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ORIGINAL ARTICLE

Timing of intervention in posthemorrhagic ventricular dilatation in preterm infants

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Abstract

Introduction and objectives: There is still significant variation in the management of post-hemorrhagic ventricular dilatation (PHVD). Recent evidence recommends cerebrospinal fluid (CSF) drainage as soon as Levene's Ventricular Index (LVI) surpasses the 97th centile, which was shown to improve neurodevelopmental outcomes and reduce the need for a ventriculoperitoneal (VP) shunt. This study aimed to assess the timing of intervention in PHVD in a level 3 Neonatal Intensive Care Unit (NICU), its impact on the need for a VP shunt, and the presence of neurological sequelae at two years of age. **Methods:** A retrospective, single-center study was conducted, comprising preterm infants who developed PHVD. Ventricular dilatation was quantified in cerebral ultrasounds and details of interventions were obtained from clinical records. Infants were categorized into three groups depending on the neurological sequelae present at two years: surviving without sequelae, surviving with sequelae, and death. **Results:** Among the 22 infants diagnosed with PHVD, 59% required CSF drainage, and all the patients received initial intervention after LVI crossed the p 97 + 4 mm line (mean 7.5 mm above the 97th centile), at a mean postmenstrual age (PMA) of 30.6 weeks (± 2.7). Ventricular stabilization occurred after lumbar punctures (LPs) in 23% (3/13); 15% (2/13) died after temporizing neurosurgical procedures; 62% (8/13) required a VP shunt, at a median PMA of 38.9 weeks (IQR 37.0-41.3). Neurological sequelae (delayed motor development, cerebral palsy, epilepsy, and/or visual impairment) were less likely to occur in infants not requiring CSF drainage ($p < 0.05$), although no significant difference was found between ventricular width at first intervention and the need for a VP shunt or outcomes. **Discussion:** This cohort, treated before international guidelines were revised, received intervention later than what is now recommended. Infants who received intervention were more likely to have neurological sequelae than those that did not require intervention. Actively considering intervention as soon as the Ventricular Index (VI) surpasses the 97th centile will certainly make it possible to lower the intervention threshold to not more than p 97 + 4 mm, as currently recommended.

Keywords: Premature infant. Intraventricular hemorrhage. Hydrocephalus. Outcomes.

Intervenção na dilatação ventricular pós-hemorrágica da prematuridade

Resumo

Introdução e objetivos: O tratamento da Dilatação Ventricular Pós-hemorrágica (DVPH) ainda é muito variável. A última revisão das recomendações internacionais sugere iniciar a drenagem de líquido cefalorraquidiano assim que o índice ventricular de Levene (IVL) ultrapassa o percentil 97, o que mostrou melhorar o neurodesenvolvimento e reduzir a necessidade

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sistemas de derivação ventrículo-peritoneal (SDVP). Este estudo teve como objetivo avaliar o momento da intervenção na DVPH numa UCIN de nível III e o seu impacto na necessidade de SDVP e na presença de sequelas neurológicas aos 2 anos de idade. **Métodos:** Foi realizado um estudo retrospetivo unicêntrico, incluindo recém-nascidos prematuros que desenvolveram DVPH. A dilatação ventricular foi quantificada em ecografias cerebrais seriadas e os detalhes relativos às intervenções foram obtidos a partir dos registos clínicos. De acordo com as sequelas neurológicas presentes aos 2 anos de idade, as crianças foram categorizadas em 3 grupos: sobrevivência sem sequelas, sobrevivência com sequelas e morte. **Resultados:** Vinte e dois recém-nascidos foram diagnosticados com DVPH, dos quais 59% (n = 13) foram intervencionados, todos após ultrapassarem o p97 + 4 mm, com uma idade pós-menstrual média de 30,6 semanas (± 2,7). Vinte e três porcento (3/13) tiveram estabilização ventricular após punção lombar; 15% (2/13) morreram após intervenções neurocirúrgicas temporizadoras; 62% (8/13) precisaram de SDVP, com uma idade pós-menstrual mediana de 38,9 semanas (AIQ 37,0-41,3). A probabilidade de ter sequelas neurológicas (atraso no desenvolvimento motor, paralisia cerebral, epilepsia, alterações visuais) foi inferior nas crianças que não precisaram de intervenção ($p < 0,05$), apesar de não haver diferença significativa entre a dilatação ventricular antes da primeira intervenção e a necessidade de SDVP ou o outcome. **Discussão:** Esta coorte foi tratada previamente à revisão das recomendações internacionais e, consequentemente, mais tarde do que é atualmente recomendado. Os recém-nascidos intervencionados revelaram ter uma maior probabilidade de ter sequelas neurológicas comparativamente aos não intervencionados. Futuramente, iniciar a drenagem de LCR assim que o IVL ultrapasse o p97 permitirá reduzir o limiar de intervenção para valores inferiores ao p97 + 4 mm, como é atualmente recomendado.

Palavras-chave: Prematuridade. Hemorragia intraventricular. Hidrocefalia. Desfechos.

Keypoints

What is known
- Posthemorrhagic ventricular dilatation in premature infants is an important cause of impaired neurodevelopment and long-term disability.
- Early intervention reduces the need for a ventriculoperitoneal shunt and neurodevelopment.

What is added
- An analysis of the management of posthemorrhagic ventricular dilatation in a renowned Portuguese neonatal care center.
- Outborn infants are at increased risk of delayed intervention for posthemorrhagic ventricular dilatation.
- Intervention in posthemorrhagic ventricular dilatation should occur earlier and early referral to specialized centers can contribute to improved outcomes.

Introduction

Posthemorrhagic ventricular dilatation (PHVD) is a major complication of preterm birth that occurs after periventricular-intraventricular hemorrhage (PIVH), and is an important cause of impaired neurodevelopment and long-term disability, increasing the risk of cognitive, motor, and sensory deficits[1,2]. PHVD is diagnosed on cerebral ultrasound (cUS) once Levene's Ventricular Index (LVI) crosses the 97th percentile for the gestational age, and is usually combined with additional ventricular measurements, including the anterior horn width (AHW)[1,3].

Various treatment modalities have been investigated[4-6], and the therapeutic approach for PHVD varies greatly across neonatal care centres[7,8]. Currently, management focuses on cerebrospinal fluid (CSF) drainage, usually starting with temporizing lumbar punctures (LPs), followed by temporary ventricular drainage devices, and lastly by implanting a ventriculoperitoneal (VP) shunt[1]. In recent years, several observational studies[8-11] and, more recently, the Early versus Late Ventricular Intervention Study (ELVIS) trial[11], have associated an early cUS-based intervention, before LVI crosses the 97th centile + 4 mm and the onset of clinical signs, with lower rates of death and need for a VP shunt, as well as better neurodevelopmental outcomes.

The aim of our study is to assess the outcomes of the need for a VP shunt and neurological sequelae at two years of corrected age in preterm neonates who required CSF drainage due to PHVD, according to the timing of the initial intervention.

Methods

Patients

This retrospective, single-center study, comprised the preterm infants (gestational age of 32 weeks and

below) born between January 2014 and December 2020, admitted to a level 3 Neonatal Intensive Care Unit (NICU), and diagnosed with periventricular-intraventricular hemorrhage, who subsequently developed PHVD, making them eligible for this study.

Patients were selected from the NICU's database of very low birth weight infants, which records babies born at less than 1,500 g, using the diagnosis of PIVH as the search criterion for the abovementioned period. Demographic and clinical data were collected both from the database and from the discharge clinical records of the eligible patients. Demographic characteristics included gestational age, birth weight, being inborn or outborn, the type of delivery, and whether it was a single or multiple birth. Complications during the neonatal period that have been reported as risk factors for the development of PIVH or PHVD were registered, namely, respiratory distress syndrome, use of inotropes, early- and late-onset sepsis, meningitis, bronchopulmonary dysplasia, patent ductus arteriosus, and necrotizing enterocolitis requiring treatment.

Cerebral ultrasound (cUS)

Serial cUS scans of eligible patients performed during their hospital stay, registered at the NICU's workstation, were reanalyzed by a single observer to assess the progression of PHVD. Ventricular measurements, including LVI and AHW were obtained, along with the date and postmenstrual age (PMA) at each scan. When cUS were not available at the workstation, LVI values were obtained from the patients' clinical records, where AHW was not recorded.

Intervention

To assess the management of PHVD, the details of the interventions performed were obtained. The number, date, and PMA at each LP were obtained from the discharge clinical records of each patient. For those with further progression of ventricular dilatation who required neurosurgical treatment, the respective date, PMA, and type of intervention were obtained from the database maintained by the Neurosurgery division. The most frequent neurosurgical procedures included ventricular reservoir (VR) and VP shunt implantation and, exceptionally, direct ventricular puncture, insertion of an external ventricular drain (EVD), and endoscopic third ventriculostomy (ETV). Complications relating to a VP shunt that required a shunt review were also recorded.

Neurological sequelae

To assess the outcomes of eligible patients, the clinical records of follow-up pediatric appointments at two years of corrected age were consulted. Owing to the retrospective nature of this study, only the presence of cerebral palsy, delayed motor development, visual impairment, and epilepsy were recorded. According to the information available on the clinical records, cerebral palsy (CP) was further classified into spastic (hemiplegia/hemiparesis, diplegia/diparesis, or quadriplegia/quadriparesis), dyskinetic, ataxic, or mixed, and the maximal locomotor function of the infant was graded using the Gross Motor Function Classification System (GMFCS)[12]. Patients were subsequently categorized into three groups according to the presence of any of the abovementioned deficits, namely 1) Surviving without neurological sequelae, 2) Surviving with neurological sequelae, and 3) Death.

Statistical analysis

The collected data was analyzed using the Statistical Package for Social Sciences® software (SPSS, version 29.0). To compare the means of continuous variables with normal distribution, the Independent-samples T-test was used, and the Mann Whitney test for non-parametric variables. Categorical variables were compared using the χ^2 test. Statistical significance was considered as p-value < 0.05.

Ethical considerations

This project was approved by our center's Ethics Committee.

Results

Between January 2014 and December 2020, among the 370 preterm infants admitted to our NICU with a gestational age of 32 weeks or less, 30% (110 out of 370) were diagnosed with PIVH of any grade, of whom 20% (22 out of 110) went on to develop PHVD. Fifty-nine percent (13 out of 22) of these also required CSF drainage interventions due to progressive ventricular dilatation. The demographic and clinical characteristics of the infants diagnosed with PHVD, as well as the information according to the need for intervention, are presented in table 1.

Both groups were comparable for all demographic and clinical characteristics. Five of the 22 infants were outborn. Of the 22 infants who developed PHVD, 23%

Table 1. Demographic and clinical characteristics of the study population

	Overall (n = 22)	No intervention (n = 9)	Intervention (n = 13)
Male, n (%)	10 (45.5)	3 (33.3)	7 (53.8)
Gestational age (weeks), mean (± SD)	27.1 (± 2.7)	26,8 (± 2.7)	27.4 (± 2.7)
Birth weight (grams), mean (± SD)	1017.5 (± 420.9)	993 (± 345.4)	1031.4 (± 470.5)
Type of delivery, n (%) Vaginal Caesarean section	 12 (54.5) 10 (45.5)	 6 (66.7) 2 (22.2)	 6 (46.1) 8 (61.5)
Multiple birth, n (%)	8 (36.4)	3 (33.3)	5 (38.5)
Outborn, n (%)	5 (22.7)	2 (22.2)	3 (23.1)
PIVH, n (%) Grade II Grade III	 5 (22.7) 17 (72.3)	 2 (22.2) 6 (66.7)	 3 (23.1) 11 (84.6)
PVHI, n (%)	6 (27.3)	1 (11.1)	5 (38.5)
Inotropes, n (%)	4 (18.2)	2 (22.2)	2 (15.4)
Early-onset sepsis, n (%)	6 (27.3)	2 (22.2)	4 (30.8)
Late-onset sepsis, n (%)	12 (54.5)	3 (33.3)	9 (69.2)
Meningitis, n (%)	1 (4.5)	0	1 (7.7)
BPD > grade 2, n (%)	8 (36.4)	1 (11.1)	7 (53.8)
Treated for NEC, n (%)	4 (18.2)	0	4 (30.8)
Treated for PDA, n (%)	12 (54.5)	5 (55.6)	7 (53.8)

PIVH: periventricular-intraventricular hemorrhage; PVHI: periventricular hemorrhagic infarction; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus.

had grade II PIVH and 77% had grade III, of whom 27% also developed PVHI (according to Papile's classification system, later adapted by Volpe)[1,13].

Cerebral ultrasound scans were available at the workstation for 91% (20 out of 22) of infants diagnosed with PHVD and were unavailable for one patient who did not receive intervention and one patient who did receive intervention.

In patients who did not receive intervention, although some newborns showed transient increases in LVI over the 97th centile and AHW over 6 mm, towards the 97th centile + 4 mm and 10 mm, respectively, there was a spontaneous reversion in ventricular size without CSF drainage, before crossing these limits.

Among the group of patients who did receive intervention, the left and right LVI of 11 patients are presented in figure 1. Four patients did not have cUS prior to their initial intervention at the workstation, and the Ventricular Index (VI) was obtained from clinical records. One patient had unreliable measurements due to a large cyst coalescing with the lateral ventricle. All of the patients were subject to the first CSF drainage procedure after crossing Levene's line of 97th centile + 4 mm, at a mean PMA of 30.6 weeks (± 2.6), with a mean VI of 7.54 mm (± 3.0 mm) above the 97th centile, and a mean AHW of 7.16 mm (± 1.9) above 6 mm.

Three of the infants who received intervention were outborn and transferred in order to be treated for PHVD: 1) Was not subject to temporizing LP in the hospital of origin due to thrombocytopenia, and was transferred to insert a ventricular reservoir (VR); 2) Had significant ventricular dilatation with concomitant ventriculitis and was transferred to insert an external ventricular drain (EVD) after a LP was performed at the hospital of birth; and 3) Was transferred after surpassing the 97th centile + 4 mm to be treated for PHVD. These patients had a significantly higher LVI at the first intervention when compared to inborn infants (Fig. 2).

Among the infants who required intervention, LP was the most common initial temporizing procedure, performed in 77% (10 out of 13) of patients who received intervention, at a mean PMA of 30.8 weeks (± 2.7); the number of LPs ranged from one to three. The ventricular size stabilized in three of these infants and they did not

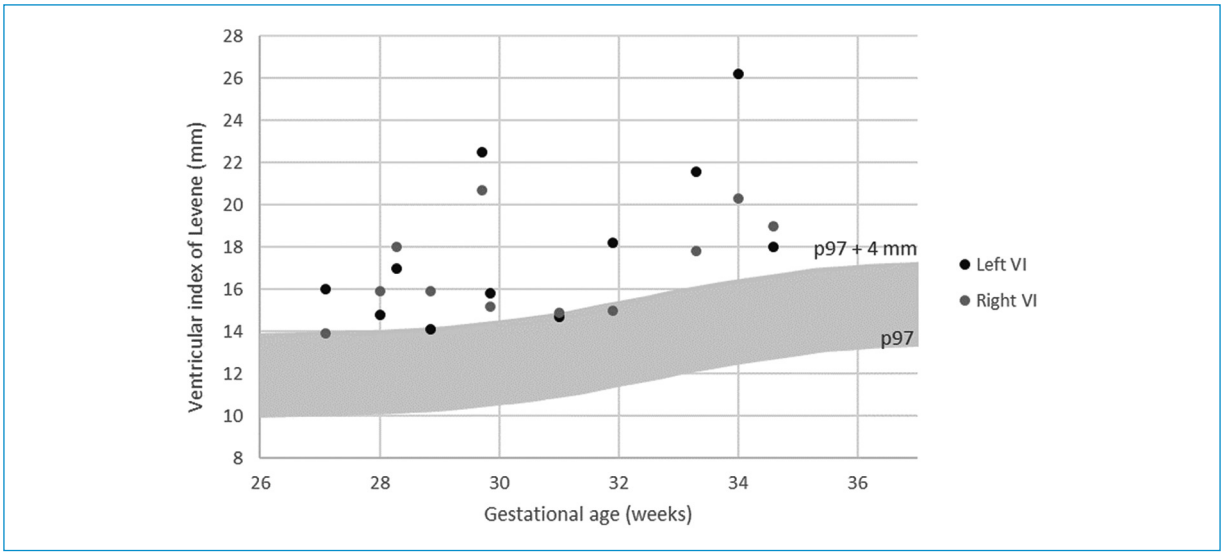

Figure 1. Left and right ventricular index of infants who received intervention, before the first procedure.

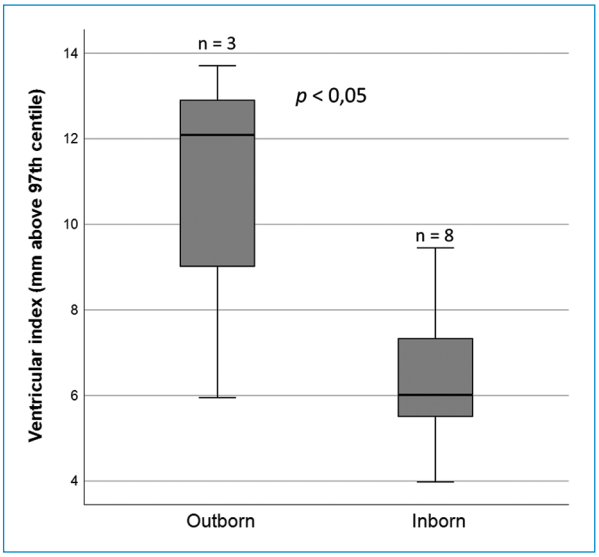

Figure 2. Ventricular index before the first intervention in outborn versus inborn patients.

require further intervention. Among the remaining seven patients, five underwent additional neurosurgical temporizing procedures (three had a VR inserted, one patient underwent an ultrasound-guided ventricular puncture due to clinical instability, and another had an EVD implanted due to refractory meningitis), and two infants had a VP shunt implanted.

Among the remaining 23% (three out of 13), a VR was inserted as an initial temporizing procedure in two patients (at a PMA of 29.7 and 29.9 weeks), one of whom also underwent an ETV, and both required a VP shunt. One infant initially underwent an ETV (at 40.7 weeks) and later required a VP shunt placement (Fig. 3).

Overall, 62% (eight out of 13) of patients who received intervention required the implantation of a VP shunt, at a median PMA of 38.9 weeks (IQR 370 – 41.3), and 23% (three out of 13) died. No significant difference was found between LVI before the first intervention and both the need for VP shunt implantation and death (Fig. 4). Two infants subsequently required VP shunt revision, one due to meningitis and the other due to peritonitis.

Follow-up clinical records were available for 91% (20 out of 22) of patients diagnosed with PHVD. Thirty-five percent (seven out of 20) of the infants died, six during their hospital stay, between one and 11 weeks of birth, one due to respiratory failure, and five owing to systemic illness. One patient was transferred and subsequently died at a PMA of 37 weeks because of refractory *Aspergillus* meningitis.

Of the patients who did not receive intervention, none of the followed-up survivors (four out of nine) had neurological sequelae at two years of corrected age. In contrast, among the survivors of the intervention group with follow-up data (nine out of 13), 78% (n = 7) had sequelae at this age, including delayed motor development (n = 1), visual impairment (n = 1), epilepsy (n = 3), and cerebral palsy (n = 5), of whom four had spastic hemiparesis and one had spastic quadriparesis. Among patients who developed CP, three had a GMFCS grade

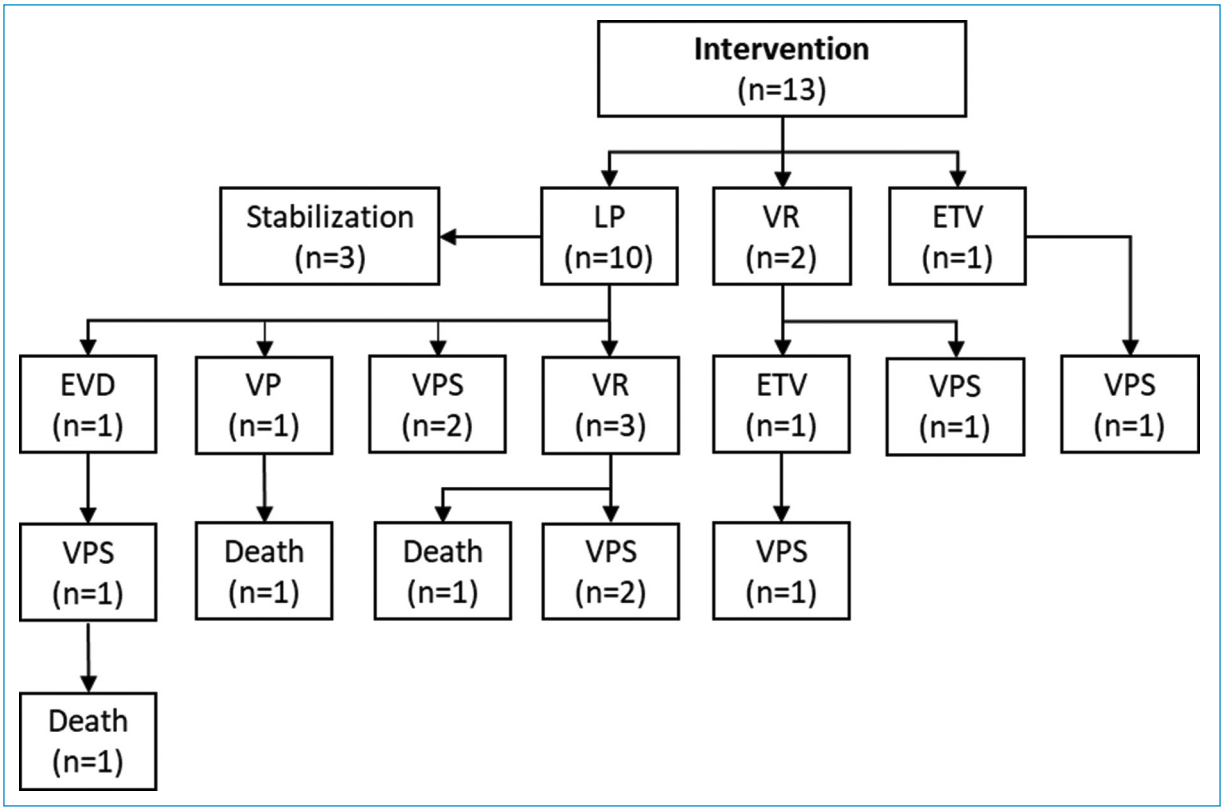

Figure 3. Flowchart of cerebrospinal fluid drainage interventions performed.
LP: lumbar puncture; ETV: endoscopic third ventriculostomy; EVD: external ventricular drain; VPS: ventriculoperitoneal shunt; VP: ventricular puncture; VR: ventricular reservoir.

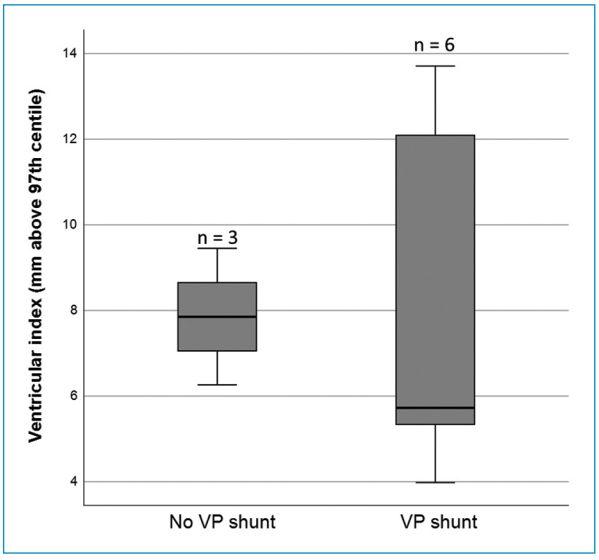

Figure 4. Ventricular index before the first intervention in infants who did and did not require ventriculoperitoneal (VP) shunt implantation.

greater than two. There was a trend towards a higher incidence of CP in infants who received intervention, although it did not reach statistical significance ($p = 0.057$). Overall, significantly more children who required CSF drainage had neurological sequelae, compared to those who did not ($p < 0.05$). VP shunt placement was not associated with an increased probability of adverse outcomes.

Considering the impact of the timing of intervention in the neurological outcome, no significant difference was found between LVI before the first intervention in infants with a favorable outcome, adverse outcome, and death (Fig. 5).

Discussion

This retrospective study aimed to assess the effect of the timing of intervention in the need for a VP shunt and the presence of neurological sequelae at two years of corrected age. It is important to note that this cohort was treated between 2014 and 2020, before the recent review of the international guidelines, which recommend an early approach to PHVD, based on the increasing evidence of its beneficial effect on the need

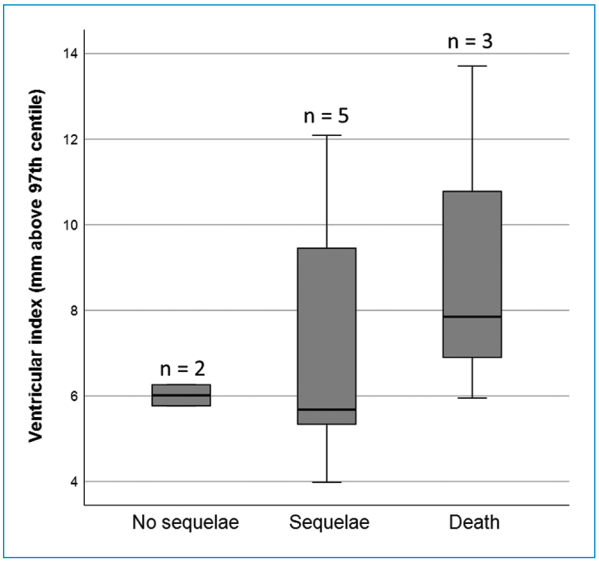

Figure 5. Ventricular index before the first intervention according to neurodevelop-mental outcome at two years of corrected age.

for a VP shunt and on the neurodevelopmental outcomes. Thus, all the infants included in this study received intervention after crossing the threshold of the 97th centile + 4 mm of LVI and 10 mm of AHW, which is later than what is currently recommended.

Among the group of infants who required CSF drainage, no differences were found between ventricular size at the initial intervention and the VP shunt implantation rate or neurodevelopmental outcome, as opposed to what had been reported in previous studies[9-11]. In fact, all the patients included in this study started intervention after surpassing 97th centile + 4 mm, contrasting with studies that compared early and late management groups, with a greater difference in ventricular size at the initial intervention.

In the group that did not receive intervention, a subset of patients showed a transient increase in ventricular size above the 97th centile that later reverted without intervention, which could support the rationale that, with early management, some infants are subject to unnecessary temporizing procedures with associated risks. Although the low threshold group in the ELVIS trial had a higher number of procedures and need for VR and VP shunt revision, severe neurodevelopmental outcomes were reported to be reduced in these patients[11].

Among patients who received intervention, 62% required the implantation of a VP shunt, which is comparable to the rate reported in the previous Ventriculomegaly Study RCT (62%)[6], where repeated lumbar punctures were performed when LVI had crossed the 97th centile + 4 mm, as well as the rate of VP shunt requirement in the late intervention group of the retrospective study conducted by De Vries et al. (62%)[9], that received intervention with a similar timing. In contrast, the VP shunt placement rate of the late approach group reported by Leijser et al.[8] was significantly higher (92%), since initial procedures were guided by the development of clinical signs of raised intracranial pressure, rather than ventricular measurements on cUS. Compared to the results of the ELVIS trial[11], this study's VP shunt rate was higher than reported for the late intervention group of the trial (23%), which may be explained by the additional aim of reducing LVI below the 97th centile, rather than solely preventing further ventricular dilatation.

Regarding outcomes at two years, Leijser et al.[8] reported that infants who received intervention after the development of clinical signs were more likely to have adverse cognitive and motor neurodevelopmental outcomes (88% vs. 27%, respectively) and cerebral palsy (94% vs. 27%) than those who did not receive intervention, as opposed to patients with an early approach, whose outcomes were identical regardless of the need for intervention. In our NICU, although the decision to initiate intervention was based on cUS measurements, with a mean LVI at the first intervention of 7.5 mm over the 97th centile, compared to 11 mm of the late approach group reported in the aforementioned study, patients who received intervention were more likely to have neurological sequelae at two years, namely delayed motor development, cerebral palsy, epilepsy, and/or visual impairment, compared to those who did not receive intervention (78% vs. none). Thirty-three percent of the patients in our study group who required CSF drainage developed CP, compared to 25% of the late intervention group (who received intervention after crossing the 97th centile + 4 mm) reported in the ELVIS trial[11]. Although there was a trend towards a higher probability of developing CP in the group of patients who received intervention, it was not statistically significant, as reported by Leijser et al.[8].

Concerning the timing of intervention in outborn patients, and although this cohort included only three outborn infants, their mean ventricular sizes at the time of the first procedure was significantly higher than that of inborn infants. Indeed, when specialized neurosurgical treatment is required, in addition to the delay in the procedure that may be imposed by the hospital's restrictions, the process of hospital transfer may further delay timely intervention. Thus, owing to the unpredictability of disease progression and the need for

neurosurgical treatment, referring these patients at the time of diagnosis would allow for timely detection and treatment of progressive ventricular dilatation.

The retrospective nature of this study limited data collection, including missing cUS and consequently ventricular measurements at relevant timings, as well as a thorough analysis of outcomes, owing to the unavailability of standardized assessments. Additionally, involving a single center and addressing an infrequent pathology resulted in a reduced study population, and consequently a lack of significant conclusions.

Conclusions

The best way to manage PHVD has been a matter of debate for several years, and different approaches have been used across different countries and units. Despite not confirming that a LVI 97th threshold is better than the + 4 mm threshold, the ELVIS trial did suggest that the 97th + 4 mm threshold should never be surpassed. This concept was translated into the current international guidelines.

We believe that sharing our experience may be of importance to improve the care for these infants, especially in avoiding very late treatment thresholds and bringing forward the referral to experienced centers that can provide full care for these infants.

Authors' contribution

Luísa Carneiro da Silva: Idea behind, and design of, the study, report, review or other type of paper; Acquisition of data from patients, research studies, or literature; Analysis or interpretation of data from patients, research studies, or literature; Drafting the article; Final approval of the version to be published. Agrees to be held accountable for the accuracy or integrity of the paper. Cláudia Coelho Faria: Conception and design of the study, report, review or other type of work or paper; Acquisition of data either from patients, research studies, or literature; Critical review of the article for important intellectual content; Final approval of the version to be published (mandatory for all authors); Agreement to be accountable for the accuracy or integrity of the work (mandatory for all authors). André Mendes da Graça: Idea behind, and design of, the study, report, review or other type of paper; Acquisition of data from patients, research studies, or literature; Analysis or interpretation of data from patients, research studies, or literature; Drafting the article; Critical review of the article for important intellectual content; Final approval of the version to be published. Agrees to be held accountable for the accuracy or integrity of the paper.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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