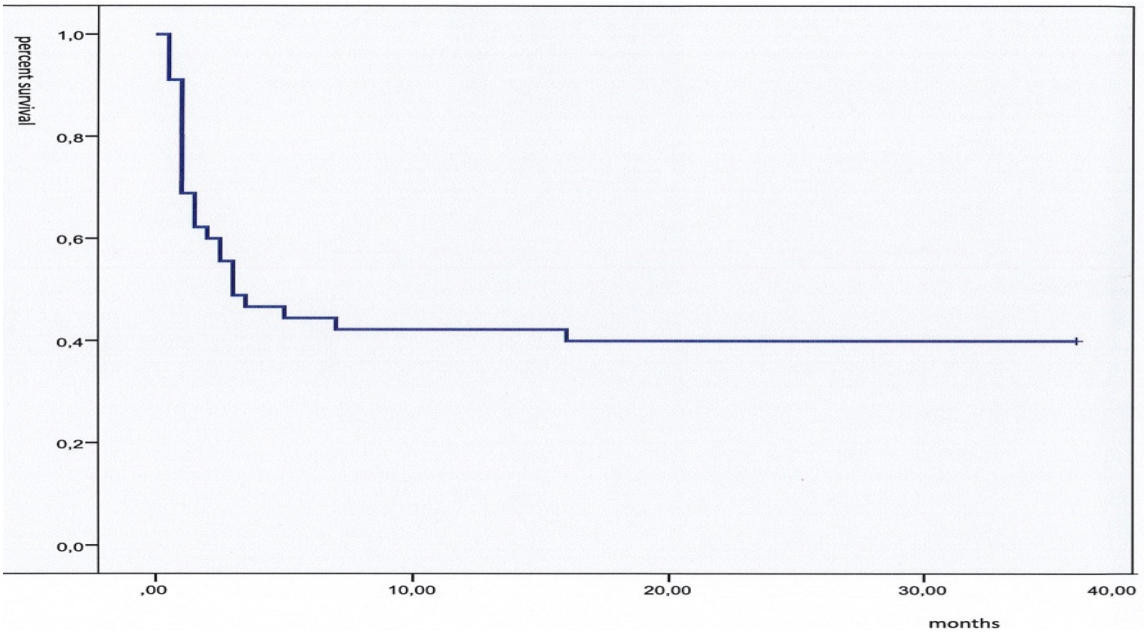
The median survival time of the 26 primarily inserted VP shunts (one patient died 2 months after VP shunt insertion because of complications of severe bronchopulmonary dysplasia) until first revision was 27.5 months (range, 0 - 52), with a 12-month survival rate of 65% and 24-month survival rate of 54% (Figure 9).

FIGURE 9: VP SHUNT SURVIVAL AFTER NEL (n = 26)



The median survival time of the initial NEL procedures until primary VP shunt insertion was 1 month (range, 0.5 - 16), with a 1-month shunt free for 69%, and 6-month shunt free for 44.5% (Figure 10).

FIGURE 10: TEMPORARY CSF DIVERSION SURVIVAL BEFORE VP SHUNT PROCEDURE AFTER NEL (n = 45)



MORTALITY

One of the 45 patients (2%) died during follow-up. This patient had a GA at birth of 23 weeks and 3 days, underwent NEL at a menstrual age of 27 weeks and 4 days, and VP shunt insertion at a menstrual age of 41 weeks and 3 days. The patient succumbed to complications of severe bronchopulmonary dysplasia at the corrected age of 2 months and 3 weeks.

DURATION OF STAY

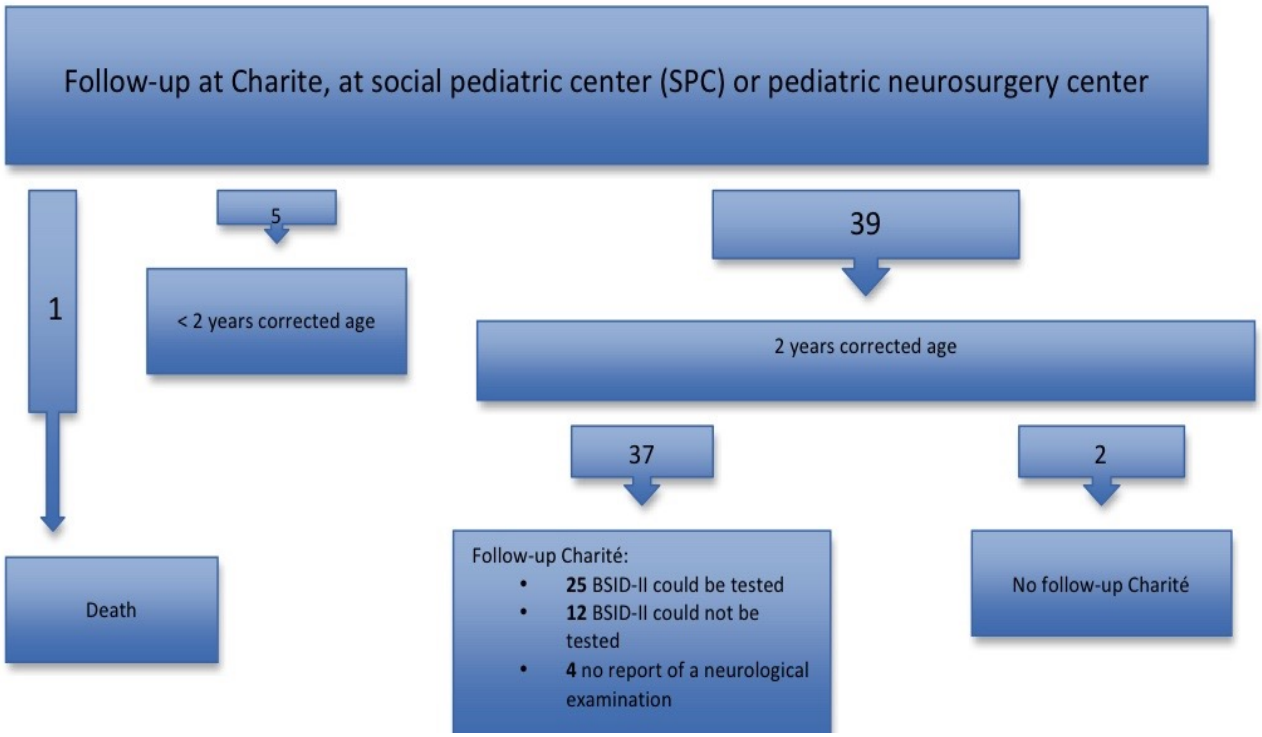
The median length of stay was 75 days. The median age at hospital discharge was 40 weeks, corrected age. A premature newborn (23 weeks and 3 days GA) was discharged to a specialized medical facility at 2 months corrected age.

OUTCOME

We were unable to retrieve all the data for each of the 45 patients included in this study. One patient died and 5 patients had not reached the corrected age of 24 months by April

2018. Two patients were not followed-up at the Charité; 12 were not evaluated by BSID-II, due to there no being no follow-up at the social pediatric center (SPC), or testing was not possible; and 4 patients did not have a written report of a neurological examination (SPC, or pediatric neurosurgery center) at the corrected age of 24 months. BSID-II analysis at 24 months corrected age at the SPC was possible for 25 patients included in the study (Figure 11).

FIGURE 11: FLOW CHART (3)



The BSID-II produced a Mental Development Index (MDI) and a Psychomotor Index. The mental scale factors were sorted into 4 categories: cognitive, language, personal/social, and motor. These had standard scores with a mean of 100 and a standard deviation of 15; a MDI < 70 was indicative of significant delay (Table 5).

TABLE 5: BSID-II SCORE CLASSIFICATIONS

BSID-II Score classifications	
≥ 115	Accelerated
85 - 114	Within normal limits
70 - 84	Mildly delayed
≤ 69	Significantly delayed

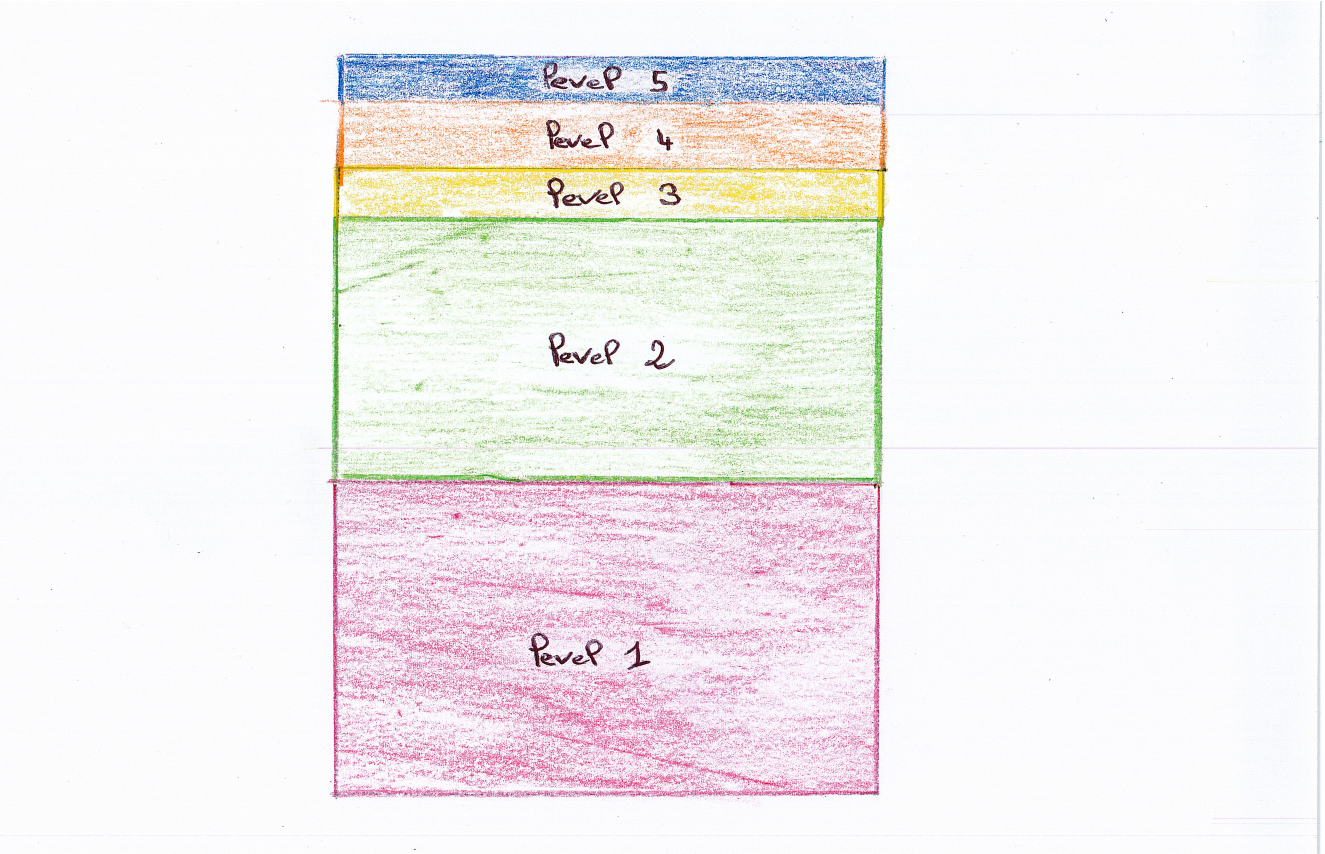
The MDI was > 70 in 11 patients (44%); the median MDI for the study population was 80 (range, 49 - 151). There was no significant influence of the timing of NEL after the initial hemorrhagic event in patients who later had a MDI < 70 (NEL after median of 22 days; range, 5 - 46), and those who had a MDI ≥ 70 (NEL after a median of 26 days; range, 9 - 58; p = 0.222). Furthermore, there was no significant difference in GA and BW, GA and weight at NEL, VP shunt or not, age at IVH and grade of IVH between children with an MDI < 70 and those with an MDI ≥ 70. There was a significant difference for comorbidities between the 2 patient groups, 7 patients (50%) had ≥ 2 comorbidities for children who had a MDI < 70, while there was only 1 patient (9%) with ≥ 2 comorbidities for those with a MDI ≥ 70 (p < 0.05; Table 6).

TABLE 6: COMPARISON OF ASSOCIATED PARAMETERS FOR PATIENTS WITH MDI SCORES < 70 vs MDI SCORES ≥ 70

	MDI score < 70 n = 14	MDI score ≥ 70 n = 11	p value
GA at Birth (weeks + days)	26 + 4 (range, 23 + 6 - 40 + 3)	29 + 2 (range, 25 + 0 - 41 + 2)	0.095
BW (grams)	1025 (range, 520 - 3370)	1390 (range, 655 - 3460)	0.183
Age at NEL (days)	22 (range, 5 - 46)	26 (range, 9 - 58)	0.222
GA at NEL (weeks + days)	31 + 1 (range, 26 + 1 - 41 + 1)	32 + 4 (range, 28 + 1 - 47 + 4)	0.572
Weight at NEL (grams)	1562 (range, 734 - 3570)	1735 (range, 1170 - 4360)	0.085
Age at IVH (days)	2 (range, 0 - 4)	1 (range, 0 - 4)	0.697
Grade 4 of IVH	7 (50%)	6 (55%)	0.324
Comorbidities (≥ 2)	7 (50%)	1 (9%)	0.042
VP shunt	10 (71%)	7 (64%)	0.99

Motor impairment and cerebral palsy was evaluated on the Gross Motor Function Classification System (GMFCS): level I, walks without limitations at home and outdoors; level II, walks with limitations, at home without hand-held mobility device, climbs stairs holding onto a railing, may require a hand held mobility device outdoors for safety; level III, walks using a hand-held mobility device, may use a manual wheelchair or powered mobility outdoors; level IV, self-mobility with limitations, physical assistance of 1-2 people is required for transfers, may operate a powered chair, otherwise is transported in a manual wheelchair; and level V, self-mobility is severely limited. Transported in a manual wheelchair in all settings. This was possible for 33 children: 14 children were categorized at level 1; 12 at level 2; 2 at level 3; 3 at level 4; and and 2 at level 5 (Figure 12).

FIGURE 12: MOTOR IMPAIRMENT AND CEREBRAL PALSY, GMFCS



With regard to epilepsy at 24 months corrected age, 8/37 patients (22%) were in need of antiepileptic medication.

DISCUSSION

IVH is a serious complication of prematurity since it can markedly impact future neurological development (24, 93, 97, 103).

IVH RISK FACTORS AND INDOMETHACIN TREATMENT

In this study 6 newborns were born at full-term. One of them had a disturbed platelet function, while no pathology was found for the other 5 patients. Seven patients developed intracerebral hemorrhages in the prenatal period; the pathophysiological hypothesis is that they resulted from infarction of the anterior cerebral artery of the fetus with secondary hemorrhage. Three of the 45 patients had coagulation disorders, 2 had disturbed platelet function, and 1 had an antithrombin III defect.

It has been demonstrated that the incidence of IVH can be decreased by maternal corticosteroid administration before 34th week of gestation (61, 66, 78). In our study from those who had premature children, 13 mothers (35%) received corticosteroids, 3 mothers (8%) received an incomplete course of treatment, 17 mothers (46%) received no corticosteroid treatment, and for 4 mothers (11%) treatment with corticosteroids was unknown (Table 2).

Birth as an outpatient is a risk factor for severe IVH (65). In our study, 2 premature babies required neonatal transfer before their IVH.

The sex ratio of this cohort was in favour of boys, 29 males/16 females. Heuchan *et al.* demonstrated male gender could be a risk factor for severe IVH (75). Weight also seems to be an important factor (65). Other authors highlight the protective nature of hypotrophy in the occurrence of severe IVH (75). The results are therefore rather discordant. In this study only 1 patient was hypotrophic.

Indomethacin is administered early (in the first 6 hours of life) to reduce the incidence of IVH, pulmonary hemorrhage, and lower PDA surgical interventions (92). The IVH-reducing effect is independent of any ductal occlusion and is based on a direct inhibition of COX-2-mediated prostaglandin synthesis in the germinal matrix (87). However, a large indication does not lead to the expected reduction in mortality and neurological morbidity, presumably due to indomethacin side effects (decreased cerebral blood flow; 82, 86, 91). Due to renal,

pulmonary, and cerebral indomethacin side effects, which are more pronounced in girls than in boys, indomethacin prophylaxis should be limited to premature infants with a high risk of IVH (85, 88, 89). IVH risk factors are low GA, male gender, lack of lung maturity, multiple pregnancies, increased IL-6 levels and hypothermia (75, 84, 90). Treatment with COX inhibitors also increases the risk for intracerebral bleeding in very low BW infants with moderate thrombocytopenia (83).

PATHOPHYSIOLOGY OF BRAIN DAMAGE

The adverse mechanisms potentially challenging neurological development are threefold (1). Firstly, there is local damage at the site of the hemorrhage in the subependymal brain parenchyma in lower grade IVH, or much more extensive damage in the infarcted area around the ventricles in grade IV. Secondly, the intraventricular extension of the hemorrhage impacts on CSF circulation and may result in posthemorrhagic hydrocephalus in up to half of children affected with grade III/IV IVH (30). The possibly untreated posthemorrhagic hydrocephalus will additionally affect normal brain development through elevated intracranial pressure and brain tissue compression (15). Thirdly, apart from the pressure mediated disturbance of brain development, there is evidence that the presence of intraventricular blood triggers inflammatory responses leading to the accumulation of cytotoxic substances, resulting in brain damage (1, 13, 14).

ACTIVE REMOVAL OF BLOOD: DRIFT (Drainage, Irrigation and Fibrinolytic Therapy)

This procedure aims to remove the blood by breaking down blood clots using drugs (fibrinolytics), draining and washing out the blood from the brain with artificial CSF and antibiotics. The procedure lasts 2 to 7 days until there is a regular transparency of the CSF. Data from the series of DRIFT studies indicate a beneficial effect from the active removal of blood components from the ventricular system once signs of posthemorrhagic hydrocephalus develop (1). In randomized controlled studies, the neurological outcome was better in infants undergoing drainage, irrigation, and fibrinolytic therapy (DRIFT), despite a relevant rate of secondary hemorrhages, as compared to standard treatment with reservoir implantation and repeated punctures (16, 17, 18, 20). To conclude, the concept of NEL was introduced to reduce intraventricular blood products, as a safer and more controllable surgical technique (1). Prior reports have demonstrated its feasibility in this patient population (1, 2, 4).

The present study is a retrospective follow-up study with NEL as the first operative intervention (1). In accordance with general practice, NEL was performed only when clinical signs of disturbed posthemorrhagic CSF circulation necessitated CSF diversion. Dilatation of the lateral ventricles as demonstrated by ultrasound is a prerequisite for NEL, and is required to allow access, orientation and maneuverability within the ventricular system.

Reduction of the intraventricular blood components is a two-part process (1). First, irrigation of the fluid within the ventricular system, which often exhibits a brownish-turbid appearance, is necessary to allow orientation with anatomical landmarks. Secondly, the solid residual hematoma clots that are soft enough can be actively aspirated (1, 4). Removal of solid hematoma is guided by its accessibility along the possible trajectories from a lateralized frontal pre-coronal entry point, which provides access to the frontal horn, cella media, atrium and occipital horn of the ipsi- and contralateral ventricle, as well as to the third ventricle; however, access of the temporal horns is beyond the reach of a rigid endoscope. If solid hematoma parts are attached to the choroid plexus or to the periventricular parenchyma, complete aspiration may not be achievable without damage to central nervous system structures. However, establishment of a regular transparency of the CSF by irrigation could be achieved in all treated patients (1). Furthermore, comparative assessment of the pre- and postoperative size of the intraventricular solid hematoma demonstrated a significant reduction of solid hematoma in the patient cohort treated by NEL and proved its efficiency (1). The procedure of NEL is verified as safe, feasible and effective in patient cohorts of relevant size, although a learning curve is certainly involved as indicated by the variability of the operative times (1, 5, 6, 7, 9, 10, 11, 12). The observed complications, with a 4.5% rate of proven infection after NEL, compared favourably to an infection rate of 14% for ventriculosubgaleal shunt (VSGS) or 17% for repeated punctures of an implanted reservoir (1, 21, 34). The documented re-hemorrhage rate of 6.7% was markedly lower than the 35% experienced in the treatment group of the DRIFT study, and was comparable to the 8% in the standard arm (18). In our cohort, the secondary hemorrhage in 2 of 3 patients was minor; neither the small subependymal in 1 patient nor a secondary hemorrhage within the transcortical access of another required further surgical treatment (1). In 1 of the 3 patients a secondary bleeding necessitated a second NEL procedure. In our study, 1 patient died, however, the death was unrelated to surgery (1). The overall mortality rate of 2% was lower

than reported rates of 17% for patients for VSGSs, 11% with repeated punctures of an implanted reservoir (21), and 6% or 14% in the DRIFT study for the treatment arm and control groups, respectively (18).

The potential benefits of NEL in posthemorrhagic hydrocephalus are firstly that clearance of the ventricular system of intraventricular blood might positively influence CSF circulation by removing the causative agent for development of posthemorrhagic hydrocephalus (1). Secondly, decreasing the amount of blood degradation products and protein load could facilitate treatment of posthemorrhagic hydrocephalus, by reducing secondary complications like shunt dysfunction or occlusion, and also reducing the risk of an isolated fourth ventricle or multiloculated hydrocephalus (1). Thirdly, removal of blood degradation products might positively influence brain development by reducing secondary damage from triggered inflammatory responses (13, 14).

VP SHUNT AFTER NEL: Lower shunt rate, Alleviation of further VP shunt treatment

When the DRIFT studies were initiated in a randomized controlled analysis, one of the hypotheses was that drainage, irrigation and fibrinolytic therapy might reduce the rate of shunt dependency. This assumption was not demonstrated by the DRIFT treatment strategy, which showed a similar shunt rate in the treatment arm and control group of 38 and 39%, respectively (18). However, the presented concept of NEL did result in a lower shunt rate of 58% as compared to an historical patient cohort before NEL was introduced (4). The presented data does confirm the previous results of a smaller patient cohort with an overall shunt rate of 60% (1). The recently published rate of 74% after repeated punctures of an implanted reservoir, and 63.5% after VSGS, are moderately higher compared to NEL, but do not allow conclusions of superiority of one treatment strategy over the other (21).

The second benefit of NEL treatment is the alleviation of further VP shunt treatment. In a previous publication, the researchers reported a median of 3.5 (range, 1 - 11) operative procedures in 10 patients over the first 12 months after conventional treatment (4). The median number of 2 (range, 1 - 7) in the previous study, calculated for the same observation period, and in the current study in a larger patient cohort, demonstrates the potential of NEL to lower the number of VP shunt failures (1, 4). Likewise, the observed 12-month shunt survival of 65% compares favourably with a previously reported survival rate of 44% (29), but remains similar to our recently published data (22).

AFTER NEL: RR or EVD?

NEL is performed at the time point when there is indication to relieve posthemorrhagic hydrocephalus; however, NEL is usually complemented by a temporary treatment option, for example RR or EVD. A RR was implanted as standard procedure in all of the patients of the present study at the Charité Berlin center. EVD was used in 8 patients at another center (1). A higher rate of arrest of hydrocephalus by EVD compared to a RR might be due to the continuous drainage of CSF through an EVD resulting in an ongoing clearance of blood degradation products from the ventricular system. These patients had a VP shunt rate of 37.5% with a complication rate of 37.5%, with 1 CSF fistula, 1 conversion of EVD to reservoir due to displacement, and 1 case of ventriculitis. These numbers are certainly too small to be able to draw solid conclusions; however, they might indicate that a lower VP shunt rate is achieved if further CSF is drained, though leaving an EVD in place results in more complications (1). This underscores the need for further investigations of a standard treatment protocol post-NEL. A similar effect of continuous drainage might be achieved by a high frequency of RR punctures, as suggested in the "Early Versus Late Ventricular Intervention Study" (38).

OUTCOME

Ultimately, the most important outcome remains the neurological development of the affected child (94, 101). The presented data did not yet allow conclusions regarding this parameter, and will require further analysis of outcome data as the children age.

Pre-term infants younger than 32 weeks without cranial ultrasound abnormalities are likely to have a 2-year cerebral palsy. Periventricular leukomalacia lesions show a dissociation from IVH (50). Comorbidities are important in the neurological prognosis of these children. Studies tend to show that the neurological examination can be variable during the follow-up and in particular in the population of premature babies. These changes are the result of several mechanisms, including actual modification of the neurological state of the child and examiner's miscalculation. In the EPICure study, the existence of a neurological abnormality at 30 months had no predictive value on the risk of disability at 6 years (104).

It is difficult to compare cerebral palsy rates between different studies because it varies according to a number of factors, such as the definition of cerebral palsy, age, assessment

method, and year of birth. In order to facilitate comparisons, we used the GMFCS. Even so, a later evaluation at 5 years would probably be more meaningful in terms of cerebral palsy diagnosis (100). It is possible we could have underestimated minor forms of cerebral palsy. However, minor forms of cerebral palsy are responsible for only small disabilities.

The documented MDI ≥ 70 in 11 patients (44%) is comparable to the DRIFT study with 49% in the treatment group, and better than the 37% in the standard arm (18). The median MDI in our cohort of 80 was higher than in the DRIFT study, which had 68 in the treatment group and < 50 in the standard arm (18).

Magnetic resonance imaging, though expensive, requiring transport of the patient and possible sedation, achieves the highest neuroimaging quality in assessing gray and white matter, the posterior fossa, and volumetric data, and has promising predictive value in both motor and cognitive outcomes (95).

Postnatal IVH can have serious consequences for the child and their family. For the child, in the short term, it is a question of enduring physical pain and repeated hospitalization. In the longer term, there is possible disability requiring comprehensive and prolonged care in specialized facilities. For parents, the immediate burden is emotional suffering, anxiety, and family or professional difficulties related to hospitalization. In the longer term, their difficulties relate to dealing with a child with chronic pathologies and disability. Quality of life has to be considered when managing a newborn with severe IVH and posthemorrhagic hydrocephalus.

LIMITATIONS

This study is limited by its retrospective character and the relatively small size of the data set. In order to increase the statistical power of the study, 11 patients from the Leipzig Pediatric Neurosurgical Center were also included (1).

CONCLUSIONS

The management of risk factors is crucial to the prevention of IVH in premature infants. NEL is confirmed to be a feasible operative technique and an effective measure for significantly lowering the amount of intraventricular hematoma in posthemorrhagic hydrocephalus of neonates. In this study, a similar reduction of shunt dependency in long-term follow-up was achieved, in addition to lower infection and mortality rates as compared to previously published data. Alleviating shunt management by reducing subsequent revision rates in comparison to historical controls was also observed. Nevertheless, more neurodevelopmental outcome data is required to more thoroughly assess the value of NEL. Further multicentric comparative cohorts are necessary to answer questions about, for example, the best time points for NEL and consecutive temporary CSF management. These questions will now be addressed by a prospective patient registry for treatment options of posthemorrhagic hydrocephalus in neonates.

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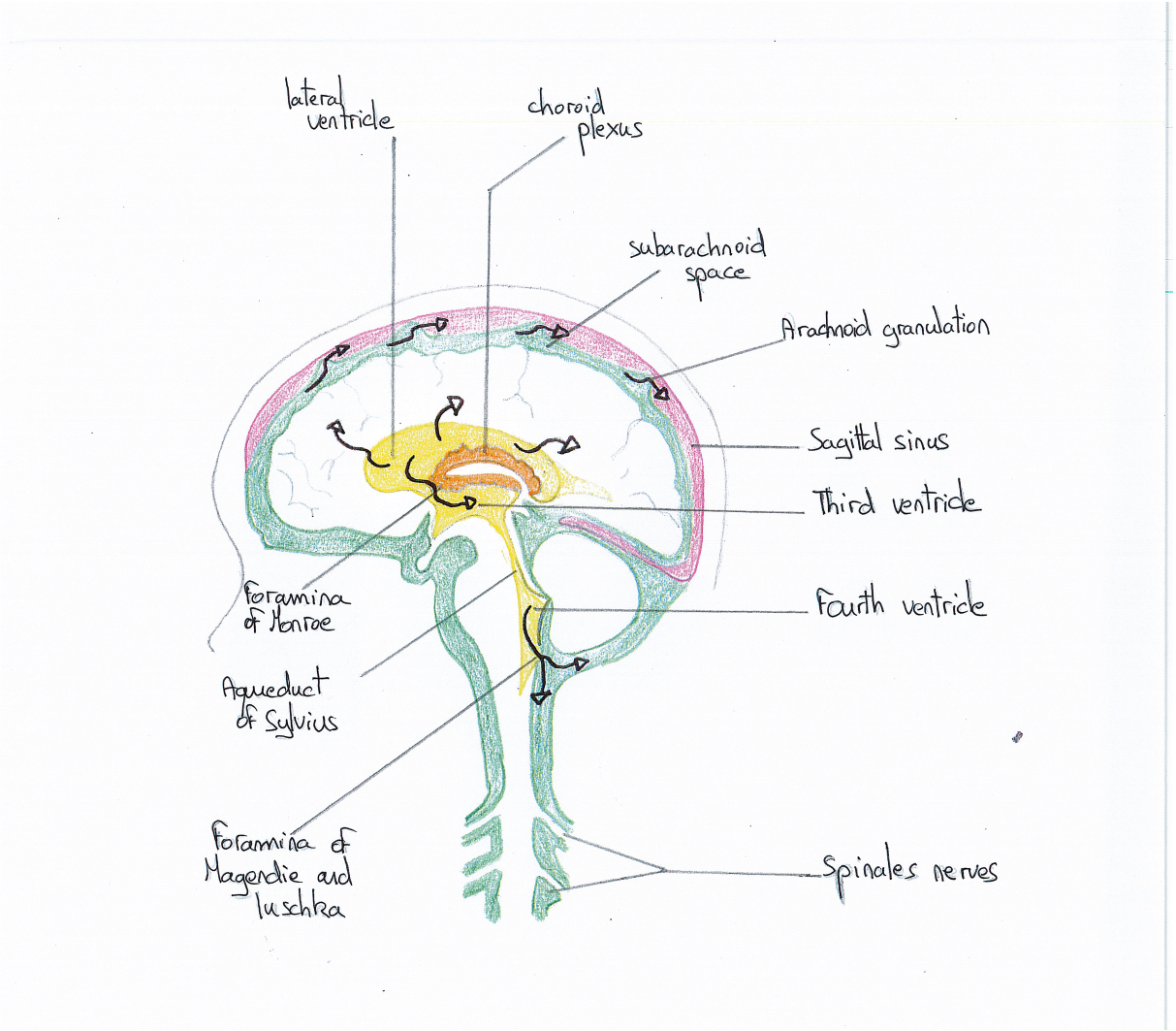
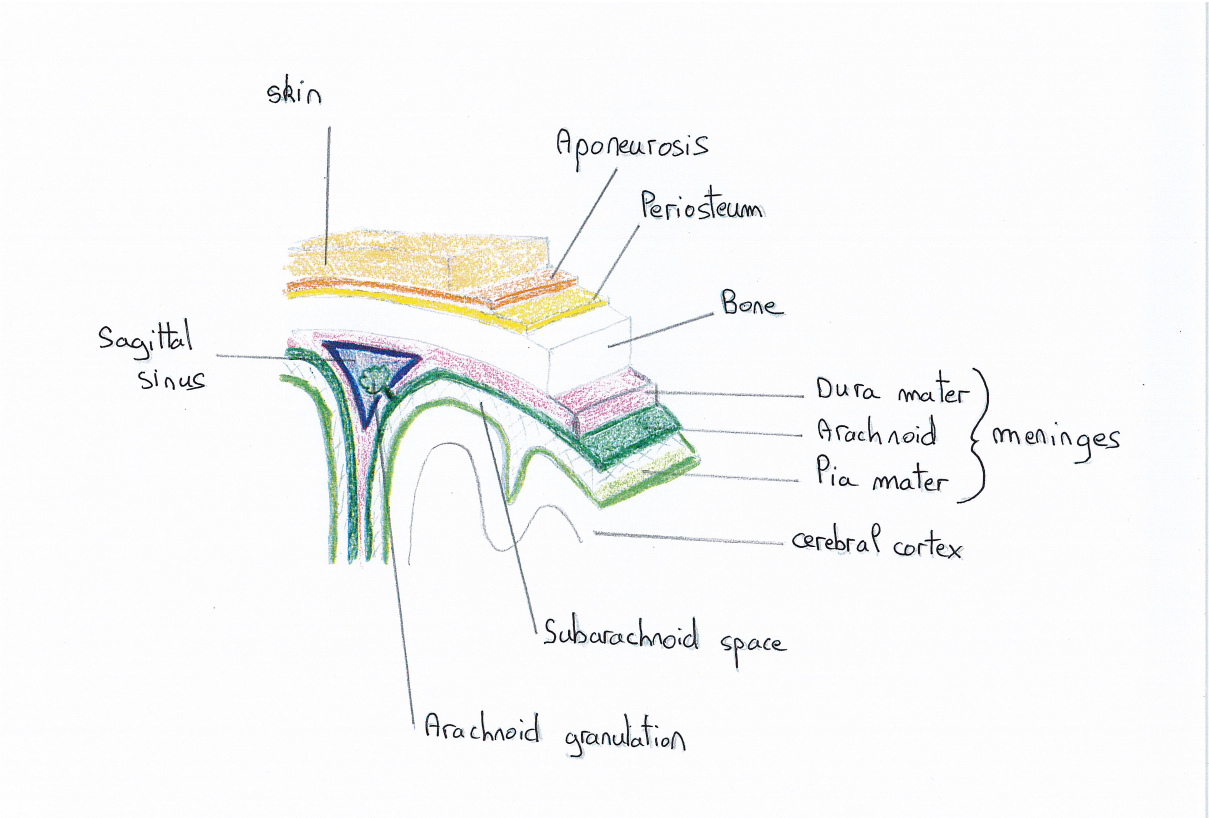
ANNEX 1: PRODUCTION AND FLOW OF CSF

This is an illustration depicting the anatomical structures involved in the production and flow of CSF through the ventricular system, brain, and spinal cord and final absorption into the blood stream.

CSF is produced by the ependymal cells in the choroid plexus, found at the inferior horn of the lateral ventricles. From the lateral ventricles it flows through the foramina of Monro to the third ventricle and then into the fourth ventricle via the cerebral aqueduct of Sylvius. CSF exits the fourth ventricle through the foramina of Magendie and Luschka to the subarachnoid space surrounding the spinal cord and the brain from where it is absorbed by the arachnoid granulations.



ANNEX 2: LAYERS OF THE MENINGES



ANNEX 3: PARAMETERS USED IN CRIB

Factor	*Score*
BW (g)	
> 1350	0
851 - 1350	1
701 - 850	4
< 700	7
GA (weeks)	
> 24	0
< 24	1
Congenital malformation	
None	0
Not acutely life-threatening	1
Acutely life-threatening	3
Maximum base excess in first 12h (mmol/l)	
> -7	0
-7 - -9.9	1
-10 - -14.9	2
< -15	3
Minimum appropriate FiO2 in first 12h	
< 40%	0
41 - 60%	2
61 - 90%	3
91 - 100%	4
Maximum appropriate FiO2 in first 12h	
< 40%	0
41 - 80%	1
81 - 90%	3
91 - 100%	5

Eidesstattliche Versicherung

„Ich, Charlotte d'Arcangues, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „NEUROENDOSCOPIC LAVAGE FOR THE TREATMENT OF POSTHEMORRHAGIC NEONATAL HYDROCEPHALUS" selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)" des ICMJE - *www.icmje.org*) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o) und werden von mir verantwortet.
Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit den Betreuern, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o) und werden von mir verantwortet.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst."

Datum 23.08.18 Charlotte d'Arcangues

Anteilserklärung an etwaigen erfolgten Publikationen

Charlotte d'Arcangues hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: d'Arcangues C, Schulz M, Bührer C, Thome U, Krause M, Thomale UW. Extended Experience with Neuroendoscopic Lavage for Posthemorrhagic Hydrocephalus in Neonates. World Neurosurg. 2018 May 2.

Ich habe eine retrospektive wissenschaftliche Arbeit in der Abteilung für Neonatologie und Pädiatrische Neurochirurgie der Charité-Universität Berlin durchgeführt um alle Patienten, die eine neuroendoscopische Lavage zur Behandlung eines posthämorrhagischen Hydrocephalus zwischen August 2010 und Mai 2016 durchgeführt haben, zu identifizieren. Diese Daten von 45 Patienten stammen aus den medizinischen Akten der Patienten (handgeschrieben und Datenbank) und sind von mir aufgezeichnet und statistisch ausgewertet.

Um die statistische Aussagekraft der Studie zu erhöhen, wurden 11 Patienten aus dem Leipziger Pädiatrischen Neurochirurgischen Zentrum mit einbezogen. Dies war die Arbeit von Wissenschaftlern aus Leipzig.

Als co-erste Autorin veröffentliche ich Teile davon (Text und Abbildung) in meiner Doktorarbeit.

Herr Prof. Dr. Christoph Bührer

_____

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers

Charlotte d'Arcangues

_____

Unterschrift des Doktoranden/der Doktorandin

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

LIST OF PUBLICATIONS

1. d'Arcangues C, Schulz M, Bührer C, Thome U, Krause M, Thomale UW. Extended experience with neuroendoscopic lavage for posthemorrhagic hydrocephalus in neonates. World Neurosurg. 2018 Aug;116:e217-24.

ACKNOWLEDGEMENTS

TO MY SUPERVISORS

Prof. Dr. Christoph Bührer, director of neonatologie, Charité University Berlin.
For agreeing to be my thesis director. For proposing this thesis subject. For guiding me kindly within this work. For being there when I needed help. For your support and your advice. For giving me the opportunity and chance of working at the neonatology at the Charité Hospital in Berlin. To teach me neonatology. Be assured of my gratitude and respect

Prof. Dr. Ulrich-Wilhelm Thomale, director of the Department of Pediatric Neurosurgery, Charité University Berlin.
For agreeing to be my second thesis director. For guiding me kindly within this work. For beeing there when I needed help. For your support and your advice. Be assured of my gratitude and respect

PD Dr. med. Matthias Schulz, Department of Pediatric Neurosurgery, Charité University Berlin.
For guiding me kindly with this work. For being there when I needed help. For your support and your advice. For helping me publish my first article. Be assured of my gratitude and respect

I THANK ALSO,

Boris Metze,
For your availability and your precious help on the dark world of Chi2 and the Mann Whitney test.

Gabriele Heinz, Frank Ording
For your help, your availability and your fast and effective work. For helping me recover all these files and documents.

TO MY FAMILY AND FRIENDS,

To my mother, for this trip Arcangues-Berlin which was the longest of my life and the beginning of a long adventure

To my parents, for your love and your trust. For your support to both during these 12 years of study. I love you

To my little sister Elena, for supporting me in all these years. For you beeing there when I needed you. I wish you all the happiness of the world

To Michael, My love. For beeing with me. For what we have to live together

To my grandparents, Jean and Aline, because I wish they were here today

To my grandmother, Oma Magret.

To Juliane, thank you for your great lovingkindness, your presence and your friendship

To my aunt Arbela, my godfather, my uncles, my aunts, and cousins

To my friends: Jessy, Hélène, Julia, Gaspard, Thomas, Fred, Samy

To those whose name does not appear but who supported me and whom I also thank

« L'importance du geste et de la technique, de plus en plus pointue grâce aux progrès incessants du domaine médical, ne doit pas faire perdre de vue à ceux qui en ont la charge que derrière chaque organe, chaque maladie, chaque défi lancé à nos compétences, se trouve un être humain. »
Chantal BIRMAN, Au monde, ce qu'accoucher veut dire, 2003

« The importance of the gesture and the technique, increasingly advanced given the incessant progress of the medical field, must not distract those responsible in this regard from the human being who is behind every organ, every disease, every challenge launched to our skills. » Chantal BIRMAN, In the world, what to give birth means, 2003