Randomized controlled early versus late ventricular intervention study in posthemorrhagic ventricular dilatation: outcome at 2 years

Cizmeci, M.N.; Groenendaal, F.; Liem, K.D.; Haastert, I.C. van; Benavente-Fernandez, I.; Straaten, H.L.M. van; ... ; ELVIS Study Grp

Randomized Controlled Early versus Late Ventricular Intervention Study in Posthemorrhagic Ventricular Dilatation: Outcome at 2 Years

Mehmet N. Cizmeci, MD[1,2,3], Floris Groenendaal, MD, PhD[1,2], Kian D. Liem, MD, PhD[4], Ingrid C. van Haastert, MA, PhD[1,2], Isabel Benavente-Fernández, MD, PhD[5], Henrica L. M. van Straaten, MD, PhD[6], Sylke Steggerda, MD, PhD[7], Bert J. Smit, MD, PhD[8], Andrew Whitelaw, MD, FRCPCH[9], Peter Woerdeman, MD, PhD[10], Axel Heep, MD[9,*], Linda S. de Vries, MD, PhD[1,2], and the ELVIS study group[†]

Objective To compare the effect of intervention at low vs high threshold of ventriculomegaly in preterm infants with posthemorrhagic ventricular dilatation on death or severe neurodevelopmental disability.

Study design This multicenter randomized controlled trial reviewed lumbar punctures initiated after either a low threshold (ventricular index of >p97 and anterior horn width of >6 mm) or high threshold (ventricular index of >p97 + 4 mm and anterior horn width of >10 mm). The composite adverse outcome was defined as death or cerebral palsy or Bayley composite cognitive/motor scores <–2 SDs at 24 months corrected age.

Results Outcomes were assessed in 113 of 126 infants. The composite adverse outcome was seen in 20 of 58 infants (35%) in the low threshold group and 28 of 55 (51%) in the high threshold (P = .07). The low threshold intervention was associated with a decreased risk of an adverse outcome after correcting for gestational age, severity of intraventricular hemorrhage, and cerebellar hemorrhage (aOR, 0.24; 95% CI, 0.07-0.87; P = .03). Infants with a favorable outcome had a smaller fronto-occipital horn ratio (crude mean difference, −0.06; 95% CI, −0.09 to −0.03; P < .001) at term-equivalent age. Infants in the low threshold group with a ventriculoperitoneal shunt, had cognitive and motor scores similar to those without (P = .3 for both), whereas in the high threshold group those with a ventriculoperitoneal shunt had significantly lower scores than those without a ventriculoperitoneal shunt (P = .01 and P = .004, respectively).

Conclusions In a post hoc analysis, earlier intervention was associated with a lower odds of death or severe neurodevelopmental disability in preterm infants with progressive posthemorrhagic ventricular dilatation. *(J Pediatr 2020;226:28-35)*.

Trial Registration ISRCTN43171322.

See related articles, p 16 and p 36

Although recent studies report a decrease in the incidence of severe intraventricular hemorrhage (IVH), it continues to be a common and significant problem in very preterm infants.[1,2] The risk of an adverse neurodevelopmental outcome increases significantly when severe IVH (grade III with or without a periventricular hemorrhagic infarction) is complicated by posthemorrhagic ventricular dilatation.[3-6] Significant cognitive and motor impairment was found among infants with posthemorrhagic ventricular dilatation at 18-24 months corrected age (CA) in several retrospective studies and in a limited number of randomized controlled trials (RCT), including the DRIFT trial.[7-11] In these RCTs, randomization for interventions was performed once

BSID-II	Bayley Scales of Infant Development-II
BSITD-III	Bayley Scales of Infant and Toddler Development-III
CA	Corrected age
CP	Cerebral palsy
ELVIS	Early versus Late Ventricular Intervention Study
FOHR	Fronto-occipital horn ratio
IVH	Intraventricular hemorrhage
RCT	Randomized controlled trial
VP shunt	Ventriculoperitoneal shunt
MRI	Magnetic resonance imaging
DRIFT	Drainage, Irrigation, and Fibrinolytic Therapy

From the [1]Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center, Utrecht; [2]University Medical Center Utrecht, Utrecht Brain Center, Utrecht, the Netherlands; [3]Division of Neonatology, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Canada; [4]Department of Neonatology, Amalia Children's Hospital, Radboud University Medical Center, Nijmegen, the Netherlands; [5]Department of Neonatology, 'Puerta del Mar' University Hospital, Cadiz, Spain; [6]Department of Neonatology, Isala Women and Children's Hospital, Zwolle, the Netherlands; [7]Department of Neonatology, Leiden University Medical Center, Leiden, the Netherlands; [8]Directorate Quality & Patient Care, Erasmus MC, University Medical Center Rotterdam, the Netherlands; [9]Neonatal Intensive Care Unit, Southmead Hospital and Neonatal Neuroscience, University of Bristol, Bristol, United Kingdom; and [10]Division of Neuroscience, Department of Neurosurgery, University Medical Center Utrecht, Utrecht, the Netherlands

*Contributed equally.
†List of members of the ELVIS study group is available at www.jpeds.com (**Appendix**).

The authors declare no conflicts of interest.

Portions of this study were presented at the Pediatric Academic Societies annual meeting, April 24-May 1, 2019, Baltimore, Maryland.

https://doi.org/10.1016/j.jpeds.2020.08.014

the ventricular index was >4 mm above the 97th percentile according to the graph of Levene.[12]

In the Early vs Late Ventricular Intervention Study (ELVIS) trial (ISRCTN43171322), infants were randomized prior to crossing this percentile, when the ventricular index was >97th percentile and progressing towards the 97th percentile + 4 mm line. We previously reported that there was no significant difference in the primary composite adverse outcome of ventriculoperitoneal shunt (VP shunt) placement or death in infants with posthemorrhagic ventricular dilatation who were treated at a lower vs higher threshold for intervention.[13] However, the number of infants who required a VP shunt was 19% and 23%, respectively, the lowest number reported so far in the literature. In a nested substudy of the ELVIS trial,[14] we subsequently reported that infants in the higher threshold group had a significantly higher global brain abnormality score, larger fronto-occipital horn ratio (FOHR), and larger ventricular volumes, using the Kidokoro score and automated volumetric analysis on the term-equivalent age MRI.[15] In the present study, we assessed neurodevelopmental outcomes of the ELVIS cohort at 24 months CA to test the hypothesis that earlier intervention would result in improved neurodevelopmental outcomes.

Methods

The ELVIS trial was a multicenter RCT enrolling 126 preterm infants from July 2006 to July 2016. Infants were eligible for inclusion if they had an IVH grade III, with or without a periventricular hemorrhagic infarction (PVHI).[6] Infants were randomly assigned to low-threshold (ventricular index >97th percentile and anterior horn width >6 mm and/or thalamo-occipital distance >25 mm) or high threshold (ventricular index of >97th percentile + 4 mm and anterior horn width of >10 mm) groups. Interventions started with lumbar punctures with a maximum number of 3. If necessary, this was followed by insertion and tapping from a subcutaneous ventricular reservoir, aiming for ventricular index <97th percentile line in both groups. Once or twice daily, 10 mL/kg were removed based on cranial ultrasound measurements. Taps were continued until stabilization occurred or until infant's weight reached 2000-2500 g, at which stage the infant became eligible for a VP shunt, if still required.[13]

Antenatal and perinatal factors including gestational age, birth weight, sex, hemorrhage severity, and timing and type of intervention were retrieved from the patient files. Approval from the research ethics board at each center and informed written parental consent were obtained for patients participating in the study before enrollment.

Neuroimaging Protocol and Assessment

All participating centers used conventional axial T1-weighted and T2-weighted imaging and followed a predefined MRI protocol according to their institutional guidelines. MRIs were acquired around term-equivalent age with a 3.0 Tesla MR magnet (Tesla Engineering, West Sussex, United Kingdom) at 4 centers, and a 1.5 Tesla MR magnet in others.[14]

For the assessment of brain injury, a global brain abnormality score was calculated as the sum of the regional total scores and classified as normal (total score of 0-3), mild (total score of 4-7), moderate (total score of 8-11), and severe (total score of ≥12) as defined by Kidokoro et al.[15] The FOHR was obtained by measuring the widest distances across the frontal horns and the occipital horns, and the average of these measurements was then divided by the largest biparietal diameter as defined by Kulkarni et al.[16] Cerebellar hemorrhage was categorized as no or punctate cerebellar hemorrhage (score of 0-2), and extensive (score of 3-4) based on their MRI findings according to Kidokoro et al.[15] Automatic segmentation of cerebral MRIs was applied on axial or coronal T2-weighted images for computerized volume analysis as described by Moeskops et al.[17] A detailed description of the neuroimaging protocol is presented elsewhere.[14]

Neurodevelopmental Assessment

Participants were followed longitudinally and neurodevelopmental outcomes were assessed as part of the standard follow-up programs of the participating centers. Examiners were blinded to treatment group assignment. Cognitive and motor outcome were assessed with either the Bayley Scales of Infant Development, second edition (BSID-II) or the Bayley Scales of Infant and Toddler Development, third edition (BSITD-III) at 24 months CA. Cognitive and motor index or composite scores were corrected for prematurity. The conversion from the BSID-II mental developmental index to the BSITD-III composite cognitive score was calculated by formula (59% of the BSID-II mental developmental index score plus 52) suggested by Lowe et al.[18] To include children who had an index score of <50 on the BSID-II or a cognitive or motor composite score of <55 or <46, respectively, on the BSITD-III, developmental quotients were calculated (developmental age equivalent [in months, based on raw test scores] divided by the corrected test age and multiplied by 100).[19] The non-English testers in Portugal, Spain, and Sweden used the administration manual of the Bayley tests in English and each examiner followed the instructions and performed the items as described.[20] In the Netherlands, the Dutch norms for the BSID-III were available from 2014 onward.[21] The scores from previously tested children were recalculated using the Dutch edition. The severity of cerebral palsy (CP) was classified according to the Gross Motor Function Classification System, with moderate to severe CP defined as levels III-V.[22,23] CP was classified as spastic, ataxic, or dyskinetic and categorized as unilateral or bilateral.[24] The primary composite outcome was death, any grade CP, or a Bayley cognitive or motor score of <−2 SD.

Statistical Analyses

Data analysis was performed by the coordinating center, the University Medical Center Utrecht. Statistical analyses were performed using IBM SPSS Statistics version 25 (SPSS Inc,

Chicago, Illinois). Continuous variables were presented as mean ± SD and median (IQR), depending on their distribution. Categorical values were presented as number and percentage. The χ^2 and Fisher exact tests were used to compare categorical variables among groups. Mann-Whitney *U* test was used to compare nonparametric variables and the Student *t* test for comparison between variables with normal distribution. Logarithmic transformation was performed to the ventricular volumes to yield variance homogeneity and Gaussian distribution. Hierarchical multiple linear regression and logistic regression analyses were applied for the significant variables detected with the univariate analysis. Gestational age was dichotomized using 28 weeks as a cut-off. Adjustment for gestational age, severity of IVH, and severity of cerebellar hemorrhage was performed in the multivariable regression models. Statistical significance was set at $P < .05$.

Results

Among the 109 survivors, a total of 100 (92%) were assessed at a mean CA of 25.1 ± 2.0 months. Of these infants, 86 (86%) were assessed with BSID-III and 14 (14%) with BSID-II. Of the 14 infants who were assessed with BSID-II, 10 were in the low threshold group and 4 in the high threshold. Four infants were further removed from the analysis owing to a missing Bayley domain, either cognitive or motor. The distribution of the participants is presented in detail in the flowchart (Figure 1). The surviving infants of the 2 treatment arms were comparable with respect to clinical characteristics, except for the larger number of infants in the low threshold arm with prolonged mechanical ventilation ($P = .05$) (Table I).

Outcomes

The composite outcome was assessed in 113 infants. Eight infants (13%) died in the low threshold group and 9 (15%) in the high threshold group.[13] In the low threshold group, 20 of 58 (35%) had an adverse composite outcome (death [n = 8], CP [n = 10], or a Bayley composite cognitive or motor score of <−2 SD [n = 6]), whereas in the high threshold group, 28 of 55 (51%) had an adverse outcome (including death [n = 9], CP [n = 14], or a Bayley composite cognitive or motor score of <2 SD [n = 11]) ($P = .07$).

In a post hoc multivariable analysis, low threshold intervention was associated with a decreased risk of an adverse outcome after correcting for gestational age, severity of IVH, and cerebellar hemorrhage (aOR, 0.24; 95% CI, 0.07-0.87; $P = .03$). CP was seen in 5 of 66 infants (8%) with a grade III IVH, and in 19 of 34 infants (56%) with a periventricular hemorrhagic infarction ($P < .001$). Topographic classification and severity of CP with respect to grade of IVH are presented in Table II (available at www.jpeds.com).

Among the survivors, the median Bayley composite cognitive scores were 95 (IQR, 85-110) in the low threshold and 91

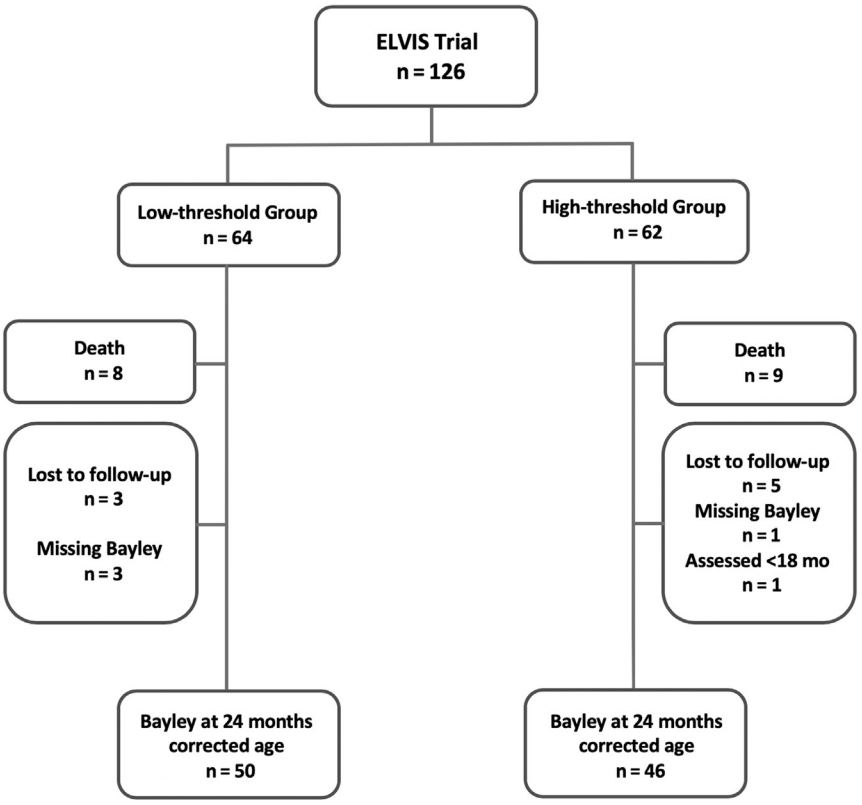

Figure 1. Flowchart of the ELVIS trial demonstrating follow-up of the study population.

Table I. Demographic and clinical characteristics of the surviving infants

Characteristics	Low threshold group (n = 56)	High threshold group (n = 51*)	*P* value
Gestational age, wk	28.1 ± 2.34	27.9 ± 2.56	.9†
Birth weight, g	1198 ± 354	1180 ± 380	.9†
Sex			.8‡
Male	32 (57)	32 (63)	
Female	24 (43)	19 (37)	
Antenatal steroids	27 (48)	19 (37)	.3‡
Early onset sepsis	10 (18)	8 (16)	.8‡
Late onset sepsis	18 (32)	21 (41)	.4‡
Mechanical ventilation >7 d	32 (57)	19 (37)	.05‡
Medical treatment for PDA	10 (34)	20 (39)	.7‡
Surgical treatment for PDA	4 (7)	5 (10)	.7‡
Medical treatment for NEC	2 (4)	3 (6)	.7‡
Surgical treatment for NEC	1 (2)	3 (6)	.4‡
Inotropes	23 (41)	17 (33)	.4‡
Postnatal corticosteroids	5 (9)	7 (14)	.5‡

NEC, necrotizing enterocolitis; *PDA*, patent ductus arteriosus.
Data are mean ± SD or number (%).
*Incomplete demographic and clinical data in 2 infants.
†*t* test.
‡χ^2 test.

(IQR, 80-101) in the high threshold group ($P = .1$). Categorical distribution of these infants is presented in detail in Table III. Survivors without CP had a higher composite cognitive score than those with CP (95 [IQR, 89-110] vs 85 [IQR, 74-96], respectively; $P = .001$). Infants without a VP shunt had higher composite cognitive score than those with a VP shunt (95 [IQR, 87-109] vs 85 [IQR, 70-99], respectively; $P = .02$). Infants in the low threshold group who required a VP shunt had a composite cognitive score similar to those without a VP shunt (median, 90 [IQR, 80-107] vs 96 [IQR, 87-110]; $P = .3$), however, those in the high threshold group with a VP shunt had a lower cognitive score than those without (80 [IQR, 62-96] vs 95 [IQR, 86-105]; $P = .01$) (Figure 2).

Among the survivors, the median Bayley motor scores were 88 (IQR, 76-106) in the low threshold and 88 (IQR, 72-101) in the high threshold group, respectively ($P = .6$). Categorical distribution of these infants is presented in detail in Table III. Survivors without CP had a higher composite motor score than those with CP (92 [IQR, 85-107] vs 73 [IQR, 55-82], respectively; $P < .001$). Infants without a VP shunt had a higher composite motor score than those with VP shunt (91 [IQR, 82-104] vs 76 [IQR, 55-94], respectively; $P = .004$). Infants in the low threshold group who required a VP shunt, had a composite motor score not significantly different from those without a VP shunt (median, 79 [IQR, 70-99] vs 90 [IQR, 81-107]; $P = .3$), but those in the high threshold group with a VP shunt had a lower composite motor score than those without (72 [IQR, 49-90] vs 91 [IQR, 84-103]; $P = .004$) (Figure 2).

Outcomes in Relation to Term-Equivalent Age MRI Variables

MRI was performed at term-equivalent age in 88 infants. Among the survivors, 0 of 3 (0%) infants with a normal, 1 of 21 (5%) with a mild, 5 of 21 (24%) with a moderate, and 25 of 37 (68%) with a severe Kidokoro score had an adverse composite outcome ($P < .001$) (Figure 3; available at www.jpeds.com). Infants with a normal or mildly abnormal Kidokoro score had a higher Bayley composite cognitive and motor score when compared with the infants with a moderate or severe score (103 [IQR, 90-110] vs 91 [IQR, 79-104] and 95 [IQR, 88-111] vs 84 [IQR, 70-98]; $P = .02$ and $P = .01$, respectively).

The mean ± SD FOHR was larger in infants with an adverse composite outcome than those without (0.49 ± 0.06 vs 0.43 ± 0.04; mean difference, 0.06 [95% CI,

Table III. Neurodevelopmental outcomes of the study population

Outcomes	Low-threshold group	High-threshold group	*P* value*
Bayley cognitive score†			.5
Normal range	39 (78)	32 (71)	
<−1 SD below the normative range	8 (16)	7 (16)	
<−2 SD below the normative range	3 (6)	6 (13)	
Bayley motor score‡			.1
Normal range	29 (61)	30 (64)	
<−1 SD below the normative range	14 (29)	7 (15)	
<−2 SD below the normative range	5 (10)	10 (21)	
Bayley cognitive score in infants with CP			.4
Normal range	4 (50)	9 (64)	
<−1 SD below the normative range	3 (38)	2 (14)	
<−2 SD below the normative range	1 (12)	3 (21)	
Bayley cognitive score in infants with VP shunt			.1
Normal range	7 (64)	6 (46)	
<−1 SD below the normative range	3 (27)	2 (15)	
<−2 SD below the normative range	1 (9)	5 (39)	
Bayley motor score in infants with CP			.7
Normal range	1 (10)	2 (14)	
<−1 SD below the normative range	6 (60)	6 (43)	
<−2 SD below the normative range	3 (30)	6 (43)	
Bayley motor score in infants with VP shunt			.2
Normal range	4 (40)	4 (31)	
<−1 SD below the normative range	5 (50)	3 (23)	
<−2 SD below the normative range	1 (10)	6 (46)	
Grade of IVH in infants with CP			
Grade-III IVH	1/36 (3)	4/30 (13)	.1
PVHI	9/17 (53)	10/17 (59)	.7

PVHI, periventricular hemorrhagic infarction.
Values are number (%).
*Fisher's exact test.
†Data available for 50 infants in the low threshold group and 45 in high threshold.
‡Data available for 48 infants in the low threshold group and 47 in high threshold.

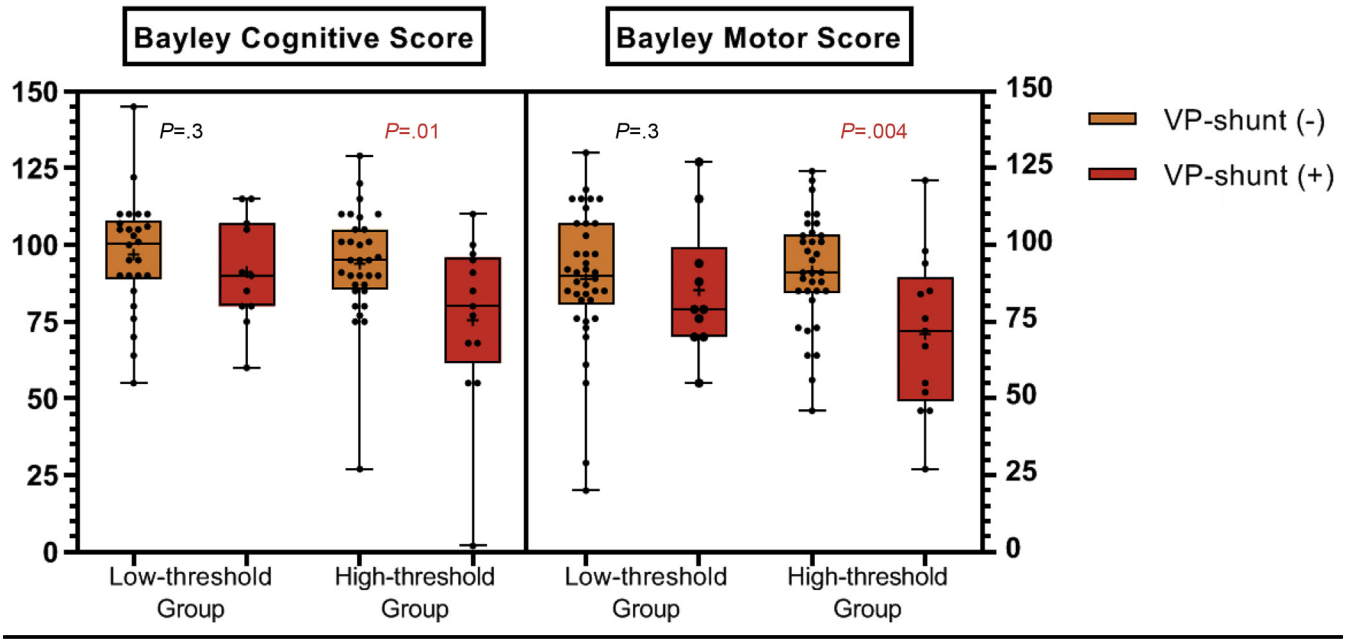

Figure 2. Box plot graphs showing the distribution of the Bayley cognitive and motor scores in relation to the timing of intervention and presence of ventriculoperitoneal shunt.

0.09-0.03]; $P < .001$). A larger FOHR was negatively associated with a composite cognitive and motor score irrespective of group allocation (β, −177 [95% CI, −247 to −109] and −162 [95% CI, −236 to −88], respectively; $P < .001$ for both) (**Figure 4**; available at www.jpeds.com). In a subgroup of infants (n = 47) who had a volumetric analysis performed, infants with a favorable composite outcome had smaller ventricular volumes than those with an adverse outcome (mean, −1.26 ± 0.22 vs −1.10 ± 0.29; crude mean difference, −0.16; 95% CI, −0.32 to −0.001; $P = .049$).

Infants with an extensive cerebellar hemorrhage (n = 8) had a lower Bayley composite cognitive and motor score than those with no or punctate cerebellar hemorrhage (75 [IQR, 42-86] vs 95 [IQR, 85-110]; $P = .009$ and 69 [IQR, 50-88] vs 91 [IQR, 76-103]; $P = .01$, respectively). Infants with an extensive cerebellar hemorrhage were also more likely to have an adverse composite outcome than those with no or punctate cerebellar hemorrhage (7 of 8 infants [88%] vs 24 of 74 infants [32%], respectively; $P = .004$). Extensive cerebellar hemorrhage was an independent risk factor for adverse outcome (OR, 19; 95% CI, 2-197; $P = .01$).

Discussion

In the ELVIS trial, we assessed outcome at 2 years of CA in very preterm infants and showed a trend toward an improved composite outcome in the low threshold group compared with the high threshold group. After adjusting for gestational age, severity of IVH, and cerebellar hemorrhage, earlier intervention reduced death or severe neurodevelopmental disability in infants with posthemorrhagic ventricular dilatation. The interventions for both arms of the study were solely based on sonographic criteria and initiated while the infants were still asymptomatic.

In infants with posthemorrhagic ventricular dilatation, CP was seen more often in infants with a periventricular hemorrhagic infarction, and the majority of these infants had unilateral CP, similar to what has been reported in the literature.[25] CP also occurred in infants with a grade III IVH, in which case bilateral CP was more common. As expected, the development of CP had a negative effect on especially motor, but also on cognitive outcome. Although there was overlap between CP and low Bayley scores, the majority of the infants with CP in both groups had Gross Motor Function Classification System level I or II. This finding likely explains why some infants with CP had normal Bayley scores. Additionally, in a post hoc analysis, infants in the low threshold group requiring a VP shunt had cognitive and motor scores that were similar to infants without a VP shunt. In contrast, infants in the high threshold group who required a VP shunt had lower Bayley cognitive and motor scores compared with those without.

In a recent study by Leijser et al, neurodevelopmental outcome was evaluated at 18-24 months in infants with posthemorrhagic ventricular dilatation.[11] Investigators found that preterm infants undergoing intervention at an early stage, even when eventually requiring a VP shunt, had developmental test scores that were similar to infants without intervention, all within the normal range. In contrast, intervention after the onset of clinical symptoms was associated with an increased risk of adverse outcome. It is not straightforward, however, to compare our findings with previous RCTs, because randomization to 1 study arm, that is low threshold, was significantly earlier in the ELVIS trial when

compared with the timing of randomization in other studies. In the first RCT, the Ventriculomegaly Study, there was no upper limit for ventricular index at enrollment and interventions were performed to prevent further dilatation, rather than bringing the ventricular size down to within the normal range.[26] Investigators found no difference in the primary outcome of VP shunt between the 2 groups.[4,26] In a subsequent RCT by the International Posthemorrhagic Ventricular Dilatation Drug Trial Group, there was again no upper limit on ventricular index and the composite outcome of death or VP shunt placement was significantly higher in the treatment group. The use of acetazolamide and furosemide were also associated with higher rates of neurological morbidity.[7,27]

In an RCT using Drainage, Irrigation, and Fibrinolytic Therapy (DRIFT trial), rates of VP shunt placement were higher (38% and 39% in the treatment and standard therapy groups, respectively) than in the ELVIS trial (19% and 23% in the low threshold and high threshold groups, respectively).[8,28] Because the entry criteria for the 2 RCTs were different, no direct comparison can be made. In the DRIFT trial, infants were enrolled once the ventricular index exceeded the 97th percentile + 4 mm line but there was no intention to bring the ventricular index down to within the normal range within 7-10 days. The ventricular index for infants in the DRIFT trial was significantly larger than for infants in the high threshold arm of the ELVIS trial (Whitelaw A, personal communication, January 2020). Comparison could only be made for infants who exceeded the 97th percentile +4 mm line, because infants were referred to the study site once this line was crossed. This observation supports our hypothesis that draining cerebrospinal fluid earlier may prevent further brain injury. Cerebrospinal fluid containing blood components and inflammatory substances may have a negative effect on the developing preterm brain, and earlier removal may have been beneficial; we were able to show that the majority of infants survived without a severe disability.[29,30]

Ventriculomegaly at term-equivalent age, even without evidence of increased intracranial pressure, has been shown to be an independent predictor of adverse cognitive and motor outcomes in preterm infants.[31-33] The pathogenesis of brain injury in infants with ventriculomegaly is a complex process and determined by both direct injury to adjacent brain tissues and secondary inflammatory interactions.[34-36] The relationship between ventricular volumes and outcome was demonstrated using 3-dimensional ultrasound imaging, and adverse outcome at 12 months was seen in preterm infants with larger ventricles.[37] However, the correlation between ultrasonographic and MRI measurements remains inconsistent and needs further investigation.[1,38] Jary et al performed manual brain segmentation on MRI and demonstrated that total cerebral volume, excluding the ventricles, correlated significantly with cognitive and motor outcomes.[39] In the ELVIS trial, automated segmentation methods to measure ventricular volumes could only be performed in around one-half of the infants with MRI owing to insufficient image quality. Infants with favorable outcomes had smaller relative ventricular volumes than those with adverse outcomes. The FOHR, which was shown to be a reliable and reproducible predictor of ventricular volumes in infants with ventriculomegaly, was assessed in a large number of infants.[14,40,41] Because we could not obtain volumetric measurements of all patients owing to technical challenges, we used FOHR instead in our previous nested substudy of the ELVIS trial.[14] In the present study, we found a larger FOHR in infants with an adverse composite outcome than those without, and greater ventricular volumes were negatively associated with Bayley cognitive and motor scores irrespective of group allocation. Preserved ventricular volumes with potentially better outcomes seem to justify the increase in additional interventions, that is, lumbar punctures and ventricular reservoirs, in the low threshold group.

An increasing Kidokoro score, which is a reliable tool to assess brain injury at term-equivalent age MRI, was also associated with an adverse composite outcome.[15] We previously hypothesized that the higher Kidokoro scores in infants in the high threshold group were caused by prolonged pressure on the periventricular white matter owing to progressive posthemorrhagic ventricular dilatation, which might be deleterious to the developing preterm brain.[14] Posthemorrhagic ventricular dilatation-induced microstructural brain injury, as stated previously by Brouwer et al, might serve as another explanation for increased Kidokoro scores.[42] In our previous study, we found more infants with a moderate or severe score in the high threshold group, and in the present study we found that a moderate or severe Kidokoro score was associated with an increased odds of death and severe neurodevelopmental disability.[14] Also of note was that infants with an extensive cerebellar hemorrhage were more likely to have an adverse composite outcome than those without, irrespective of the group allocation, which is in agreement with the literature.[43]

The present study has several limitations. The ELVIS trial was powered for the primary outcome of death or VP shunt, and not for the secondary long-term outcomes, which may explain why our study found only a trend toward an improved outcome. In the post hoc analysis adjusting for gestational age, the severity of IVH, and the severity of cerebellar hemorrhage, we found a significant benefit for early intervention in reducing the composite adverse outcome. Because the infants were enrolled over a 10-year period, perinatal care may have changed in the participating centers. However, this would have similar effects on both study arms. Although the majority of infants were tested with the BSITD-III, a small group was tested with the BSID-II. To overcome this difference, we used the conversion formula from Lowe et al on BSID-II scores for calculating equivalent BSITD-III scores.[18] We were not able to collect data on socioeconomic status from the records of all infants and could not adjust the outcomes for this variable. Because the infants were born in different countries and the BSID-III has not been widely validated, we were not able to present data on language outcomes. Finally, not all survivors had a term-equivalent age MRI and in only around one-half of these was the MRI quality was sufficient to perform automated segmentation. The major strength of the present study is the high follow-up rate in centers with experience in neonatal neurology practices.

In conclusion, in this multicenter RCT, there was a beneficial effect of early intervention for posthemorrhagic ventricular dilatation on reducing mortality and severe neurodevelopmental disability, after adjusting for gestational age and severity of IVH and cerebellar hemorrhage. ■

We thank the neurosurgeons, neonatal intensive care nurses, developmental specialists, and data managers for their dedicated help to obtain the pertinent data and records.

Submitted for publication Mar 25, 2020; last revision received Jul 16, 2020; accepted Aug 6, 2020.

Reprint requests: Linda S. de Vries, MD, PhD, Emeritus Professor of Neonatal Neurology, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht & UMC Utrecht Brain Center, KE 04.123.1 Lundlaan 6, 3584 EA Utrecht, the Netherlands. E-mail: l.s.devries@umcutrecht.nl

References

1. Leijser LM, de Vries LS. Preterm brain injury: germinal matrix–intraventricular hemorrhage and post-hemorrhagic ventricular dilatation. In: de Vries LS, Glass HC, eds. Handbook of clinical neurology. New York (NY): Elsevier; 2019. p. 173-99.
2. Yeo KT, Thomas R, Chow SS, Bolisetty S, Haslam R, Tarnow-Mordi W, et al. Improving incidence trends of severe intraventricular haemorrhages in preterm infants <32 weeks gestation: a cohort study. Arch Dis Child Fetal Neonatal Ed 2020;105:145-50.
3. Fernell E, Hagberg G, Hagberg B. Infantile hydrocephalus in preterm, low-birth-weight infants-a nationwide Swedish cohort study 1979-1988. Acta Paediatr 1993;82:45-8.
4. Ventriculomegaly Trial Group. Randomised trial of early tapping in neonatal posthaemorrhagic ventricular dilatation: results at 30 months. Arch Dis Child Fetal Neonatal Ed 1994;70:129-36.
5. Persson EK, Hagberg G, Uvebrant P. Disabilities in children with hydrocephalus-a population-based study of children aged between four and twelve years. Neuropediatrics 2006;37:330-6.
6. Volpe JJ. Intraventricular hemorrhage in the premature infant–current concepts. Part II. Ann Neurol 1989;25:109-16.
7. Kennedy CR, Ayers S, Campbell MJ, Elbourne D, Hope P, Johnson A. Randomized, controlled trial of acetazolamide and furosemide in posthemorrhagic ventricular dilation in infancy: follow-up at 1 year. Pediatrics 2001;108:597-607.
8. Whitelaw A, Evans D, Carter M, Thoresen M, Wroblewska J, Mandera M, et al. Randomized clinical trial of prevention of hydrocephalus after intraventricular hemorrhage in preterm infants: brain-washing versus tapping fluid. Pediatrics 2007;119:1071-8.
9. Adams-Chapman I, Hansen NI, Stoll BJ, Higgins R , NICHD Research Network. Neurodevelopmental outcome of extremely low birth weight infants with posthemorrhagic hydrocephalus requiring shunt insertion. Pediatrics 2008;121:1167-77.
10. Bassan H, Eshel R, Golan I, Kohelet D, Ben Sira L, Mandel D, et al. Timing of external ventricular drainage and neurodevelopmental outcome in preterm infants with posthemorrhagic hydrocephalus. Eur J Paediatr Neurol 2012;16:662-70.
11. Leijser LM, Miller SP, van Wezel-Meijler G, Brouwer AJ, Traubici J, van Haastert IC, et al. Posthemorrhagic ventricular dilatation in preterm infants: when best to intervene? Neurology 2018;90:698-706.
12. Levene MI. Measurement of the growth of the lateral ventricles in preterm infants with real-time ultrasound. Arch Dis Child 1981;56:900-4.
13. de Vries LS, Groenendaal F, Liem KD, Heep A, Brouwer AJ, van 't Verlaat E, et al. Treatment thresholds for intervention in posthaemorrhagic ventricular dilation: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2019;104:70-5.
14. Cizmeci MN, Khalili N, Claessens NHP, Groenendaal F, Liem KD, Heep A, et al. Assessment of brain injury and brain volumes after posthemorrhagic ventricular dilatation: a nested substudy of the randomized controlled ELVIS trial. J Pediatr 2019;208:191-7.
15. Kidokoro H, Neil JJ, Inder TE. New MR imaging assessment tool to define brain abnormalities in very preterm infants at term. AJNR Am J Neuroradiol 2013;34:2208-14.
16. Kulkarni AV, Drake JM, Armstrong DC, Dirks PB. Measurement of ventricular size: reliability of the frontal and occipital horn ratio compared to subjective assessment. Pediatr Neurosurg 1999;31:65-70.
17. Moeskops P, Viergever MA, Mendrik AM, de Vries LS, Benders MJ, Isgum I. Automatic segmentation of MR brain images with a convolutional neural network. IEEE Trans Med Imaging 2016;35:1252-61.
18. Lowe JR, Erickson SJ, Schrader R, Duncan AF. Comparison of the Bayley II mental developmental index and the Bayley III cognitive scale: are we measuring the same thing? Acta Paediatr 2012;101:55-8.
19. Jary S, Kmita G, Whitelaw A. Differentiating developmental outcome between infants with severe disability in research studies: the role of Bayley developmental quotients. J Pediatr 2011;159:211-4.
20. Bayley N. Bayley Scales of Infant and Toddler Development. 3rd ed. San Antonio (TX): Harcourt Assessment; 2006.
21. Van Baar AL, Steenis LJP, Verhoeven M. Bayley Scales of Infant and Toddler Development - Derde Editie, Nederlandstalige Bewerking, Technische Handleiding. Amsterdam: Pearson Assessment and Information B.V; 2014.
22. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl 2007;109:8-14.
23. Palisano RJ, Hanna SE, Rosenbaum PL, Russell DJ, Walter SD, Wood EP, et al. Validation of a model of gross motor function for children with cerebral palsy. Phys Ther 2000;80:974-85.
24. Novak I, Morgan C, Adde L, Blackman J, Boyd RN, Brunstrom-Hernandez J, et al. Early, accurate diagnosis and early intervention in cerebral palsy: advances in diagnosis and treatment. JAMA Pediatr 2017;171:897-907.
25. Cizmeci MN, de Vries LS, Ly LG, van Haastert IC, Groenendaal F, Kelly EN, et al. Periventricular hemorrhagic infarction in very preterm infants: characteristic sonographic findings and association with neurodevelopmental outcomes at age 2 years. J Pediatr 2020;217:79-85.
26. Ventriculomegaly Trial Group. Randomised trial of early tapping in neonatal posthaemorrhagic ventricular dilatation. Arch Dis Child 1990;65:3-10.
27. International PHVD Drug Trial Group. International randomised controlled trial of acetazolamide and furosemide in posthaemorrhagic ventricular dilatation in infancy. Lancet 1998;352:433-40.
28. Whitelaw A, Jary S, Kmita G, Wroblewska J, Musialik-Swietlinska E, Mandera M, et al. Randomized trial of drainage, irrigation and fibrinolytic therapy for premature infants with posthemorrhagic ventricular dilatation: developmental outcome at 2 years. Pediatrics 2010;125:852-8.
29. Habiyaremye G, Morales DM, Morgan CD, McAllister JP, CreveCoeur TS, Han RH, et al. Chemokine and cytokine levels in the lumbar cerebrospinal fluid of preterm infants with post-hemorrhagic hydrocephalus. Fluids Barriers CNS 2017;14:35.
30. Morales DM, Silver SA, Morgan CD, Mercer D, Inder TE, Holtzman DM, et al. Lumbar cerebrospinal fluid biomarkers of posthemorrhagic hydrocephalus of prematurity: amyloid precursor protein, soluble amyloid precursor protein alpha, and L1 cell adhesion molecule. Neurosurgery 2017;80:82-90.
31. Whitaker AH, Feldman JF, Van Rossem R, Schonfeld IS, Pinto-Martin JA, Torre C, et al. Neonatal cranial ultrasound abnormalities in low birth weight infants: relation to cognitive outcomes at six years of age. Pediatrics 1996;98:719-29.
32. Ment LR, Vohr B, Allan W, Westerveld M, Katz KH, Schneider KC, et al. The etiology and outcome of cerebral ventriculomegaly at term in very low birth weight preterm infants. Pediatrics 1999;104:243-8.
33. Fox LM, Choo P, Rogerson SR, Spittle AJ, Anderson PJ, Doyle L, et al. The relationship between ventricular size at 1 month and outcome at 2 years in infants less than 30 weeks' gestation. Arch Dis Child Fetal Neonatal Ed 2014;99:209-14.
34. Savman K, Blennow M, Hagberg H, Tarkowski E, Thoresen M, Whitelaw A. Cytokine response in cerebrospinal fluid from preterm infants with posthaemorrhagic ventricular dilatation. Acta Paediatr 2002;91:1357-63.

35. Whitelaw A, Cherian S, Thoresen M, Pople I. Posthaemorrhagic ventricular dilatation: new mechanisms and new treatment. Acta Paediatr Suppl 2004;93:11-4.
36. Srinivasakumar P, Limbrick D, Munro R, Mercer D, Rao R, Inder T, et al. Posthemorrhagic ventricular dilatation-impact on early neurodevelopmental outcome. Am J Perinatol 2013;30:207-14.
37. Lo M, Kishimoto J, Eagleson R, Bhattacharya S, de Ribaupierre S. Does ventricular volume affect the neurodevelopmental outcome in infants with intraventricular hemorrhage? Childs Nerv Syst 2020;36:569-75.
38. Beijst C, Dudink J, Wientjes R, Benavente-Fernandez I, Groenendaal F, Brouwer MJ, et al. Two-dimensional ultrasound measurements vs. magnetic resonance imaging-derived ventricular volume of preterm infants with germinal matrix intraventricular haemorrhage. Pediatr Radiol 2020;50:234-41.
39. Jary S, De Carli A, Ramenghi LA, Whitelaw A. Impaired brain growth and neurodevelopment in preterm infants with posthaemorrhagic ventricular dilatation. Acta Paediatr 2012;101:743-8.
40. O'Hayon BB, Drake JM, Ossip MG, Tuli S, Clarke M. Frontal and occipital horn ratio: a linear estimate of ventricular size for multiple imaging modalities in pediatric hydrocephalus. Pediatr Neurosurg 1998;29:245-9.
41. Radhakrishnan R, Brown BP, Kralik SF, Bain D, Persohn S, Territo PR, et al. Frontal occipital and frontal temporal horn ratios: comparison and validation of head ultrasound-derived indexes with MRI and ventricular volumes in infantile ventriculomegaly. AJR Am J Roentgenol 2019;213:925-31.
42. Brouwer MJ, de Vries LS, Kersbergen KJ, van der Aa NE, Brouwer AJ, Viergever MA, et al. Effects of posthemorrhagic ventricular dilatation in the preterm infant on brain volumes and white matter diffusion variables at term-equivalent age. J Pediatr 2016;168:41-9.
43. Boswinkel V, Steggerda SJ, Fumagalli M, Parodi A, Ramenghi LA, Groenendaal F, et al. The CHOPIn Study: a multicenter study on cerebellar hemorrhage and outcome in preterm infants. Cerebellum 2019;18:989-98.

50 Years Ago in *The Journal of Pediatrics*

Best Practices to Control Fever in Children

Steele RW, Tanaka PT, Lara RP, Bass JW. Evaluation of sponging and of oral antipyretic therapy to reduce fever. J Pediatr 1970;77:824-9.

Fever is the body's physiologic response to underlying infection or inflammation, and hence it is pertinent to look for this underlying cause and treat the same. However, fever is associated with discomfort, and it is believed that antipyretics should be administered to relieve discomfort rather than to lower the body temperature.

Fifty years ago, Steele et al evaluated the role of sponging and oral antipyretic therapy to reduce fever in children. The study compared acetaminophen alone with acetaminophen and sponging with various solutions (tepid water, ice water, and equal parts of 70% isopropyl alcohol and tepid water). They concluded that sponging with ice water or alcohol in water was equally effective, and superior to sponging with tepid water, but associated with significantly more discomfort. They also demonstrated the effectiveness of combining sponging with acetaminophen.

In the last 50 years, nothing much has changed as far as parental anxiety and concern regarding high body temperature. Many parents administer antipyretics or resort to sponging even though there is minimal or no fever. As many as one-half of the parents administer incorrect doses of antipyretics, with approximately 15% giving supratherapeutic doses of acetaminophen or ibuprofen.[1]

The American Academy of Pediatrics recommends the use of either acetaminophen or ibuprofen in children with fever who seem to be distressed, and not solely for reducing body temperature.[2] External cooling methods such as tepid water or ice water sponging can lower the body temperature without improving comfort. The use of alcohol baths is not recommended because there have been reports of adverse events associated with systemic absorption of alcohol. According to the National Institute for Health and Care Excellence guidelines, physical modalities like fanning and sponging are no longer recommended.[3] Mefenamic acid is not recommended for use in children owing to its serious side effects. Physical methods may also cause shivering if the cooling is too much or too quick. The saga confirms the age-old saying that the simplest of problems do not have simple solutions!

Vikram Bhaskar, MD
Piyush Gupta, MD, FAMS
Department of Pediatrics
University College of Medical Sciences
Delhi, India

References

1. Li SF, Lacher B, Crain EF. Acetaminophen and ibuprofen dosing by parents. Pediatr Emerg Care 2000;16:394-7.
2. Sullivan JE, Farrar HC. Fever and antipyretic use in children. Pediatrics 2011;127:580-7.
3. NICE Guideline Updates Team (UK). Fever in under 5s: assessment and initial management. London: National Institute for Health and Care Excellence (UK). www.nice.org.uk/guidance/ng143. Accessed May 20, 2020.

Appendix

ELVIS Study Group Members.

1. Kuo S. Han, MD, PhD, Division of Neuroscience, Department of Neurosurgery, University Medical Center Utrecht, Utrecht, the Netherlands.

2. Hendrik J. ter Horst, MD, Department of Neonatology, University Medical Center Groningen, Groningen, the Netherlands.

3. Koen P. Dijkman, MD, Department of Neonatology, Máxima Medical Center, Veldhoven, the Netherlands.

4. David Ley, MD, Department of Pediatrics, Institute of Clinical Sciences, Lund, Sweden.

5. Vineta Fellman, MD, Department of Pediatrics, Institute of Clinical Sciences, Lund, Sweden.

6. Timo R. de Haan, MD, Department of Neonatology, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, the Netherlands.

7. Annemieke J. Brouwer, MD, Department of Neonatology, University Medical Center Utrecht, Utrecht, the Netherlands; University of Applied Sciences, Utrecht, the Netherlands.

8. Manon J.N.L. Benders, MD, PhD, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands; University Medical Center Utrecht, Utrecht Brain Center, the Netherlands.

9. Jeroen Dudink, MD, MSc, PhD, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands; University Medical Center Utrecht, Utrecht Brain Center, the Netherlands.

10. Ellen van't Verlaat, MD, Department of Neonatology, Erasmus Medical Center, Rotterdam, the Netherlands.

11. Paul Govaert, MD, Department of Neonatology, Erasmus Medical Center, Rotterdam, the Netherlands.

12. Renate M.C. Swarte, MD, Department of Neonatology, Erasmus Medical Center, Rotterdam, the Netherlands.

13. Monique Rijken, MD, Department of Neonatology, Leiden University Medical Center, Leiden, the Netherlands.

14. Gerda van Wezel-Meijler, MD, PhD, Department of Neonatology, Isala Women and Children's Hospital, Zwolle, the Netherlands.

15. Thais Agut Quijano, MD, Department of Neonatology, Hospital Sant Joan de Deu, Barcelona, Spain.

16. Uli Barcik, MD, Department of Neonatology, Hospital Sant Joan de Deu, Barcelona, Spain.

17. Amit M. Mathur, MD, Division of Newborn Medicine, Edward Mallinckrodt Department of Pediatrics, Washington University School of Medicine, St Louis, Missouri, USA.

18. Andre M. Graca, MD, PhD, Department of Neonatology, Hospital de Santa Maria, Lisbon, Portugal.

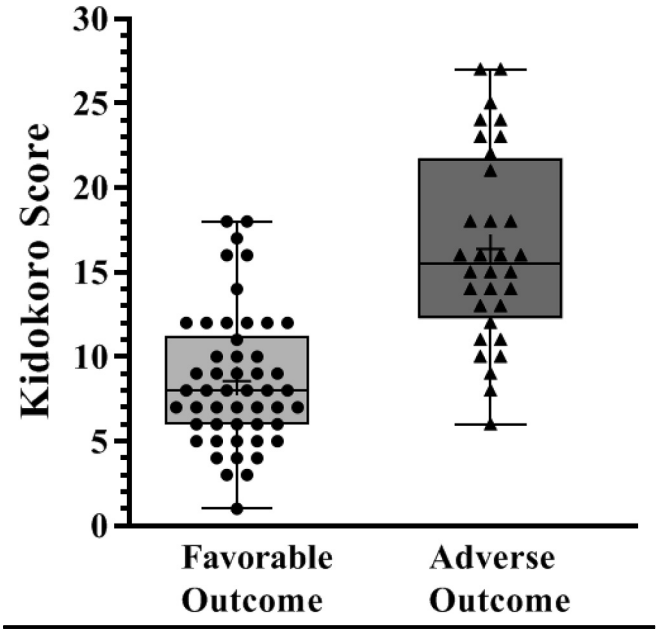

Figure 3. Box plot graphs showing the distribution of the Kidokoro scores in relation to the outcome.

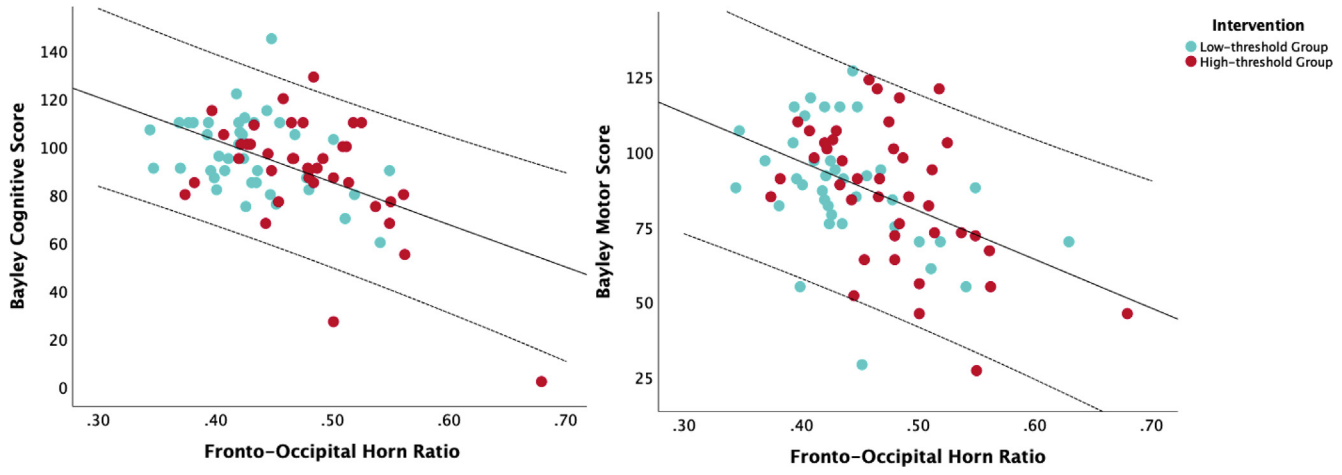

Figure 4. Scatter plot graphs with linear regression lines showing the relationship between the Bayley cognitive (*left*) and motor score (*right*), and frontal and occipital horn ratio. *Solid line* represents the mean and *dashed lines* represent 95% CIs.

Table II. Type and severity of CP with respect to grade of IVH

Variables	Low threshold group	High threshold group
Grade III	1/36 n = 1, GMFCS level III bilateral spastic CP	4/30 n = 1, GMFCS level I-II unilateral spastic CP n = 1, GMFCS level I-II bilateral spastic CP n = 2, GMFCS level III ataxic/dyskinetic
PVHI	9/17 n = 5, GMFCS level I-II unilateral spastic CP n = 1, GMFCS level II bilateral spastic CP n = 3, GMFCS level III-V bilateral spastic CP	10/17 n = 8, GMFCS level I-II unilateral spastic CP n = 1, GMFCS level III-V unilateral spastic CP n = 1, GMFCS level III-V bilateral spastic CP

GMFCS, Gross Motor Function Classification System; *PVHI*, periventricular hemorrhagic infarction.
Data are presented as numbers.