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RESEARCH ARTICLE

Outcomes of Severe Intraventricular Hemorrhage and Posthemorrhagic Hydrocephalus in Premature Infants: A Single-Center Experience

Prematüre Bebeklerde Şiddetli Intraventriküler Kanama ve Posthemorajik Hidrosefali Sonuçları: Tek Merkez Deneyimi

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ABSTRACT

Objective: Intraventricular hemorrhage (IVH) and subsequent development of hydrocephalus are of the most serious complications of prematurity, with an enormous potential impact on mortality, morbidity and neurodevelopmental outcome. The aim of this study was to describe the outcomes of the preterm infants with severe IVH

Material and Method: Eighty-four preterm infants, who born with a birth weight < 1500 g and diagnosed with severe IVH between 2014 and 2020, were retrospectively reviewed. The primary outcome were mortality, the development of posthemorrhagic hydrocephalus and motor outcome. Uni- and multivariate analysis were used to identify factors influencing the outcomes.

Results: Thirty patients (35.7%) died within the first three weeks of life, and severity of IVH and need for early red blood cell (RBC) transfusion were each independently associated with the death ($p < 0.05$). Among the survivors, 36 patients developed posthemorrhagic hydrocephalus, for which the severity of IVH was independently a risk factor ($p < 0.01$). Of 40 patients evaluated at least 18 months of corrected ages, 55% had varying degrees of motor disability. The need for early RBC transfusion and permanent ventriculoperitoneal shunt were each independently associated with severe motor disability ($p < 0.05$).

Conclusion: The severity of IVH is associated with an increased risk of death, posthemorrhagic hydrocephalus and poor motor outcome. Need for early RBC transfusion in infants with severe IVH seems also to be associated with either death or severe motor disability in those survived, suggesting that it can be used by clinicians when counseling parents.

Keywords: Intraventricular Hemorrhage, Posthemorrhagic Hydrocephalus, Preterm Infant, Treatment, Outcome.

ÖZET

Amaç: İntraventriküler kanama (IVK) ve sonrasında hidrosefali gelişimi, prematüreliğin en ciddi komplikasyonlarından olup ölüm, sakatlık ve nörogelişimsel sonuçlar üzerinde büyük bir potansiyel etkiye sahiptir. Bu çalışma ile şiddetli IVK tespit edilen preterm bebeklerin sonuçlarının belirlenmesi amaçlandı.

Gereç ve Yöntem: 2014 ile 2020 yılları arasında doğum ağırlığı < 1500 g olan ve şiddetli IVK tanısı konulan 84 preterm bebek geriye dönük olarak incelendi. Ölüm, posthemorajik hidrosefali gelişimi ve motor gelişim birincil sonuç olarak tanımlandı. Sonuçları etkileyen faktörleri belirlemek için tek ve çok değişkenli analiz kullanıldı.

Bulgular: Otuz hasta (%35,7) yaşamlarının ilk üç haftasında kaybedilmiş olup, hem IVK'nın şiddeti hem de erken dönemde eritrosit süspansiyonu transfüzyon (EST) ihtiyacı bağımsız olarak mortalite ile ilişkili idi ($p < 0,05$). Sağ kalan hastaların 36'sında, IVK şiddetinin bağımsız olarak bir risk faktörü olduğu posthemorajik hidrosefali gelişti ($p < 0,01$). Düzeltilmiş yaşı en az 18 aylık iken değerlendirilen 40 hastanın %55'inde değişen derecelerde motor sakatlık vardı. Erken dönem EST ihtiyacı ve kalıcı ventriküloperitoneal şant birbirinden bağımsız olarak ciddi motor sakatlık ile ilişkili idi ($p < 0,05$).

Sonuç: Preterm bebeklerde gelişen IVK'nın şiddeti, sonraki mortalite, posthemorajik hidrosefali ve zayıf motor gelişim riskini artırmaktadır. Şiddetli IVK gelişen preterm bebeklerde erken dönemde EST'ye ihtiyaç duyulması, hem mortalite

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ile hem de yaşayanlarda ciddi motor sakatlık ile ilişkili görünmektedir ve bu bulgu, ebeveynlere danışmanlık yaparken klinisyenler tarafından kullanılabilir.
Anahtar Sözcükler: Intraventricular Hemorrhage, Posthemorrhagic Hydrocephalus, Preterm Infant, Treatment, Outcome.

Despite advances in perinatal and neonatal care have resulted in improved survival rates for preterm babies, intraventricular hemorrhage (IVH) remains a serious complication of premature birth, which has lifelong consequences. Approximately 15- 20% of preterm infants with less than 1500 g birthweight develop IVH (1, 2). Of them, who survived after first weeks of life, 30 to 50% develop post-hemorrhagic ventricular dilation (PHVD) (3-5).

Despite various treatment options have been proposed for PHVD, the main goal is to protect the vulnerable white matter from further injury caused by raised intracranial pressure and subsequent treatment-related complications (6, 7). Indications and optimal timing of intervention for PHVD remain challenging due to severe condition, extremely low weight, and instability of the patient (8). Since ventriculo-peritoneal (VP) shunt insertion at very low-weight infants is not recommended as initial treatment, different options have been described to provide temporary cerebrospinal fluid (CSF) drainage until the evaluation of patient's eligibility for permanent VP shunting (6, 7). However, there is not yet conclusive evidence to support the superiority of any of the currently available temporizing measures in the initial treatment of PHVD over others (9, 10). The lack of conclusive recommendations for the management of PHVD makes it difficult to have a consensus or standardized protocol, and eventually leads to practice variations between institutions (11, 12).

The aim of this study was to retrospectively assess the outcomes of the preterm infants with severe IVH over course of six years in a tertiary center, with focus on the interventions for symptomatic PHVD, complications, and gross motor functions and adverse language development at 18-24 months.

MATERIAL AND METHOD

Patients

In this retrospective study, medical records of the hospital was searched to identify all preterm infants born with a birth weight of less than 1500 g and who admitted to the neonatal intensive care unit within the first two days of life between 2014 and 2020. The medical records of the patients with severe IVH were further reviewed for demographic characteristics, the progression of hydrocephalus, treatment course, complications of temporary and permanent CSF diversion, comorbidities, and outcomes. Infants with missing data, congenital malformations, syndromes, chromosomal abnormalities or ventricular dilation related to any other cause than perinatal IVH were excluded. The study protocol was approved by the Institutional Committee on Clinical Research Ethics (09.05.2022/003).

Definitions

The diagnosis of IVH was established by cranial ultrasound, and it was graded based on Volpe's classification (13). The most severe grade was used to categorize the infants. Serial head ultrasounds were performed in the infants with severe IVH (grades III or periventricular hemorrhagic infarction (PVHI), which named grade IV previously), to monitor for the development of PHVD. The definition of PHVD, which also covers the term of posthemorrhagic hydrocephalus, was made using measurement of ventricular index (VI) as described by Levene (14). In case of ventricles do not expand laterally but become rounded or expand occipitally, the measurements involving anterior horn width, thalamo-occipital distance and 3rd ventricle width, as described by Davies (15), were used. When patients meet a threshold where the VI > 4 mm above the 97th percentile or other measurements > 1 mm above the 95th percentile specified for gestational age, the intervention was considered. When ventricular dilation on serial cranial ultrasonography studies was accompanied by excessive increase in head circumference (> 2 cm/week) and other clinical signs of increased intracranial pressure (ICP), it was considered as rapidly progressive. When PHVD had not needed any more temporizing or permanent neurosurgical procedure, it was considered as transient. All comorbidities of prematurity, including respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity and patent ductus arteriosus, were based on the latest updated diagnostic criteria in standard textbooks of neonatology (16). During the first 10 days of life, red blood cell (RBC) transfusion was considered in the settings of hemoglobin ≤ 10 g/dL or acute blood volume loss of ≥ 10% with symptoms of decreased oxygen delivery or acute blood volume loss > 20%, and it was defined as early RBC transfusion. Bruising was defined as cutaneous or subcutaneous hemorrhage (ecchymosis) in extensive or multiple locations present during the first admission whereas small lesions in a single location were neglected.

Interventions

All surgeries in this series were performed by only one neurosurgeon during the study period. Lumbar puncture (LPs) and occasionally ventricular puncture (especially in small premature infants with unstable clinical condition) were initially performed in the patient with PHVD with signs of ICP. If there was excessive blood in the CSF, the punctures failed to adequately control ventricular dilation or more than three to five serial LPs were need, a ventricular access device (VAD), also termed a ventricular reservoir (Ommaya reservoir,

Medtronic, USA), had been inserted to drain CSF. In case of VAD was not available either due to importing difficulties or being not covered by general health insurance, external ventricular drainage (EVD) was an alternative option. If the infants were otherwise stabile and a value below 1.5 g/L of CSF protein was once achieved, a VPS was inserted as soon as possible, even if they weighed less than 2000 g. Indication for surgical treatment was established in close cooperation between the neurosurgeon and the neonatologist. The frequency and the volume of the drainage (usually 10 ml/kg of CSF for each tap) was adjusted according to ultrasound measurements. All procedures including tapping and puncture were done at bedside under sterile conditions. CSF was analyzed for cell count, protein, glucose, and bacterial culture at least twice a week. The drainage was continued until fulfilling criteria for permanent VP shunt placement at which the patient's weight reached at least 2000 g, the CSF protein was below 1.5 g/L, and erythrocyte count was less than 100/mm^3. Cranial computer tomography was performed for each patient before the surgery.

Outcomes

The primary outcome were mortality, the development of PHVD and motor outcome in preterm newborns with severe IVH. Secondary outcome included the development of reservoir and shunt dysfunction including infection, skin dehiscence, hemorrhage, CSF leak and need for revision. The motor assessment was carried out and classified by predominantly care-givers or health-service providers using the Motor Function Classification System - Expanded & Revised (GMFCS - E&R) at 18-24 months of corrected ages (17, 18). Language development was evaluated by the information provided by the caregivers (preferably the mother) using Ankara Developmental Screening Inventory (19). The absence of words association at 24 months of corrected age was accepted as an indication of adverse language development.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 20; SPSS, Chicago, IL, USA). Student's t-test was used to compare continuous parametric variables, the Mann-Whitney U test was used to compare continuous nonparametric variables, and χ^2 or Fisher's exact tests were used for categorical variables when appropriate. A two-tailed p-value of < 0.05 was considered to be statistically significant. Potential factors associated with increased risk of mortality, development of PHVD and poor motor outcome were identified using univariate analysis. Of them, variables with 2-tailed p <0.05 were included in the multivariate logistic regression model to calculate the strength of any association.

RESULTS

Of 984 infants born with birthweight < 1500 gram during the study period, 84 (8.5%) infants with severe IVH were identified, and their records were reviewed (Figure 1).

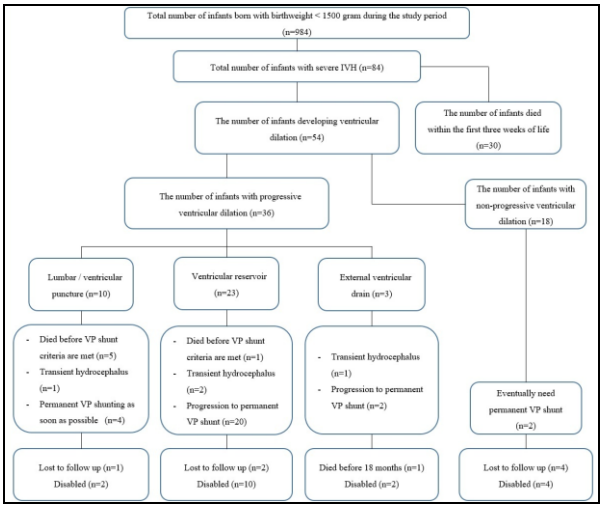

Figure 1. Flow chart of the study (IVH, intraventricular hemorrhage; VP, ventriculo-peritoneal).

The mean gestational age at birth and birth weight were 26.6 ± 1.9 weeks and 864 ± 253 gr, respectively. Of the study group, 64.3% consisted of infants with birthweight < 1000 g, and 65.5% were infants born gestational age < 28 weeks. Based on ultrasound scanning at the first days of life, 34 (40.5%) patients had grade III IVH, and 50 (59.5%) had PVHI.

Thirty patients (35.7%) died within the first three weeks of life. The factors associated with significantly increased risk of death at univariate analyses were shown in table 1.

Table 1. Perinatal characteristics of the patients diagnosed with severe IVH during the study period.

Features	Survivor (n =54)	Non-survivor (n =30)†	p
Gestational age, w	27 ±1.8	26±1.9	**0.003**
Birth weight, g	919±254	765±222	**0.005**
Male gender	26 (48.1%)	11 (36.7%)	0.110
PPROM	7 (13%)	8 (26.7)	0.07
Antenatal steroids	27 (50%)	16 (53.3%)	0.822
Inborn	25 (46.3%)	16 (53.3%)	0.356
Cesarean section delivery	49 (90.7%)	23 (76.7%)	0.057
APGAR score at the 5th m	6.13±1.1	5.3±1	**0.001**
Bruising related to birth	25 (46.3%)	23 (76.7%)	**0.028**
Intubation at delivery room	41 (75.9%)	25 (83.3 %)	0.308
Initial blood gas measurements			
pH	7.27 ± 0.1	7.21±0.1	**0.045**
pCO2	48.8±11.1	52.9±12.6	0.147
HOC3	20.1±5.8	18.5±3.9	0.15
Patent ductus arteriosus	19 (35.5%)	19 (71.4)	**0.03**
Convulsion	16 (29.6%)	6 (20.6%)	0.440
Need for inotropes	22 (40.7%)	23 (76.6%)	**0.005**
Severity of IVH, PVHI	23 (42.6%)	27 (90%)	**< 0.001**
Serum albumin level (g/dL)	3.1±0.41	2.59±0.46	**<0.001**
Age at the first RBC transfusion, d	13.1±10.4	3.6±1.7	**0.001**

† It includes the patients died within the first three weeks of life. Data are expressed as mean ± SD or number (%). IVH, intraventricular hemorrhage; PPROM, preterm premature rupture of the membranes; PVHI, periventricular hemorrhagic infarction; RBC, red blood cell; w, week; m, minute; g, gram; d, day. Note: Statistically significant values are shown in bold.

In the multivariate analyses, it was found that PVHI and early RBC transfusion were each independently associated with the death (OR:13.1, CI:1.48-115.8, p =0.021; OR: 10.6, CI: 1.18-96.5, p =0.035, respectively).

Among the 54 survivors at three weeks of life, 36 patients developed progressive PHVD necessitating an intervention. The remaining 18 patients with severe IVH, of which 5 had no PHVD, didn't progress to a symptomatic PHVD until the time of discharge (Table 2).

Table 2. Clinical characteristics of the patients with post hemorrhagic ventricular dilation.

Features	Progressive (n =36)	Non-progressive (n =18)	p
Gestational age, w	26.9±1.8	27.3±1.6	0.430
< 27 w (n, %)	16 (44.4%)	7 (38.9%)	0.776
Birth weight, g	881.7±269	995±206	0.064
< 750 g (n, %)	14 (38.9%)	2 (11.1%)	**0.033**
Male gender	19 (52.8%)	7 (38.9%)	0.251
Antenatal steroids	15 (41.7%)	12 (66.7)	0.074
Convulsion	11 (30.6%)	5 (27.8%)	0.548
Severity of IVH, PVHI	20 (55.6%)	2 (11.8%)	**0.003**
Age at the first RBC transfusion, d	10.8±9.2	18.5±11.3	**0.028**
Need for platelet transfusion	8 (22.2%)	None	**0.041**

Data are expressed as mean ± SD or number (%). PPROM, preterm premature rupture of the membranes; RBC, red blood cell; IVH, intraventricular hemorrhage; PVHI, periventricular hemorrhagic infarction; w, week; g, gram; d, day. Note: Statistically significant values are shown in bold.

However, after discharge from the NICU, two patients (11.1%) required VP shunt placement at ages 4 and 6 month. During neonatal period, PVHI was each independently associated with developing progressive PHVD (OR: 17.4, CI: 1.9-152.1, p =0.01)

Of 36 patients with progressive PHVD, which requiring temporary CSF drainage, 23 patients were managed with a VAD placement. However due to unavailability of reservoir, following a few punctures, three patients underwent permanent VP shunt insertion as the initial neurosurgical procedure, and other three patients were managed with an EVD placement. In the remaining 7 patients, the punctures were performed as need to control ventricular dilation, in one of them a VP shunt insertion was eventually required. Characteristics and outcomes of 36 patients stratified by initial treatment are shown on table 3.

Table 3. Characteristics and outcomes of the patients who required temporizing intervention for progressive ventricular dilation.

Features	Serial punctures (n =10)	Ventricular reservoir (n =23)	External ventricular drain (n =3)
Gestational age, w	28 (25-29.3)	27 (25-28)	26, 26, 28
Birth weight, g	990 (597-1085)	850 (600-1150)	600, 700, 1000
Severity of IVH, PVHI (n, %)	5 (50%)	13 (56.5%)	2 (66.7%)
Age at the first intervention, d	30 (25.8-35)	27 (24-31) †	31, 38, 42
Bodyweight at the first intervention, g	1360 (960-1497)	1210 (885-1420)	1080, 1360,1780
Frequency of CSF aspiration, per week	3.3±1.4	5.7 ± 1.4	Daily
Temporizing intervention-related complication, n	Porencephalic cyst (1)	Subcutaneous CSF leakage (2) Multiloculated hydrocephalus (2) Infection (1) Malposition (1) Additional reservoir placement (1)	Infection (3/3) Multiloculated hydrocephalus (2/3)
Progression of PHVD, n Need for VP shunt placement Arrest of PHVD after intervention Death before fulfilling criteria of VPS placement	 4 (40%) 1 (10%) 5 (50%)	 20 (87%) 2 (8.7%) 1 (4.3%)	 2/3 (66.7%) 1/3 (33.3%)
Age at VPS insertion, d	32, 32, 52, 126	110 ± 48	90 and 114
Bodyweight at VPS insertion, g	1560, 1870, 1920, 3300	2713 (2189-3568)	2100, 2260
VPS-related outcomes (n/n, %)	Occlusion (2/4, 50%) Infection (1/4, 25%)	Occlusion (2/20, 10%) Additional shunt placement (2/20, 10%) Abdominal abscess (1/20, 5%) Infection (2/20, 10%)	Occlusion (2/2, 100%) Infection (1/2, 50%)
The patients requiring revision within 3 months	3 (75%)	2 (10%)	2 (100%)
Number of VPS revisions < 2 years, (n/number of patient)	0/1, 1/2, 6/1	0/15, 1/3, 2/1, 3/1	1/1, 3/1
GMFCS score ≥ 2, (n/number of patients evaluated, %)	2/3 (75%)	10/20 (50%)	2/2 (100%)
Adverse language development, (n/number of patients evaluated, %)	2/3 (66.7%)	10/18 (55.6%)	1/1 (100%)

† Mean age of insertion of the device was 39 (30-48) day. Data are expressed as mean ± SD, median (interquartile range), number (%), or direct values when data points < 5. IVH, intraventricular hemorrhage; PVHI, periventricular hemorrhagic infarction; CSF, cerebrospinal fluid; PHVD, posthemorrhagic ventricular dilation; VPS, ventriculo-peritoneal shunt; GMFCS, Gross Motor Function Classification System; w, week; g, gram; d, day.

Of 36 patients necessitating a temporary intervention, six (16.7%) died before fulfilling criteria of VP shunt placement, and in four (11.1%) patients, ventricular dilation was arrested on follow-up. Three patients developed late progression of the disease, and a permanent VP shunt was placed at ages 4-6 months after discharge. Of total 28 patients (included two patients from non-progressive group) with a permanent VP shunt, 7 (25%) patients needed revision within 3 months, with lower rate for VAD group (10%) than serial puncture group (75 %) or EVD group (%100) (p =0.006), and 10 (35.7%) patients required one or more revisions within 18-24 months.

Of total 84 patients diagnosed with severe IVH, 48 (57.1%) survived to discharge. After discharge, 7 patients were lost to follow-up, and one patient died before the age of 18 months. Gross motor function was assessed for 40 patients survived at least 18 months of corrected ages. Of them, GMFCS score was 1 in 18 (45%), 2 in 3 (7.5%), 3 in 2 (5%), 4 in 6 (15%) and 5 in 11 (27.5%) patients. Factors affecting motor outcome are shown on table 4.

Table 4. Factors affecting motor outcome in infants with severe IVH at 18-24 months of corrected ages.

Variable	Good motor outcome (n =18)	Poor motor outcome (n =22)	p†
Gestational age, w	28 (26-29)	17 (25-28)	0.240
Birth weight, g	1110 (860-1200)	875 (600-1080)	**0.012**
Duration of invasive ventilation support, d	13 (7-19)	28 (16-54)	**0.001**
Early RBC transfusion, n	5 (27.8%)	14 (63.6%)	**0.031**
Severity of IVH, PVHI	2 (11.1%)	13 (59.1%)	**0.003**
Need for a temporary intervention	8 (44.4%)	18 (81.8%)	**0.021**
Age at the first intervention, d	25.5 (22.5-30)	28.5 (26-40)	0.115
Permanent VPS, n	8 (44.4%)	17 (77.3%)	**0.050**
Need for VPS revision (< 18-24 months, n)	1 (12.5%)	9 (52.9%)	0.088
In the model using logistic regression (backward stepwise) analyses it was revealed that; a) PVHI (OR: 14.4, 95% CI: 2.18-95.34, p = 0.006) and invasive ventilation support longer than three weeks (OR: 7.84, 95% CI: 1.47-41.68, p = 0.016) were associated with poor motor outcome (GMFCS score of ≥ 2) at 18-28 months of corrected ages. b) The need for early RBC transfusion (OR: 10.94, 95% CI: 1.87-63.8, p = 0.008) and permanent VPS insertion (OR: 10.87 95% CI: 1.63-72.66 p = 0.014) were associated with severe motor outcome (GMFCS score ≥ 4) at 18-28 months of corrected ages.			

† p values were calculated using univariate analysis. Data are expressed as median (interquartile range) or number (%), IVH, intraventricular hemorrhage; RBC, red blood cell; PVHI, periventricular hemorrhagic infarction; VPS, ventriculo-peritoneal shunt; GMFCS, Gross Motor Function Classification System; OD, odds ratio; CI, confidence interval; w, week; g, gram; d, day. Note: Statistically significant values are shown in bold.

Among the 36 patients who were assessed for language development at 24 months of corrected ages, 14 (38.9%) patients could not have spoken even with the first words, and in 6 (23%) of the remaining had no association of two words. A significant association was determined between the GMFCS score of ≥ 2 and adverse language development ($p < 0.05$).

DISCUSSION

In this study, preterm infants with severe IVH were retrospectively reviewed and evaluated for some points of neurodevelopmental outcome. It was found that the incidence of severe IVH, compared with previously published studies, remained relatively high, and that severity of IVH is associated with an increased risk of death, the development of PHVD and unfavorable motor outcome. Additionally, early RBC transfusion in infants with severe IVH seems to be associated with either death or severe motor disability in those survived.

In this study, the overall incidence of severe IVH among VLBW admissions to the unit was 8.5 %, which is comparable with many studies published over the past two decades (3, 20-22), but remains slightly higher than the rate of 5-7% in high-income countries (2, 23), indicating a need for better implementation of optimal care guidelines.

Despite factors related to degree of immaturity or indicating a critical clinical course after birth seemed to be associated with early death, the patients demonstrate a dependency of survival on IVH severity and RBC transfusion within the first days of life. The finding of low survival in infants with PVHI has also been highlighted in previous studies (26, 28). Although it was an expected finding, the association of early RBC transfusion with the mortality may be an indication of the extent of the hemorrhage, which can be either intraparenchymal or bilaterally intra-ventricular, in the absence of possible other comorbidities such as pulmonary hemorrhage. This high rate of mortality can be explained by that in the presence of extensive hemorrhage, which described previously as PVHI severity score and predicts a very poor outcome with multiple disabilities (28, 29), and on the request of the parents, many centers may prefer to withdraw intensive care treatment or at least perform no heroic measures to resuscitate the infant, despite debatable the legal and ethical considerations (3, 27).

In this series, two-thirds of the surviving infants at three weeks of life developed PHVD requiring any form of intervention. This rate is consistent with some previous reports (10, 26, 27, 30), though reports with lower rate have also been described (22, 24, 25, 31). The association between severity of IVH and the risk for developing PHVD in this study has also been reported by previous studies (3, 26, 31-33). Despite lumbar puncture was initially performed in all patients here, the subsequent intervention varied depending on the patient's clinical condition, individual surgeon preference of technique, the availability of VAD and the affordability of VAD by the parents. VAD and VSG shunt are the most commonly used temporizing measures (9), whereas later has not been performed at our center due to neurosurgeon preference. In infants treated with VAD, the results presented herein are consisted with the rates of VP shunt requirement, device infection, and other complications in which reported by other studies (9, 10, 25, 30, 34). Despite the infection rate from serial tapping of reservoir has ranged from 0 to 22%, employing infection control measures during both surgical implantation of the reservoirs and reservoir tapping provide controlled removal of CSF over a prolonged period (30, 35, 36). In this series, the rates of infection and revision of VPS following a temporizing intervention was lower in VAD subgroup when compared to other options. It has been reported that delaying VPS conversion, when compared to earlier, is associated with low infection and revision rate of subsequent VP shunting and better neurodevelopmental outcome

(37, 38). Therefore, using VAD as a temporization technique, is able to allow delaying VP shunting for a long period of time.

In the subgroup of infants treated with only serial punctures, mortality was higher due to severe clinical condition of the infants. The aim of early VPS insertion in the stable ones was to avoid further lumbar or ventricular punctures, which both are not recommended as the mainstay treatment due to high risk of the failure to remove sufficient quantities of CSF, infection and parenchymal injury (5, 6). Unfortunately, both methods are still widely used in some centers (11). EVD has been used an alternative option to serial lumbar or ventricular punctures, or when other primary temporizing measures have failed. Despite the rate of permanent VP shunt placement after an EVD has been proposed to be lower when compared to other options (6, 39). EVD has fallen out of favor due to both higher risk of infection and nursing care difficulties (5-7, 40).

In this study, the mean age of infants at first intervention is comparable to most previous studies (8, 24), but higher than those in the studies objecting to assess the effects of early intervention (41, 42). It has been reported that older age at temporizing neurosurgical procedure is associated with the increased risk of conversion to VPS and neurodevelopmental impairment (8). Despite the timing and definitive criteria of the first intervention are still a matter of debate, the ventricular measurements based on ultrasound appear rational to help in determining the optimal time of early intervention, as to prevent the hazardous effects of hydrocephalic state and blood products on the developing brain (7, 41, 43).

In this series, the rate of a permanent VP insertion following a temporary intervention was comparable with previous studies, in which it has been reported as ranging between 25% and 95% (25, 30, 33, 34, 37, 41, 44). However, in the recent randomized controlled trial it has been reported as low as 19%, which is the lowest in the literature (42), presumably thanks to very early intervention. Conversely, VP shunt conversion rates have been reported to be higher if initial intervention was not commenced until the onset of clinical signs (37, 41). Growing evidence has shown that intervention at early stage, based on ventricular measurements using ultrasound, prior to development of clinical symptoms and severe dilation of the lateral ventricles, is associated with lower rates of VP shunting and favorable neurodevelopmental outcomes, even when a VP shunt is eventually needed (8, 29, 41, 42). However, choice of temporization techniques, particularly VAD and VGS, does not appear to influence rates of conversion to permanent ventricular CSF diversion, infection, obstruction, subsequent shunt infection, mortality, long-term disability (8-10, 44).

Overall, in this series, considering motor outcomes at 18 to 22 months' corrected age, 55% of the patients had varying degrees of motor disability, in which GMFCS score was $\geq$ 2. This rate is comparable to previous studies (10, 26, 27, 29, 41, 43), in which CP rates have been reported from 23% to 91% in infants with severe IVH. Despite in multivariate analyses nothing was significantly associated to motor disability, due to probably small sample size of the study, the severe motor disability appears to be predicted by early RBC transfusion and permanent VP shunt. Some studies have reported that worse outcome was associated with the severity of IVH, in particular when complicated by PHVD requiring neurosurgical intervention (3, 4, 43), whereas early control of ventricular dilation may provide better results (41,42), suggesting to avoid large degrees of ventricular dilation. The finding of that the association of early RBC transfusion with severe motor outcome may be explained by that severe drop in hemoglobin level requiring RBC transfusion may indirectly be an indication of the extent of the hemorrhage or the burden of extracellular hemoglobin to which the developing brain is exposed, which all eventually contribute to neurodevelopmental disability. Although not statistically significant in this series, recurrent shunt dysfunctions may also affect neurodevelopmental outcome by causing recurrent rapid increase in ICP (43).

There were some limitations in this study, in which database only contained infants with severe IVH. Therefore, the results are not generalizable to the population of all preterm infants. Given the retrospective nature of the study, the data may not have included some necessary variables which can contribute to various outcomes (such as periventricular leukomalacia). The single-center character, with a relatively small patient cohort and substantial heterogeneity in the option for management, and a high rate of loss to follow-up reduced statistical power. Additionally, other components of neurodevelopmental outcome could not be assessed due to various reasons. Despite these limitations, the study was conducted in a geographic area, where no comprehensive relevant data available, and included the 6-year experience of a center in respect to the various outcomes in small preterm infants with severe IVH.

Conclusions

This study showed that the incidence of severe IVH in VLBW infants has not changed significantly in the last decades, supporting that IVH is still an active area of research. The severity of IVH is associated with an increased risk of death, PHVD and poor motor outcome. Need for early RBC transfusion in infants with severe IVH seems also to be associated with either death or severe motor disability in those survived, suggesting that it can be used by clinicians when counseling parents. Well-designed multicenter studies aimed at describing both the clinical and neurodevelopmental impacts of different approaches with adequate patients may reduce institution-specific referral models and practices, establishing standardized care algorithms.

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