Association Between Early Echocardiography Screening of Low Systemic Blood Flow and Intraventricular Hemorrhage in Preterm Infants: a Multicenter Study

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Abstract

Objective

To determine whether early screening for low systemic blood flow is associated with reduced intraventricular hemorrhage in preterm infants.

Study design

Prospective, observational multicenter study in nine neonatal intensive care units. Preterm infants younger than 33 weeks of gestational age were eligible. The exposure was protocolized early echocardiography screening for low systemic blood flow. Our main outcome was ≥ grade II intraventricular hemorrhage or death within the first 7 days of life. The main analysis used the inverse probability of treatment weighting based on propensity scores.

Results

332 preterm infants (131 in the intervention group and 201 in the control group) were included. Early echocardiography screening was associated with a significant reduction in ≥ grade II intraventricular hemorrhage or early death [odds ratio 0.285 (95% CI: 0.133–0.611); p = 0.001].

Conclusions

Early echocardiography screening for low systemic blood flow may reduce the incidence of intraventricular hemorrhage in preterm infants.

INTRODUCTION

Low systemic blood flow (LSBF) is the hallmark of a transient circulatory insufficiency that may occur during the transition from fetal to neonatal physiology, especially in preterm infants. Myocardial contractility and relaxation are inherently impaired in preterm infants compared to full-term neonates [1–4] As a result, the preterm myocardium has poor tolerance to increased afterload after separation from the placenta and limited ability to deal with increased preload after the establishment of pulmonary blood flow.[5–7] These factors contribute to decreased cardiac output and may cause end-organ hypoperfusion and predispose preterm infants to brain ischemia and intraventricular hemorrhage (IVH). Other factors, such as a ductal left-to-right shunt, pulmonary hypertension or mechanical ventilation, may further compromise systemic perfusion. LSBF, as determined by echocardiography measurement of superior vena cava flow (SVCf), has been associated with IVH.[8] However, the use of inotropes to increase SBF has not demonstrated to prevent IVH or to have an effect on long-term outcomes in small and underpowered studies.[9,10] In addition, the use of vasoactive drugs, especially dopamine, has been associated with increased morbimortality.[11–14] As a consequence, the use of inotropes to treat LSBF or even the clinical utility of measuring SVCf in daily practice remains controversial.[9,10,15–17]

Our predefined hypothesis was that attaining a normal and stable SBF during the transitional period may preserve brain perfusion and contribute to preventing ischemic-reperfusion injury to the brain. Therefore, the objective of the present study was to assess whether early echocardiography screening for LSBF and guided inotropic therapy (abbreviated as ECHO) are associated with a reduced occurrence of IVH in preterm infants.

METHODS

Cohort

A prospective multicenter study was carried out in 9 neonatal intensive care units from September 1, 2020, to September 1, 2021. Infants born less than 33 weeks of gestational age were eligible. The exclusion criteria included hypotension requiring vasopressors or clinically suspected pulmonary hypertension at the time of echocardiography screening; congenital heart disease; genetic syndromes; major congenital malformations; IVH detected in the first 3 hours of life; unavailable researcher; and a lack of informed consent.

Exposure

Our exposure variable was protocolized early echocardiography screening of LSBF (ECHO). Accordingly, we defined an intervention group consisting of 5 centers that performed early echocardiography and used this information to guide inotrope therapy and a control group consisting of 4 centers that did not perform early ECHO (see supplemental data).

Protocol for echocardiography and hemodynamic management in the intervention and control groups.

By definition, all centers in the intervention group had a policy for echocardiographic diagnosis and treatment of LSBF in place during the study period, while centers in the control group did not. Researchers from both groups were asked to record SBF measurements at 6, 12, 24, 48 and 72 hours of life as part of the study protocol. However, the thresholds to indicate treatment with an inotrope reflected current practice and varied among centers within the intervention group: a low SVCf < 45 to < 55 ml/kg/min, a low right ventricular output (RVO) from < 100 to < 150 ml/kg/min and a low main pulmonary artery peak Doppler velocity (MPA_{Vpeak}) from < 0.45–0.6 m/sec. In the intervention group, preterm infants who met the unit criteria for LSBF received an inotrope per protocol. Most centers used dobutamine as a first-line treatment at an initial dose of 5 mcg/kg/min and a maximal dose of 10–15 mcg/kg/min. In the intervention group, inotropic treatment was titrated according to echocardiography during the first 72 hours. In the control group, echocardiography information was not provided to the treating physician unless a specific request was made. The use of echocardiography for clinical reasons outside the study protocol schedule was permitted in both groups. The definition and hemodynamic approach to arterial hypotension as well as the management of patent ductus arteriosus (PDA) were protocolized in all units (see supplemental methods and Table s1).

To assess whether ECHO resulted in different uses of vasoactive medications during the first 3 days of life we arbitrarily defined 3 different strategies post hoc: the pure inotropic strategy (any dobutamine or milrinone dose or epinephrine dose up to 0.2 mcg/kg/min); the pure vasopressor strategy (dopamine dose > 5 mcg/kg/min or epinephrine dose > 0.2 mcg/kg/min or any norepinephrine dose); and the mixed inotropic vasopressor strategy (dopamine up to 5 mcg/kg/min as a sole agent or a combination of dobutamine/milrinone with > 5 mcg/kg/min of dopamine or > 0.2 mcg/kg/min of epinephrine or any dose of norepinephrine).

Intraventricular hemorrhage diagnosis

IVH diagnosis and grading were based on cranial ultrasound. IVH was graded according to the Volpe criteria.[18] The sonographer was not involved in the study and was blinded to the information regarding echocardiography or vasoactive treatment. Cranial ultrasound was performed on the 1st, 3rd, 7th, 14th and 28th days of postnatal life and at 36 weeks of postmenstrual age. For study purposes, IVH grading was defined as the maximal Volpe grade recorded until the seventh day of life.

Data collection

Each participant center designated one or two researcher collaborators. Collaborators were centrally trained in the study protocol and were responsible for data acquisition and performance of echocardiography. These researchers had at least 3 years of experience in targeted neonatal echocardiography. Clinical data were prospectively recorded according to the SEN-1500 national registry.[19] The data were entered by the collaborators into a general database using a web-based application.

Outcomes

The main outcome was ≥ grade II IVH (grade II, grade III and/or periventricular infarct) or early death (ED)[20,21]. We chose this outcome because there is evidence that grade II IVH is associated with a significantly worse prognosis than grade I IVH. [20] ED was defined as death in the first 7 days of life and was included in the composite outcome given that more than 90% of IVH cases occur within the first week of life.[22] The secondary outcomes were any grade IVH, grade III IVH-periventricular infarct, Grade III IVH-periventricular infarct and/or ED and posthemorrhagic ventricular dilatation requiring shunt placement.

Statistical analysis

The data are summarized as the mean (standard deviation) and median (interquartile range) according to the data distribution, and categorical data are summarized as numbers (percentages). Multiple imputation was used to deal with missing data if less than 30%. Otherwise, complete-case analysis was performed. The echocardiographic parameters of SBF were analyzed using ANOVA for repeated measures. The effects of time and time by group interactions were assessed to investigate whether SBF trajectories differed between preterm infants with and without the main outcome (≥ grade II IVH or ED) according to which study group they belonged to or whether they received inotropes for the treatment of LSBF.

For outcome analysis, we used a propensity score (PS)-based approach, namely, inverse probability of treatment weighting (IPTW), with the aim of controlling confounding factors that may influence the occurrence of IVH.[23–25 22,26–28] Briefly, IPTW uses weights based on

the PS to create a synthetic sample in which the distribution of chosen covariates is balanced independent of treatment assignment. The PS was estimated by logistic regression with the study group as the dependent variable in relation to the prognostic variables (supplemental digital content). Outcomes were compared between the intervention and control groups in the IPTW cohort by generalized estimating equation regression with a robust variance estimator to account for correlated data. A generalized mixed-effects model regression with hospital as a random effect and study group as a fixed effect was also used to account for the clustered nature of data.

Complementary analysis included multivariate logistic regression models in the original cohort for the main outcome and selected secondary outcomes, multivariate logistic regression in the subgroup of preterm infants younger or older than 29 weeks of gestational age for the main outcome, a negative outcome control analysis in the original cohort and in the IPTW cohort and a sensitivity analysis using IPTW (with a new specification of the PS) after excluding infants exposed to any hemodynamic intervention that may have been triggered by the use of echocardiography.[29]

Sample size

Assuming recruitment at a 1:1 ratio and a potential loss rate of 10%, 120 preterm infants in each of the study groups were necessary to detect a difference of 10% compared to 25% in the main outcome (≥ grade II IVH or ED) between the intervention and control groups. [30] (power of 0.8 and alpha error of 0.05). [31]

RESULTS

During the study period, 456 preterm infants below 33 weeks of gestational age were assessed for eligibility. One hundred thirty-one and 201 preterm infants completed the analysis in the intervention and control groups, respectively (Figure 1). There were no differences in the proportions of excluded infants or in specific reasons for exclusion between the study groups (supplementary Table s2).

The clinical characteristics and hemodynamic management of the patients are summarized in Table 1. Twenty-nine (22.1%) preterm infants in the intervention group were diagnosed and treated for LSBF per protocol, whereas 6 (2.9%) received open-label inotrope for LSBF in the control group (p<0.001). The need to treat arterial hypotension was not different between the intervention and control groups [21 (16%) vs 23 (11.4%); p=0.228]. The use of inhaled nitric oxide for pulmonary hypertension was more frequent in the intervention group [11 (8.4%) vs 4 (2%); p=0.007]. Overall, thirty-six (27.5%) preterm infants in the intervention group and 27 (13.4%) preterm infants in the control group were treated with vasoactive medications during the first 3 days of life (p=0.001). Dobutamine was more frequently used in the intervention group (86.1% vs. 25.9%, p<0.001), while dopamine was more frequently used in the control group (88.9% vs. 27.8%, p<0.001). There were no differences in the use of epinephrine or norepinephrine, but the maximal dose of epinephrine was greater in the control group than in the intervention group (0.55 vs. 0.20 mcg/kg/min, p=0.037). Overall, a purely inotropic strategy (63.5%) predominated in the intervention group, and a purely vasopressor strategy (55.6%) predominated in the control group.

All echocardiography measurements had >30% missing values, so the data were not imputed. Complete data on echocardiography measurements of SBF were available for 191 infants from 7 centers (121 in the intervention group and 70 in the control group). Preterm infants in the intervention group had higher values of MPAVpeak and RVO at 6, 12, 24 and 48 hours compared to the control group (p<0.05 in all instances) (supplemental Table s3) The analysis of the trajectories of the echocardiography parameters showed that preterm infants who experienced the main outcome (≥ grade II IVH or ED) had lower SBF values and remained in a low-flow zone from 6 to 24 hours of life despite belonging to the intervention or control group or receiving inotropic drugs per-protocol or as open-label treatment for LSBF (Figure 2)

Overall, 86 (26%) preterm infants in the cohort experienced IVH of any grade, 45 (13.6%) experienced ≥ grade II IVH, and 27 (8.2%) experienced grade III IVH and/or periventricular infarct. IVH was first detected by ultrasound at a mean (SD) of 35 (22) hours of life, without significant differences between the study groups. No IVH was detected beyond the first 7 days of life.

The IPTW attained an adequate balance of measured prognostic factors of IVH between the intervention and control groups (see Table 2 and supplemental Table s4). The results of the primary analysis based on IPTW are shown in Table 3. Preterm infants in the intervention group had a lower incidence of ≥ grade II IVH or ED than did those in the control group in the original cohort [9.9% vs. 19.4%, odds ratio (OR) 0.458 (95% CI: 0.234-0.895); p=0.022] and in the IPTW cohort [8% vs. 23%, OR 0.285 (0.133-0.611); p=0.001]. The mixed effect model accounting for clustering within neonatal units also confirmed the association between the intervention and reduced ≥ grade II IVH or ED [OR=0.292 (95% CI=0.149-0.572); p<0.001]. The occurrence of any grade IVH or high-grade IVH as well as posthemorrhagic ventricular dilatation was also lower in the intervention group.

Supplementary analysis

Complementary analysis using multivariate regression was concordant with the primary analysis, revealing an independent association between the intervention and ≥ grade II IVH or ED [OR=0.227 (0.09-0.556), p=0.001]. The use of dopamine [OR: 4.8 (95% CI: 2.1-13.3, p=0.001], delivery room resuscitation [OR 3.2 (95% CI: 1.5-.7.4; p=0.003] and CRIB II [OR 1.3 (95% CI: 1.2-1.4); p<0.001] were other factors independently associated with ≥ grade II IVH or ED (supplemental Table s5). Subgroup analysis revealed a significant association between the intervention and > grade II IVH or ED only in preterm infants younger than 29 weeks of gestational age [OR=0.140 (95% CI=0.04-0.451); p=0.001] but not in older infants (supplemental Table s6 and s7)

A new propensity score was estimated by logistic regression after excluding infant who received any hemodynamic intervention (namely, vasoactive medications, hydrocortisone, fluid boluses, inhaled nitric oxide or PDA treatment) during the first 3 days of life. Balance diagnostics were analogous to the main analysis. IPTW achieved a good balance of all prognostic factors used to estimate the PS between the intervention and control groups (standardized differences ranging -4.8% to +10.1%). This sensitivity analysis did not reveal a reduced incidence of > grade II IVH or ED in the intervention group compared to the control group neither in the original cohort [OR 0.402 (95% CI: 0.11-1.4; p=0.165] nor in the IPTW cohort [OR 0.389 (0.17-1.4) p=0.142] (supplemental Table s8)

Multivariate regression also showed a significant association between the intervention and reduced grade III IVH-periventricular venous infarct or ED [OR: 0.359 (95% CI: 0.130-0.991); p=0.048] and reduced grade III IVH-periventricular infarct [odds ratio 0.253 (95% CI: 0.08-0.756); p=0.014] (supplementary Table s9 and s10)

The negative control analysis did not reveal an association between the intervention and a set of selected preterm morbidities (need for mechanical ventilation, PDA treatment, late-onset sepsis, necrotizing enterocolitis bronchopulmonary dysplasia and death) nor in the original cohort neither in the IPTW cohort (supplemental Table s11)

DISCUSSION

IVH is still a common complication causing significant morbidity and mortality[32]. In this prospective, multicenter observational study, early ECHO screening for LSBF was associated with a reduction in the occurrence of IVH and posthemorrhagic ventricular dilatation. As in previous studies, we confirmed the association between LSBF and the occurrence of IVH. Ischemia–reperfusion injury is one of the main pathogenic mechanisms of IVH.[30,33] The germinal matrix is vulnerable to fluctuations in blood flow due to impaired cerebral autoregulation.[34] A period of relative end-organ hypoperfusion followed by an abrupt increase in cerebral blood flow often precedes IVH.[35] Our limited analysis of echocardiography data showed that infants with ≥ grade II IVH or EDs remained in the low-flow zone during the first 24 hours of life, irrespective of the study group or inotropic treatment. Our findings reinforce the concept that attaining a stable SBF during the first 24 hours of life is important for preventing IVH.

Only a few studies have assessed the impact of echocardiography-guided inotropic treatment of LSBF on preterm brain injury. Most of these studies failed to identify a benefit from measuring and treating LSBF, but these studies were largely underpowered.[9,10,17] Recently, a large before-after single-center study of extremely preterm infants with a gestational age < 27 weeks showed that the implementation of early targeted neonatal echocardiography-guided hemodynamic management improved survival rates without high-grade IVH from 66–81%. [36] Our results are in line with this study.

There are several reasons why ECHO screening may reduce the incidence of IVH. First, early detection of LSBF triggers the indication of inotropic drugs irrespective of blood pressure. As expected, the use of early ECHO resulted in the use of different vasoactive drugs, with a preference for inotropes over vasopressors. Vasopressors increase systemic vascular resistance and may cause cerebral vasoconstriction without necessarily increasing SBF, which in turn may worsen ischemia–reperfusion injury.[37] The use of vasopressors, especially dopamine, has been associated with IVH and worse neurological outcomes.[12,36] In fact, in our complementary analysis, dopamine use was an independent predictor of ≥ grade II IVH or ED.

Second, early ECHO screening may detect other hemodynamic conditions that need to be addressed specifically, such as hypovolemia, pulmonary hypertension or clinically silent hemodynamically significant PDA.[36,38] For instance, in our study, infants in the intervention group were treated more frequently with inhaled nitric oxide for pulmonary hypertension and received a greater cumulative dose of crystalloids than the control group. Also, early treatment of hemodynamically significant PDA may attenuate the negative effect of left-to-right shunts on cerebral perfusion.[39] In the study by Giesinger RE et al., the introduction of routine echocardiography screening for extremely preterm infants was associated with an increase in medical treatment for PDA and a reduction in the need for surgical or

percutaneous interventions.[36] However, in our study, there were no differences in the proportion of preterm infants who received medical treatment for hemodynamically significant PDA or in the timing of treatment between the intervention group and the control group. This can be explained by the use of early echocardiography screening of hsPDA in both groups and by the use of similar treatment criteria. In addition, serial echocardiography may help to better titrate the dose of vasoactive drugs or refine other aspects of hemodynamic management, such as the potential deleterious effect of mechanical ventilation.[40] According to our sensitivity analysis excluding infants exposed to hemodynamic interventions that may have been triggered by the use of early ECHO, the risk of IVH or death was not lower in the intervention group, which suggested that the sum of cointerventions and not only inotropes played a role in the observed reduction in IVH. Notably, the main difference between the present study and previous LSBF trials is that we assessed the effect of exposure to echocardiography rather than to inotropes. We speculate that exposure to echocardiography may have additional benefits beyond the indications for inotropes, but these need further exploration.

Limitations

Our study has several limitations. This was an observational study; therefore, there is an inherent risk of confounding. We tried to mitigate this bias using a PS-based approach. However, there may be unmeasured confounding factors that influenced our results apart from the use of ECHO. Additionally, the intervention and control groups were split between centers. There may be many differences in procedures, policies and complexity between units that may have contributed to improved IVH. These included but were not limited to ventilator management, feeding advancement, type and frequency of monitoring. We tried to account for these hospital-level factors by using generalized mixed effects regression for clustered data, which was consistent with the primary analysis. Additionally, our negative control analysis did not reveal an association between the study group and improvements in other outcomes. The results of our sensitivity analysis suggest that other cointerventions associated with ECHO may have played a role in the observed reduction in the occurrence of IVH. However, in our study, we focused on ECHO-guided vasoactive medication use; therefore, it is impossible to ascertain which other specific cointerventions triggered by ECHO may have contributed to our results. Finally, although the SBF measurements were consistent and standardized, each center included in the intervention group used its own thresholds to treat LSBF. These are important sources of heterogeneity that preclude a clear recommendation of how ECHO should be used to define and treat LSBF.

CONCLUSIONS

In this multicenter study, routine echocardiography screening for LSBF was associated with a reduced incidence of IVH. However, the precise role of inotropes in the observed benefit is uncertain. Our results warrant a multicenter randomized trial of echocardiography-guided hemodynamic management in preterm infants.

Abbreviations

Hs-PDA, hemodynamically significant patent ductus arteriosus

IPTW, inverse probability of treatment weighting

IVH, intraventricular hemorrhage

LSBF, low systemic blood flow

$MPA_{Vpeak,}$ main pulmonary artery peak Doppler velocity

PDA, patent ductus arteriosus

PS, propensity score

RVO, right ventricular output

SVCf, superior vena cava flow

Declarations

ETHICAL APPROVAL

The study protocol was approved by the Institutional Review Board at the participating centers. Parents were approached before study entry and gave their consent for participation.

Conflicts of interest

Authors have no conflicts of interest to declare.

Ethical approval and consent to participate:

The study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board (CEIm Complejo Asistencial Universitario de León, Spain). Parents were approached before study entry and gave their consent for participation.

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Contributors statement

Sandra Terroba-Seara and Ignacio Oulego-Erroz conceived and designed the study, acquired the data, analyzed the data and drafted the manuscript.

Daniel Palanca-Arias, Zenaida Galve-Pradel, Sara Delgado-Nicolás, Alicia Pérez-Pérez, Jorge Rodríguez-Ozcoidi, Ana Lavilla-Oíz, María Carmen Bravo, Paula Mendez-Abad, Lorena Rodeño-Fernández, Jon Montero-Gato, Cristina Vega-Del Val, Javier Rodríguez-Fanjul, Juan Mayordomo-Colunga and Iosune Alegría-Echauri participated in the study design and suggested protocol modifications, acquired the data, and critically reviewed the first and subsequent drafts.

Alicia Pérez- Álvarez provided advice on the statistical plan analysis and performed advanced statistics.

All the authors approved the final manuscript for submission and agree to be accountable for all the aspects of the work.

Data sharing statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Tables

Table 1: Clinical characteristics and in-hospital clinical course during the first week life

	INTERVENTION (n=131)	CONTROL (N=202)	MISSING /IMPUTED	P
Newborn characteristics				
Ethnicity			6	
-Caucasian	82 (62.6%)	147 (73.1%)		
-Hispanic	20 (15.3%)	17 (8.5%)		
-African	9 (6.9%)	13 (6.5%)		.013
-Arabic	10 (7.6%)	9 (4.5)		
-Gipsy	4 (3.1%)	14 (7%)		
-Asiatic	6 (4.6%)	1 (0.5%)		
Sex (male)	68/131 (51.9%)	114/201 (56.7)	5	.390
Gestational age (weeks)	29.5 (2.7)	29.3 (2.3)	0	.683
<29 weeks	53 (40.4%)	75 (37.3%)	0	.565
Height (cm)	38.2 (4.7)	38 (3.9)	23	.652
Birth weight (grams)	1281 (471)	1218 (374)	3	.202
DR resuscitation	30/131 (22.9%)	44/201 (21.8%)	1	.829
Apgar score at 1 min	5.8 (2.3)	6.2 (2.2)	2	.765
Apgar score at 5 min	7.5 (2.2)	8.1 (1.7)	1	.133
CRIB II	6.9 (4.9)	6.4 (4)	30	.147
Surfactant for RDS	68/131 (51.9%)	82/201(40.7%)	1	.047
Mechanical ventilation	47/131 (35.9%)	70/201 (34.8%)	0	.845
Pneumothorax	2 (1.5%)	2 (1%)	0	.665
Minimal pCO_2*	35.4 (7.9)	37.4 (6.8)	4	.204
Hypocapnia (pCO_2 <30 mmHg)*	31 (23.7%)	26 (12.9%)	4	.011
Early-onset sepsis (<72 h)	6/131 (4.5%)	27/201 (13%)	0	.008
Maximum CRP (<72 h) (mg/dl)	5.4 (12)	5.2 (11.5)	9	.848
Minimum hemoglobine*	14.4 (2.6)	15.2 (2.7)	2	.017
Early anemia (Hb<12 gr/dl)*	23 (17.6%)	26 (12.9%)	2	.246
Thrombocytopenia ($<100.000/mm^3$)*	12 (9.2%)	18 (9%)	6	.949
Maternal and gestation characteristics				
Maternal age	32.8 (6)	32.9 (6)	0	.955
Maternal smoking	17 (13%)	28 (13.9%)	32	.804
Maternal obesity	8 (6.1%)	16 (8%)	38	.666
Gestational diabetes	15 (11.5%)	17 (13.4)	0	.595
Preeclampsia	18/131 (13.7%)	35/201 (17.4%)	1	.372
Maternal chorioamnionitis	34/131 (25.9%)	16/201 (8%)	1	.000
IUGR	18/131 (13.7%)	34/201 (16.9%)	2	.437

Antenatal steroids	117/131 (89.3%)	186/201 (92.5%)	1	.309
Magnesium sulfate	92/131 (70.2%)	144/201 (71.6%)	9	.781
Twin pregnancy	44/131 (33.6)	41/201 (20.4%)	0	.007
Cesarean delivery	84/131 (64.1%)	105/201 (52.2%)	0	.033
Approach to cardiovascular support				
Treatment of LSBF*	29 (22.1%)	6 (3%)	0	<.001
Treatment of aHT*	21 (16%)	23 (11.4%)	0	.228
Hydrocortisone for aHT*	9 (6.9%)	6 (3%)	0	.096
Fluid boluses *	13 (9.9%)	18 (9%)	0	.778
Cumulative fluid dose (ml/kg)*	15 (10-20)	10 (10-10)	0	.028
Inhaled nitric oxide for PH*	11 (8.4%)	4 (2%)	0	.007
Hs-PDA	27 (20.6%)	36 (17.9%)	0	.540
PDA medical treatment	17 (13%)	30 (14.9%)	0	.619
Early treatment (<72h)	11 (8.4%)	15 (7.5%)	0	.757
Use of vasoactive medications*	36 (27.5%)	27 (13.4%)	0	.001
-Dobutamine	31 (86.1%)	7 (25.9%)	0	<.001
-Dopamine	10 (27.8%)	24 (88.9%)	0	<.001
-Epinephrine	14 (38.9%)	8 (29.6%)	0	.446
-Norepinephrine	2 (5.6%)	3 (11.1%)	0	.419
-Vasoactive strategy				
• Pure inotropic • Pure vasopressor • Inotropic/vasopressor	23 (63.8%) 2 (5.6%) 11 (30.6%)	10 (37%) 15 (55.6%) 2 (7.4%)	0	<0.001

*Refers to the first 3 days of life. aHT, arterial hypotension, CRIB II, Clinical Risk Index for Babies 2nd version; CRP, C-reactive protein; DOL, day of life; DR, delivery room; hsPDA, hemodynamically significant patent ductus arteriosus; IUGR, intrauterine growth restriction; LSBF, low systemic blood flow; MV, mechanical ventilation, PH, pulmonary hypertension; RDS, respiratory distress syndrome. Categorical variables were compared using the chi-square test or Fisher's exact test, while continuous variables were compared using Student's t test for independent samples.

Table 2: Distribution of prognostic risk factors used in the calculation of the propensity score between the intervention and control groups before and after inverse probability of treatment weighting.

	ORIGINAL COHORT			IPTW COHORT		
PS calculation variable	**INTERVENTION (n=131)**	**CONTROL (n=201)**	**SD**	**INTERVENTION (n=317)**	**CONTROL (n=326)**	**SD**
Non-caucasian	49 (37.4%)	54 (26.9%)	**12.8%**	108 (34.1%)	101 (31%)	3.7%
Maternal age	32.8 (6)	32.9 (6)	-1.6%	32.8 (6.2)	32.6 (6.2)	3.3%
Maternal smoking	17 (13%)	28 (13.9%)	-0.9%	43 (13.6%)	44 (13.5%)	0.1%
Sex (male)	68 (51.9%)	114 (56.7)	-9.3%	168 (52.8%)	178 (54.6%)	-3.2%
Gestational age (weeks)	29.5 (2.7)	29.3 (2.3)	3.9%	29.3 (2.5)	29.3 (2.4)	0%
Birth weight (grams)	1281 (471)	1218 (374)	1.4%	1230 (436)	1218 (383)	2.9%
Cesarean delivery	84 (64.1%)	105 (52.2%)	**24.2%**	195 (61.3%)	187 (57.4%)	6.1%
Twin pregnancy	44 (33.6)	41 (20.4%)	**30.2%**	87 (27.4%)	82 (25.1%)	-2.6%
Chorioamnionitis	34 (25.9%)	16 (8%)	**49.2%**	49 (15.4%)	50 (15.3%)	0.1%
Gestational diabetes	15 (11.5%)	17 (13.4)	-2%	40 (12.6%)	38 (11.7%)	1%
Magnesium sulfate	92 (70.2%)	142 (71.6%)	-3%	229 (72%)	235 (72.1%)	-0.2%
Antenatal steroids	117 (89.3%)	186 (92.5%)	-1.2%	293 (92.1%)	301 (92.3%)	-0.6%
Preeclampsia	18 (13.7%)	35 (17.4%)	**-10.2%**	57 (17.9%)	53 (16.2%)	2.1%
DR resuscitation	30 (22.9%)	44 (21.8%)	2.2%	73 (23%)	82 (25.1%)	-2.4%
Apgar score at 5 min	7.5 (2.2)	8.1 (1.7)	3%	7.8 (1.9)	7.9 (1.9)	-4.7%
CRIB II	6.9 (4.9)	6.4 (4)	1%	6.7 (4.5)	6.7 (4.4)	0%
Early anemia*	23 (17.6%)	26 (12.9%)	5.1%	45 (14.2%)	51 (15.6%)	-1.5%
Early hypocapnia*	31 (23.7%)	26 (12.9%)	**12%**	53 (16.7%)	51 (15.6%)	1.2%
Thrombocytopenia*	12 (9.2%)	18 (9%)	0.2%	22 (6.9%)	27 (8.3%)	-1.4%
Surfactant	68 (51.9%)	82 (40.7%)	**23%**	148 (46.7%)	154 (47.2%)	-0.7%
Mechanical ventilation	47 (35.9%)	70/201 (34.8%)	2.2%	109 (24.4%)	123 (37.7%)	-4.1%
Early-onset sepsis	6 (4.5)	27/201 (13)	**-20%**	27 (8.5%)	34 (10.4%)	-2%
Maximal CRP value*	5.4 (12)	5.2 (11.5)	1.7%	4.8 (9.8)	4.6 (10.4)	2.3%

* refers to the first 3 days of life. DR, delivery room resuscitation; CRIB II, Clinical Risk Index for Babies 2nd version; CRP, C-reactive protein. SDs, standardized differences. Standardized differences were calculated as the difference in the means divided by the pooled standard deviation for continuous variables ($X_{Intervention}$-$X_{Control}$)/$\sqrt{(S^2_{Intervention} + S^2_{control})/2}$ and as the phi coefficient ($P_{intervention}$-$P_{control}$/$\sqrt{[(1 - P_{intervention})P_{intervention} + (1 - P_{control})P_{control}/2)]}$ for binary variables.(49)

Table 3: Outcome analysis in the intervention and control groups (the main outcome ≥ grade II IVH or ED is highlighted in bold type)

	ORIGINAL COHORT			IPTW COHORT			
OUTCOMES	**INTERVENTION (N=131)**	**CONTROL (N=201)**	**OR (95% CI)[a]**	**INTERVENTION (N=317)**	**CONTROL (N=326)**	**OR (95% CI)[a]**	**OR (95% CI) [b]**
Any grade IVH	23 (17.6%)	64 (31.8%)	0.456 (0.266-0.782);p=.004	46 (14.6%)	118 (36.2%)	0.296 (0.160-0.549);p<0.001	0.301 (0.128-0.702);p=0.006
Any grade IVH or ED	26 (19.8%)	67 (33.3%)	0.495(0.294-0.833);p=0.008	53 (16.8%)	122 (37.4%)	0.332 (0.193-0.6);p<0.001	0.337 (0.166-0.682);p=0.003
≥ grade II IVH	10 (7.6%)	36 (17.9%)	0.379 (0.181-0.793); p=.010	18 (5.8%)	71 (21.8%)	0.217 (0.09-0.502)p<0.001	0.223 (0.102-0.487);p<0.001
≥ grade II IVH or ED	**13 (9.9)**	**39 (19.4%)**	**0.458 (0.234-0.895) P=.022**	**25 (8%)**	**75 (23%)**	**0.285(0.133-0.611);p=0.001**	**0.292 (0.149-0.572);p<0.001**
Grade III IVH-PVI	8 (6.1%)	20 (9.9%)	0.589 (0.251-1.38); p=.222	14 (4.4%)	37 (11.3)	0.364(0.133-0.995);p=0.049	0.452 (0.254-0.822);p=0.009
Grade III IVH-PVI or ED	11 (8.4%)	24 (11.9%)	0.676 (0.319-1.43) p=.306	21 (6.7%)	43 (13.1)	0.473(0.193-0.114)p=0.096	0.522 (0.306-0.889);p=0.017
PHVD needing intervention	5 (3.8%)	17 (8.5%)	0.430 (0.154-1.19) P=.105	10 (3.2%)	33 (10.1%)	0.278 (0.09-0.893)p=0.032	0.249 (0.07-0.905);p=0.035

[a]The associations between the study group and outcomes were estimated by generalized estimating equations with robust variance estimator. [b]Generalized mixed effect model with the hospital as the random effect and the study group as the fixed effect. IPTW, inverse probability of treatment weighting; intraventricular hemorrhage intraventricular hemorrhage; msWMI, moderate-severe white matter injury; ED, early death (death within the first 7 days of life); GA, gestational age; PMA, postmenstrual age; PLV, periventricular leukomalacia; PVI, periventricular infarct.

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