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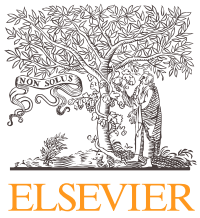

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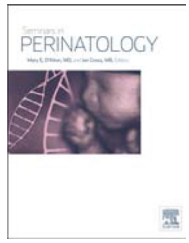

Impact of early screening echocardiography and targeted PDA treatment on neonatal outcomes in "22-23" week and "24-26" infants

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ABSTRACT

The hemodynamically significant patent ductus arteriosus (hsPDA) is a controversial topic in neonatology, particularly among neonates at the earliest gestational ages of 22^{+0}-23^{+6} weeks. There is little, to no data on the natural history or impact of the PDA in extremely preterm babies. In addition, these high-risk patients have typically been excluded from randomized clinical trials of PDA treatment. In this work, we present the impact of early hemodynamic screening (HS) of a cohort of patients born 22^{+0}-23^{+6} weeks gestation who either were diagnosed with hsPDA or died in the first postnatal week as compared to a historical control (HC) cohort. We also report a comparator population of 24^{+0}-26^{+6} weeks gestation. All patients in the HS epoch were evaluated between 12-18h postnatal age and treated based on disease physiology whereas the HC patients underwent echocardiography at the discretion of the clinical team. We demonstrate a two-fold reduction in the composite primary outcome of death prior to 36 weeks or severe BPD and report a lower incidence of severe intraventricular hemorrhage (n=5, 7% vs n=27, 27%), necrotizing enterocolitis (n=1, 1% vs n=11, 11%) and first-week vasopressor use (n=7, 11% vs n=40, 39%) in the HS cohort. HS was also associated with an increase in survival free of severe morbidity from the already high rate of 50% to 73% among neonates <24 weeks gestation. We present a biophysiological rationale behind the potential modulator role of hsPDA on these outcomes and review the physiology relevant to neonates born at these extremely preterm gestations. These data highlight the need for further interrogation of the biological impact of hsPDA and impact of early echocardiography directed therapy in infants born less than 24 weeks gestation.

Introduction

In the field of neonatology there is wide variation in the approach to patent ductus arteriosus (PDA) evaluation and management. Although observational studies have consistently linked a hemodynamically significant PDA (hsPDA) with many complications of prematurity including intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), adverse neurodevelopmental outcome and mortality[1-3], uncertainty regarding

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treatment remains. Over 60 randomized trials have failed to demonstrate improved outcomes with medical treatment[4]; however, these trials have major methodological limitations. Most trials have randomized few, if any, preterm infants born at 22- or 23- weeks' gestational age (GA). In addition, hemodynamic significance has not been adjudicated according to standardized echocardiography criteria with high rates of spontaneous closure in control groups, medical therapy in the treatment arm is not universally successful, and substantial rates of open-label medical therapy is being provided to control patients. Importantly, these trials fail to focus on the highest risk group of neonates, namely those born <27 weeks and especially the 22^{+0}-23^{+6} week GA cohort. Extremely preterm infants are surviving in greater numbers[5] and at even earlier GAs leading to neonatologists caring for higher risk patients who may have greater risk of PDA attributable morbidity. Biophysiologic contributors to increased burden of illness include a less muscularized ductus[3], an imbalance of vasodilators and vasoconstrictors to which the neonates' response is immature[1], delayed postnatal cardiopulmonary adaptation[6], impaired response to afterload[7], more severe respiratory distress syndrome (RDS)[1,7] and immature antioxidant defenses.[8] These factors combine to heighten the possible impact of acute and chronic ductal shunt on both morbidity and mortality.

Severe BPD[9] is a predictor of morbidity and mortality and has been associated with hsPDA tolerant management in a variety of studies.[10-12] As compared to neonates with grade 1-2 BPD, patients with grade 3 BPD have a greater than 2-fold higher risk of adverse outcomes including severe IVH, retinopathy of prematurity, NEC or bowel perforation, supplemental oxygen at discharge and length of stay.[13] It is biologically plausible, as suggested by a recent post-hoc analysis of a pilot randomized trial[14], that successful early elimination of hsPDA shunt may be associated with a reduced risk of BPD among extremely preterm neonates. In our center, a comprehensive hemodynamic screening program with a standardized approach to PDA evaluation and therapy was introduced in 2018. The primary aim of this study was to evaluate the impact of early hsPDA management based on targeted neonatal echocardiography (TnECHO) evaluation in extremely preterm infants born at 22^{+0}-23^{+6} weeks GA, as compared to a historical epoch during which exclusively clinically "symptomatic" treatment after postnatal day 7 in the presence of echocardiography confirmed PDA in a prior epoch, on the primary composite outcome of death <36 weeks or severe BPD.

Methods

A cohort of neonates born < 27 weeks GA who were either inborn or admitted within 24h postnatal age to a single quaternary Neonatal Intensive Care Unit (University of Iowa) was evaluated. The study was approved by the Institutional Review Board. Patients were identified from a clinically maintained database and the patient's electronic medical record was used to abstract data.

Criteria for eligibility

All neonates during the study period were considered eligible unless major anomalies, congenital heart disease [other than PDA, small ventricular septal defect (<1mm) or atrial communication] were present, or resuscitation was either incomplete or not provided. Patients born at 22^{+0}-23^{+6} weeks were analyzed and compared between two epochs. Babies born 24^{+0}-26^{+6} weeks were analyzed as an exploratory comparative subgroup. Patients were recruited in two distinct epochs; Hemodynamic Screening (HS; 10/2018-04/2022) or Historical Controls (HC; 01/2010-12/2017). All patients were included if diagnosed with hsPDA or died in the first postnatal week. The inclusion of patients who died in the first postnatal week in the historical epoch was to account for unknown hsPDA status, particularly among HC patients who routinely had echocardiography on approximately postnatal day 7, due to the strong association of early mortality and presence of PDA on day 3.[15] To further justify this approach, in the HS epoch, all but 1 patient (n=1/5, 20%) who died in the first postnatal week had a hsPDA; a similar assumption was, therefore, made for the HC epoch given no overall change in PDA prevalence was observed. HsPDA was defined based on the Iowa PDA score ≥6[16] [Table 1]. The dates 01/2018-09/2018 were not analyzed to account for the introduction of a new clinical program and implementation of a modified approach to management.

Clinical data collection

Factors associated with severe BPD were collected. This includes maternal and pregnancy variables (e.g., maternal illnesses, fertility treatment, obesity, chorioamnionitis, preterm, prolonged rupture of membranes (PPROM)[17], maternal smoking, selective serotonin reuptake inhibitor (SSRI) use, substance use disorders and age). Delivery mode, fetal presentation (breech), antepartum steroids, magnesium sulfate, antibiotics, tocolysis and delayed cord clamping were abstracted. Neonatal factors that were collected included gestational age and birthweight. Elements of the Score for Neonatal Acute Physiology Perinatal Extension-II score[18] was used to adjudicate illness severity in the first 24 postnatal hours and characteristics of cardiovascular therapy were collected as was adequacy of oxygenation using oxygenation index (OI) and/or respiratory severity score (RSS) if partial

Table 1 – Iowa PDA score.[1]

Measurement	0	1	2
Pulmonary vein D wave (cm/s)	<30	30-50	≥50
Mitral valve E wave (cm/s)	<45	45-80	≥80
Isovolumetric relaxation time (ms)	>50	30-50	≤30
Left atrium to aortic root ratio	<1.3	1.3-2.2	≥2.2
Left to Right Ventricular output ratio	≤1.5	1.5-2.0	≥2.0
Aortic/Peripheral Doppler flow reversal	Forward/Absent		Reversed
Ductus diameter indexed to weight (mm/kg)	<1.5	1.5-3.0	≥3.0

pressure of arterial oxygen was not available. As a measure of ventilation stability, the highest partial pressure of carbon dioxide (CO_2) and lowest CO_2 in the first 24h were collected and used to calculate the maximal change in CO_2 on the first postnatal day. Details of hsPDA management were abstracted. Duration of hsPDA was defined from the first echo demonstrating hsPDA until interventional closure or the first echo demonstrating hemodynamic non-significance after which no re-manifestation occurred. If the first echo demonstrated hsPDA, day 0 was designated the start date of PDA exposure.

Evaluation and management of hsPDA in the HS epoch

In addition to standard neonatal care, described below, during the HS epoch, all neonates underwent comprehensive TnECHO between 12- and 18-hours postnatal age followed by physiology-guided therapy. TnECHOs were exclusively performed by 5 neonatologists (REG, ARB, AHS, PJM, DRR) with advanced hemodynamics training.[19] Each TnECHO consisted of 80-110 clips and included a comprehensive appraisal of systemic and pulmonary hemodynamics, objective measurement of biventricular cardiac function and characterization of shunts. Additionally, a screen for major congenital heart disease, head ultrasound and an assessment of central line position were performed as part of the same study. Studies were conducted using a GE Vivid E90 with a 12mHz multisector probe (GE Medical, Milwaukee, Wisconsin) with warmed, sterile gel and archived for co-review by pediatric cardiology. The usual duration of TnECHO evaluation was less than 20 minutes. Management was guided by the specific physiology identified by the Neonatal Hemodynamics team as in Fig. 1. The usual approach to hsPDA treatment was to administer acetaminophen 15mg/kg Q6h for 3 days followed by repeat TnECHO; a further 4 days of therapy with acetaminophen is provided if response was demonstrated. Indomethacin 0.2mg/kg followed by 2 doses of 0.1mg/kg at 12h intervals was used as second line therapy. Shunt modulation strategies, including avoidance of anemia (transfusion threshold 11.7), avoidance of hypocapnemia and tolerance of lower target saturations (85-90%) were commonly used. Prior to 2019, bedside surgical closure was the standard of care for definitive closure if there was failure of 2-3 courses of medical therapy or contraindication to pharmacotherapy. Since 2019, percutaneous device closure in the pediatric catheterization laboratory has been the standard of care; specifically, either the Amplatzer Piccolo Occluder (Abbott, Santa Clara USA) or Micro Plug Set (KA Medical, Roseville, USA) were used endovascularly, or surgical ligation was performed if contraindications to percutaneous closure were present. All medical treatment was followed by a re-appraisal within 24h of the end of therapy. Follow-up evaluations for patients without hsPDA were performed at a minimum of postnatal day 7, between day 14-21 and at 8 postnatal weeks with more frequent TnECHOs as dictated by clinical condition. If TnECHOs were clinically indicated prior to the screening window, a repeat evaluation was performed between 12-18h to re-appraise physiology.

Evaluation and management of hsPDA in the HC epoch

During the HC period, echocardiograms were performed by pediatric sonographers and interpreted by Pediatric Cardiologists. It was standard of care for some clinicians to perform an echocardiogram on postnatal day 6 or 7 to screen for PDA, whereas others relied exclusively on the appearance of clinical signs of hemodynamic significance. The first echocardiogram was a complete anatomic study of sufficient quality to rule out congenital heart disease. Thereafter, a focused study was typically performed to evaluate for ductal patency. Follow-up evaluations were performed at the request of the

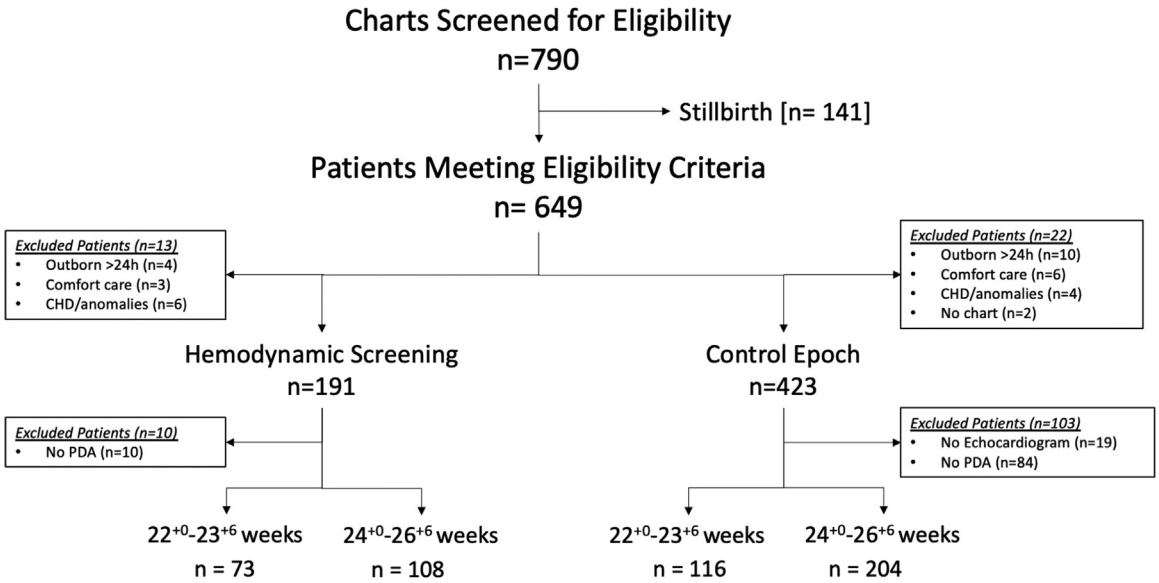

Fig. 1 – Management Algorithm used for Neonates in the Hemodynamic Screening Epoch. GA=gestational age; TnECHO = targeted neonatal echocardiography; PDA = patent ductus arteriosus; iNO = inhaled nitric oxide; HRF = hypoxemic respiratory failure; mod = moderate; PH = pulmonary hypertension; ppm = parts per million; LV = left ventricle; RV = right ventricle.

clinical team when signs of hsPDA were judged to be present. A standard report was provided for each echocardiogram via the electronic medical record. Each report contained ductal size, direction, and a qualitative assessment of left heart size but there was no standardized echocardiography definition of hemodynamic significance. Echocardiograms were routinely performed within 24h of the completion of a course of therapy.

Management of hsPDA when diagnosed included up to 3 courses of indomethacin (0.2mg/kg followed by 0.1mg/kg x 2 doses at 12h intervals) followed by surgical ligation if the ductus remained significant.

Standard neonatal care

The approach to care of extremely preterm infants includes active obstetric management with antepartum steroids beginning at 21^{+5}, cesarean section for fetal indications starting at 23^{+0} weeks, magnesium sulfate for IVH prophylaxis, standard latency antibiotics for preterm prolonged rupture of membranes (PPROM) and routine delayed cord clamping (DCC) for 30 seconds [introduced in 2012]. The approach to neonatal respiratory care includes the utilization of 2.0 endotracheal tubes as needed, first intention high frequency jet ventilation (HFJV), surfactant prophylaxis ≤24 weeks, no early extubation, universal caffeine administration, vitamin A prophylaxis, and midline positioning for the first 14 days.

Outcome

The primary outcome was a composite of death before 36 weeks or severe BPD defined using Jensen[9] criteria as grade 3. Secondary outcomes included death and severe BPD as individual outcomes, survival free of morbidity (severe IVH using Papile's criteria[20] as ≥ grade 3, any necrotizing enterocolitis, grade 3 BPD using the Jensen[9] criteria), pulmonary hemorrhage, pneumothorax, PDA therapy (medical and interventional), intestinal complications and retinopathy of prematurity treatment. In addition, the approach to cardiovascular and PDA care were compared between the two epochs.

Statistics

This cohort was recruited from a prospectively collected clinical cohort of all neonates meeting GA criteria (<27 weeks) for screening [Fig. 2]. The original Iowa Hemodynamics Screening cohort (unpublished to date) included 646 patients and sample size was calculated to detect a 20% reduction in the composite of death or severe IVH. All eligible patients from the larger cohort were screened for inclusion in this sub-study. The 24^{+0}-26^{+6} week cohort was included as a comparator because of previous data suggesting that the benefits of PDA treatment are less significant in older patients.[10] Data was evaluated for normal distribution using the Shapiro-Wilk test. Univariate analysis was performed. Normally distributed and non-normally

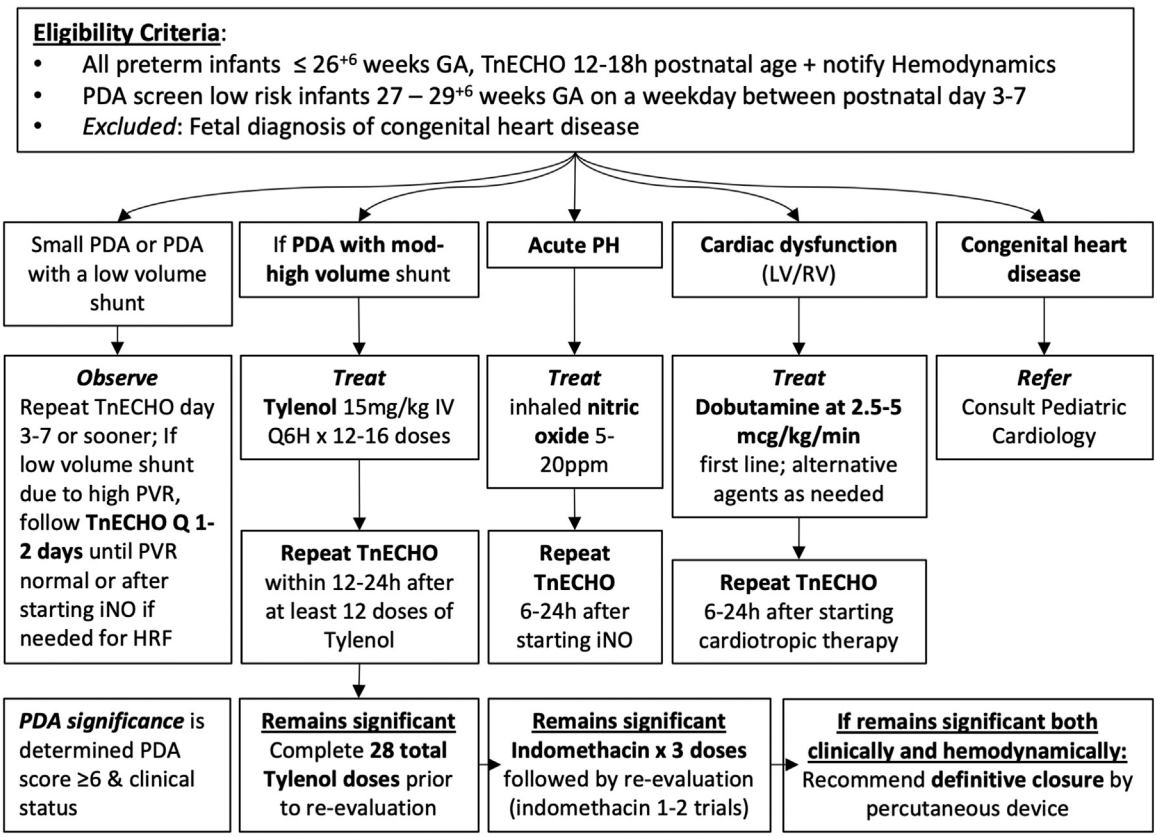

Fig. 2 – Consort diagram of charts screened to ultimate distribution of patients. CHD = congenital heart disease; PDA = patent ductus arteriosus.

distributed data was tested using mean, standard deviation and Student's t-test and median, interquartile range and the Wilcoxon-signed rank test respectively. A p-value of <0.05 was considered significant. In the 22^{+0}-23^{+6} week cohort, binary logistic regression was used to adjust the composite of survival free from grade 3 BPD for birth year in the context of HS. Other independent variables significant on univariate analysis were included in this interrupted time series to account for natural improvement over time due to known and unknown factors. Three models were created which included all variables potentially associated with the primary composite outcome ($p<0.05$) on univariate analysis. The first model adjusted for year of birth to prove a linear relationship. The second model included HS alone and the final model included both birth year and HS epoch to evaluate if HS was associated with outcome independent of birth year. SPSS Version 29 (IBM Corp., Armonk, NY, USA) was used.

Results

From the original cohort of 646 patients, 189 were included in the 22^{+0}-23^{+6} (n=73 HS, n=116 HC) cohort and 312 were included in the 24^{+0}-26^{+6} (n=108 HS, n=204 HC) cohort. In the 22^{+0}-23^{+6} week cohort, the HC patients had lower birth weight (p=0.036) and more likely to be female (p=0.007). The HS epoch was characterized by an increase in peri-natal treatments potentially associated with improved outcome including maternal magnesium sulfate (p=0.002) and delayed cord clamping (p=0.005); however, this epoch was also characterized by maternal factors associated with adverse neonatal outcomes including older maternal age (p=0.031), two-fold increase in obesity (p=0.001), a four-fold increase in SSRI use (p=0.01) and a higher rate of maternal drug use ($p<0.04$) [Table 2]. This pattern was similar in the 24^{+0}-26^{+6} week

Table 2 – Neonatal demographics, pregnancy characteristics and perinatal risk factors for extremely preterm infants born at 22^{+0}-23^{+6} and 24^{+0} – 26^{+6} weeks in hemodynamic screening epoch vs historical controls.

	22-23^{+6}			24-26^{+6}		
	Hemodynamic Screening (n=73)	Historical Controls (n=116)	p-value	Hemodynamic Screening (n=108)	Historical Controls (n=204)	p-value
Gestational age (weeks)	23 [22.5, 23.4]	22.9 [22.5, 23.4]	ns	25.6 ± 0.8	25.6 ± 0.9	ns
Birthweight (grams)	556 ± 86	528 ± 95	0.036	776 ± 186	801 ± 162	ns
Female	23 (32)	61 (53)	0.007	56 (52)	112 (55)	ns
Inborn	65 (89)	102 (88)	ns	90 (83)	149 (74)	0.065
5-minute Apgar score	7 [5, 7]	6 [4, 7]	ns	7 [6, 8]	7 [7, 8]	ns
Intubation in delivery room	71 (97)	112 (97)	ns	98 (91)	173 (86)	ns
Maternal/Delivery Protective Factors						
Antepartum steroids			ns			0.016
• None (0)	5 (7)	9/114 (8)		9 (8)	40 (20)	
• Partial (1)	16 (22)	34/114 (30)		24 (22)	51 (25)	
• Complete (2)	52 (71)	71/114 (62)		75 (69)	113 (55)	
Maternal magnesium sulfate	59/71 (83)	50/83 (60)	0.002	88 (90)	72 (41)	<0.001
Delayed cord clamping	33/69 (48)	18/74 (24)	0.005	65/98 (66)	27/190 (14)	<0.001
Maternal antibiotics	60/72 (83)	60/84 (71)	0.089	80/97 (83)	100/171 (59)	<0.001
Pregnancy/Delivery Risk Factors						
Maternal age	30 [25.5, 32]	26 [22, 31]	0.031	29 [25, 33]	28 [23, 32]	0.06
Breech presentation	32/68 (47)	34 (29)	0.018	47 (48)	68 (34)	0.016
Multiple birth	26 (36)	35 (30)	ns	30 (28)	51 (25)	ns
Fertility treatment	6/70 (9)	11/114 (10)	ns	5/93 (5)	16/203 (8)	ns
Antepartum NSAID exposure	4/68 (6)	2 (2)	ns	8/93 (9)	2/202 (1)	0.002
Obesity	29/70 (41)	21 (18)	0.001	39/97 (40)	20/199 (10)	<0.001
Gestational diabetes	5/72 (7)	5 (4)	ns	5/102 (5)	11/202 (6)	ns
Hypertension of pregnancy	2/72 (3)	9/115 (8)	ns	18/106 (17)	23 (11)	ns
Chorioamnionitis	13/71 (18)	13 (11)	ns	6/105 (6)	21/203 (10)	ns
Prolonged rupture of membranes	35 (48)	43 (37)	ns	28 (26)	40 (19)	ns
Maternal smoking	7/71 (10)	21 (18)	ns	25 (23)	44 (22)	ns
Maternal SSRI use	9/72 (13)	3 (3)	0.012	10 (10)	8 (4)	0.04
Maternal Drug use			0.042	79/107 (74)	186/201 (93)	<0.001
• None	58 (80)	105 (90)		20 107 (19)	6/201 (3)	
• Cannabis	9 (12)	8 (7)		3/107 (3)	3/201 (2)	
• Methamphetamine	0 (0)	1 (1)		2/107 (2)	3/201 (2)	
• Opiates	5 (7)	0 (0)		3/107 (3)	3/201 (2)	
• Alcohol	1 (1)	2 (2)				
Induction of labor	2/71 (3)	10/76 (13)	0.032	5 (5)	1 (1)	0.02
Vaginal Delivery	49 (67)	92 (79)	0.09	33 (31)	57 (28)	ns

Mean ± standard deviation; median [interquartile range]; frequency (percent); NSAID = nonsteroidal anti-infalmmatory drug; SSRI = selective serotonin reuptake inhibitior; Gestational hypertension = any hypertensive disorder during pregnancy.

cohort with an additional higher rate of antepartum steroids ($p<0.02$) and more NSAID exposure ($p=0.002$). In both groups, there was a higher rate of breech presentation in the HS epoch.

Influence of HS on hsPDA exposure

In the HS epoch, the first echocardiogram was conducted on postnatal day 0 for all neonates in the $22^{+0-}23^{+6}$ week cohort as compared to a median of day 7 in the HC. There were no episodes of hypothermia or cardiorespiratory instability during or after TnECHO evaluation in the HS epoch. In addition, hsPDA was diagnosed earlier and the median duration of exposure was 13 days shorter ($p<0.001$) [Table 3]. The use of vasopressors in the first postnatal week was lower ($p<0.001$) and restricted to the group of patients who had an earlier prescreening (<12-hours) TnECHO, all of whom had either sepsis (n=3) or perinatal hypoxic ischemic injury (n=4). The rate of medical therapy for PDA was higher ($p<0.001$); however, this was exclusively accounted for by the introduction of acetaminophen as first line therapy in the first postnatal week because there was no difference in indomethacin therapy. In the HS epoch, the rate of interventional closure was 33%, compared to 47% in the HC epoch ($p<0.001$). There was no difference in the rate of hypocapnemia, major fluctuation of CO_2 in the first 24h or incidence of thrombocytopenia. Although hemoglobin was higher in the HS epoch, likely related to DCC, the magnitude of the difference was not deemed clinically significant. In the 24^{+0}-26^{+6} week cohort, there was a reduced need for indomethacin ($p<0.001$) and a reduction in interventional closure by approximately 50%.

Efficacy of acetaminophen therapy in HS epoch

In the cohort of 22^{+0}-23^{+6} week neonates 30 (47%) were treated on postnatal day 0-1 while the remaining 34 treated patients qualified on later TnECHO evaluations at a median of postnatal day 3.[2,5] Of the 64 patients at 22^{+0}-23^{+6} who received medical therapy, 32 (50%) responded with resolution of hemodynamic significance; however, 20/32 (63%) remanifested later and therefore required second line therapy. In the 24^{+0}-26^{+6} group, 46 (62%) qualified for treatment on postnatal day 0-1 while the remaining were treated at a median of postnatal day 4.[2,7] In this group, 52/74 (70%) had a positive response with resolution of hemodynamic significance of whom 23/52 (44%) remanifested. There was, however, no difference in either acetaminophen response (n=0.11) or PDA recurrence (n=0.18) between the GA subgroups. Liver enzymes were not systematically measured; however, there were no noted side effects of acetaminophen. In comparison to the HC epoch, in which 85% of (116/137) in the $22^{+0-}23^{+6}$ and 204/286 (71%) of the 24^{+6}-26^{+6} had hsPDA at day 7, in the HS epoch, only 41/77 (53%) and 56/137 (41%) respectively continued to have hsPDA at a similar time-point.

Impact of HS on acute illness severity

A total of 20/73 neonates (27%) in the 22^{+0}-23^{+6} week cohort underwent clinically indicated echocardiography assessment prior to the official screening window in the HS epoch. Of these, the primary indication for evaluation was either clinician-defined systemic hypoperfusion (n=15) or hypoxemic respiratory failure (n=5). These evaluations occurred at a

Table 3 – Neonatal risk factors, echocardiography trends and approach to cardiovascular management for extremely preterm infants born at 22^{+0}-23^{+6} and 24^{+0} – 26^{+6} weeks in hemodynamic screening epoch vs historical controls.

	22-23^{+6}			24-26^{+6}		
	Hemodynamic Screening (n=73)	Historical Controls (n=116)	p-value	Hemodynamic Screening (n=108)	Historical Controls (n=204)	p-value
Risk factors for PDA						
Thrombocytopenia (platelets < 100)	2/71 (3)	1/83 (1)	ns	5 (5)	10/190 (5)	ns
Change in CO_2	65 [57, 77]	67 [59, 79]	ns	55 [32, 68]	53 [48, 61]	0.084
Lowest CO_2	37 [33, 41]	38 [32, 40]	ns	35 [32, 39]	36 [32, 39]	ns
Mean hemoglobin	13.5 [12.5. 14.6]	12.9 [12.0, 13.9]	0.004	14.2 [13.1, 15.9]	14.2 [12.8, 15.5]	ns
Lowest hemoglobin	12.0 ± 1.6	11.0 ± 2.3	0.001	13.2 [11.2, 14.7]	12.9 [11.5, 14.5]	ns
Echocardiography trends						
Age of first echo (days)	0 [0, 0]	7 [6, 7.8]	< 0.001	0 [0, 0]	6 [5, 7]	<0.001
Age PDA diagnosed (days)	1 [0, 2]	7 [6,8]	< 0.001	0 [0, 3]	6 [5, 7]	<0.001
Days of hsPDA exposure	9 [5, 12]	22 [17, 31]	<0.001	8 [4, 13]	20 [14, 28]	<0.001
First week vasopressor use	7/61 (11)	40/103 (39)	<0.001	4/70 (6)	31/198 (16)	0.038
PDA Medical treatment	64 (88)	58/90 (64)	<0.001	74 (69)	165 (85)	0.002
Doses of Acetaminophen	28 [17, 48]	0 [0, 0]		27 [16, 35]	0 [0, 0]	
Doses of Indomethacin	6 [3, 6]	4 [3,9]	ns	3 [3, 6]	6 [3, 9]	<0.001
PDA Intervention (surgery/ percutaneous)	24 (33)	55 (47)	<0.001	24 (22)	79 (43)	<0.001

PDA = patent ductus arteriosus; CO_2 = partial pressure of carbon dioxide; mean ± standard deviation; median [interquartile range]; frequency (percent); Respiratory severity score = mean airway pressure * fraction of inspired oxygen; SNAPPE-II = Score for Neonatal Acute Physiology Perinatal Extension-II.

Table 4 – Comparison of adverse neonatal outcomes for extremely preterm infants born at 22^{+0}-23^{+6} and 24^{+0} – 26^{+6} weeks in hemodynamic screening epoch vs historical controls.

	$22\text{-}23^{+6}$			$24\text{-}26^{+6}$		
	Hemodynamic Screening (n=73)	Historical Controls (n=116)	p-value	Hemodynamic Screening (n=108)	Historical Controls (n=204)	p-value
Primary Outcome						
Death/Grade III BPD at 36 weeks	17 (23)	53 (46)	0.002	14 (13)	38 (19)	ns
Secondary Outcomes						
Survival free of severe morbidity [NEC, Grade III BPD, Severe IVH]	53 (73)	58 (50)	0.002	92 (85)	138 (68)	<0.001
Neurological						
Severe IVH	5 (7)	27/101* (27)	<0.001	6 (6)	39 (20)	<0.001
Respiratory						
Bronchopulmonary Dysplasia [at 36 weeks]	4/60 (7)	16/79 (20)	0.028	7 (7)	19 (10)	ns
• Ventilator dependent [Grade III]	52/60 (87)	48/79 (61)	0.001	64 (63)	111 (60)	ns
• Non-invasive positive pressure [Grade II]						
Pulmonary hemorrhage	0/69 (0)	6/108 (6)	0.08	2 (2)	7 (4)	ns
Pneumothorax	3 (4)	9 (8)	ns	2 (2)	19 (9)	0.015
Gastrointestinal						
Intestinal perforation	6/72 (8)	13/100 (13)	ns	3 (3)	7 (4)	ns
Necrotizing enterocolitis	1 (1)	11/99 (11)	0.01	0 (0)	11 (5)	0.01
Ophthalmologic						
Laser/Avastin treatment for ROP	10 (14)	6/76 (8)	ns	5 (5)	11 (6)	ns
Mortality characteristics						
Death	14 (19)	38 (33)	0.045	6 (6)	28 (14)	0.035
Age at death (days)	12.5 [3, 40]	2 [1, 8]	0.014	10 [8, 37]	15 [3, 120]	ns
Death in the first postnatal week	5 (7)	26 (22)	0.005	1 (1)	11 (5)	0.064
Acute Illness Severity in the first 24h						
Inhaled nitric oxide	8/71 (11)	35/111 (32)	0.002	1 (1)	14 (7)	0.024
Vasoactive use	34/72 (47)	45/109 (41)	ns	31 (29)	36 (18)	0.042
Mean respiratory severity score	2.2 [1.8, 2.7]	2.7 [2.2, 3.6]	< 0.001	1.9 [1.6, 2.1]	1.8 [1.5, 2.4]	ns
Mean oxygenation index	4.5 [3.7, 6.1]	5.6 [4.2, 7.5]	0.001	3.5 [2.8, 4.5]	3.6 [2.6, 4.9]	ns
Sodium bicarbonate administraion	3/71 (4)	35/109 (32)	< 0.001	5 (5)	57 (29)	<0.001
SNAPPE-II score	29 [21, 34.5]	38 [29, 49]	< 0.001	14 [9, 22]	19 [14, 30]	0.001
Highest lactate (mmol/L)	5.1 [3.9, 8.2]	7.1 [3.6, 13]	ns	4.6 [3.2, 7.1]	5.1 [2.9, 8.8]	ns
Lactate > 4mmol/L for ≥ 6 hours	31/71 (44)	43/87 (49)	ns	32 (31)	28 (26)	ns
Hydrocortisone treatment in the first week	49 (67)	69 (60)	ns	50 (46)	59/198 (30)	0.006
Maximum vasopressor-inotrope score	6.5 [4.5, 12.6]	10 [5, 14]	ns	5 [5, 10]	10 [5, 15]	0.086

* of patients who survived to have a head ultrasound; Median [interquartile range]; frequency (percent); BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; ROP = retinopathy of prematurity; NEC = necrotizing enterocolitis; PDA = patent ductus arteriosus.

median of 4.5 [1.9, 7.3] hours; of note, all patients had echocardiography re-evaluation during the screening window. The echocardiography findings included acute pulmonary hypertension alone (n=1), acute pulmonary hypertension with right ventricular dysfunction (n=7), biventricular dysfunction (n=3), hsPDA (n=6), transitional circulation (n=1) and vasodilator shock (n=2). Treatment was prescribed based on physiology. As can be seen from Table 4, physiology-guided therapy was associated with a lower rate of iNO use (p<0.002), lower respiratory requirements (p<0.001) and fewer sodium bicarbonate boluses (p<0.001). The SNAPPE-II score was also lower (p<0.001) in the HS epoch. Similar findings were seen in the cohort of more mature patients. Hydrocortisone use in the first week was frequent but similar in both epochs among the 22^{+0}-23^{+6} week infants whereas administration of hydrocortisone was more frequent in the HS epoch in the ≥24 week patients (p=0.006).

Impact of HS on neonatal morbidities

There was a 50% reduction (p<0.002) in the primary composite outcome of death before 36 weeks or grade 3 BPD in the 22^{+0}-23^{+6} week patients. This was accompanied by an increase (p=0.002) in survival free of severe morbidity to 73% and a reduction of a variety of other important neonatal outcomes [Table 4]. Of note, reductions in the rate of severe IVH (p=0.001), and NEC (1% incidence, p=0.01) were seen in both subgroups. Of note, the patient in the <24-week cohort

Table 5 – Logistic regression to adjust composite of survival without severe BPD at 36 weeks for confounders among 22^{+0}-23^{+6} week neonates.

	Model 1		Model 2		Model 3	
Variable	Odds ratio [95% CI]	p-value	Odds ratio [95% CI]	p-value	Odds ratio [95% CI]	p-value
Hemodynamic Screening			5.4 [2.2, 12.9]	<0.001	5.1 [1.3, 20.4]	0.023
Birth year	1.3 [1.08, 1.47]	0.003			1.1 [0.80, 1.3]	ns
Birthweight	1.0 [0.99, 1.1]	ns	1.03 [0.99, 1.01]	ns	1.8 [1.5, 2.0]	ns
Delayed cord clamping	1.6 [0.64, 3.9]	ns	1.3 [0.54, 3.3]	ns	1.0 [0.99, 1.08]	ns
Magnesium sulfate	1.8 [0.73, 4.5]	ns	1.6 [0.65, 4.2	ns	1.64 [0.65, 4.2]	ns
Breech presentation	0.81 [0.36, 1.8]	ns	0.88 [0.38, 2.0]	ns	0.88 [0.38, 2.03]	ns
Female	1.15 [0.75, 1.8]	ns	1.03 [0.44, 2.42]	ns	1.03 [0.44, 2.4]	ns
Maternal SSRI exposure	0.96 [0.18, 5.1]	ns	0.91 [0.17, 4.8]	ns	0.92 [0.17, 4.9]	ns
Induction of Labor	0.39 [0.08, 2]	ns	0.36 [0.07,1.8]	ns	0.37 [0.07, 1.5]	ns
Maternal obesity	0.70 [0.29, 1.7]	ns	0.65 [0.26, 1.6]	ns	0.65 [0.26, 1.7]	ns
Maternal drug use	0.65 [0.16, 2.7]	ns	0.83 [0.19, 3.6]	ns	0.83 [0.19, 3.6]	ns

SSRI = selective serotonin reuptake inhibitor.

categorized as NEC initially presented with inspissated meconium with a prolonged post-operative course before developing septic shock with NEC on autopsy near term and is therefore may not be considered representative of classic NEC. Although an increase in the burden of grade 2 BPD was seen in the 22^{+0}-23^{+6} week subgroup, it is not unexpected; specifically, this may be due to the noted reduction in death (survival advantage) and ventilator dependence. Additionally, an increase in requirement for non-invasive positive pressure support is likely among survivors. In the HS epoch, fewer of the 22^{+0}-23^{+6} week infants died (p=0.045); in addition, death occurred at an older median age (p=0.014) and was less likely in the first postnatal week(p=0.005). There were no cases of pulmonary hemorrhage, a non-significant but relevant trend of an already very low rate. In the older cohort, there was no difference in the primary outcome or rates of BPD; there was an increase in survival free of severe morbidity (p<0.001) and major reductions in the rate of NEC (p=0.01) and severe IVH (p<0.001) were seen [Table 4]. After adjustment for confounders in the 22^{+0}-23^{+6} week cohort, year of birth (model 1) and HS era (model 2) were independently associated with survival without severe BPD. After adjustment for both HS and year of birth (model 3), only HS predicted a higher likelihood of survival free from severe BPD with an odds ratio of 5.1 [1.3, 20.4] (p=0.023) [Table 5].

Discussion

The literature available to guide an approach to hsPDA among the population of infants born <24 weeks gestation is limited. In this cohort study we present both acute illness severity and neonatal outcomes of the first and largest published single cohort of 22^{+0}-23^{+6} week neonates with hsPDA. Further, we compared a modern epoch in which all neonates underwent screening echocardiography-guided physiological assessment and physiology-guided therapy at <24h postnatal age, to a historical population which already had exceptional clinical outcomes with 67% overall survival and 54% survival free of severe BPD. We demonstrate that the addition of HS was independently associated with a reduction in the composite primary outcome of death before 36 weeks or grade 3 BPD with an OR of 5.1, independent of year of birth and other relevant variables. Overall mortality for infants receiving early PDA treatment in the HS epoch was 14%. In comparison amalgamated Vermont Oxford Network data suggest that a similar demographic (neonates 22^{+0}–23^{+6} weeks gestation) had 43% mortality before 36 weeks. This is among other important clinically meaningful improvements in neonatal morbidities such as a reduction in severe intraventricular hemorrhage and necrotizing enterocolitis.

Unlike the term ductus which is biologically designed to constrict and functionally close shortly after the loss of the placental circulation at birth, the preterm ductus has several factors that contribute to its persistent patency. *First*, extremely preterm infants, particularly those at 22-23 weeks' gestation, have no mural vessels in the medial layer, which is exclusively nourished from diffusion or from adventitial vessels. *Second*, there is less intrinsic tone[21], and the walls contain neither intimal folds nor circumferential medial musculature.[22] *Third*, and importantly, the preterm ductus is less responsive to oxygen and more sensitive to both prostaglandin E_2 and nitric oxide.[23] Based on these facts, it is not surprising that the incidence of persistent ductal patency increases with decreasing GA and the median time to spontaneous closure is in excess of 70 days[24] for neonates born at the earliest gestations. It also stands to reason that extremely preterm neonates born at 22-23 weeks may experience the greatest burden of both acute and chronic consequences that may be PDA attributable. In the short term this may equate to the greatest burden of IVH through a putative ischemia-reperfusion mechanism[25,26], the use of early vasopressor therapy including exposure to dopamine with a greater frequency than caffeine[27], and the highest burden of pulmonary hemorrhage.[28] Neonatal morbidities including NEC and BPD are more frequent at the earliest gestation[29,30] and, while certainly multifactorial, hsPDA exposure may be a significant contributor to this burden of illness. Unlike the older cohort presented as a comparator, with its intrinsically low burden of early mortality and severe BPD, it is likely that the high-risk profile may give the extremely preterm infant the greatest likelihood of benefit from this early intervention

approach. That 22-23 weekers are at the canalicular stage lung may be of particular importance. The canalicular lung is more prone to ventilator induced lung injury, in part, due to deficient mature collagen and elastin elements, and surfactant which reduce lung resilience and increase likelihood of micro-atelectasis.[31] Stretching forces at the border of open and atelectatic lung may be up to 5-fold larger than in other ventilated areas.[32] The ventilator induced lung injury which then occurs results in an inflammatory cascade which produces chemokines, cytokines and neutrophil invasion which disrupt lung growth and development.[33].

It is biologically plausible that early acetaminophen may be associated with successful mitigation of ductal shunt for several reasons. *First*, because of the architecture of the preterm ductus, ischemia of the medial muscle is only possible with complete obliteration of trans-luminal flow. Because the decline in pulmonary vascular resistance after birth leads to a progressive left-to-right transductal pressure gradient and therefore establishment of an increasing volume of highly oxygenated blood flow, this may nourish the ductal musculature and promote patency. *Second*, the ductal mural vessels contain progressively more nitric oxide synthase after the first 15 postnatal days, making the preterm duct less sensitive to prostaglandins and therefore non-steroidal medications.[22,34] *Finally*, the cumulative exposure to circulating mediators associated with systemic inflammation which is suspected to be a major contributor to neonatal morbidity[35] may also predispose to ductal patency. Early treatment, with lower cumulative exposure to ductal shunt may be the mechanism by which the rate of severe BPD was reduced in our cohort.

The efficacy of first line acetaminophen of 50-70% in the <24 weeks and ≥24 week GA cohorts respectively is comparable with the literature for non-steroidals.[36,37] Although 40-50% of those that responded to the first course went on to receive either additional courses of acetaminophen or indomethacin, the duration of exposure to shunt was lower than in the HC epoch. Ductal recurrence after initial successful functional closure, although known to occur, has not been well described in the literature. One study, randomizing neonates to standard 3 dose vs 5 days of indomethacin therapy quote a 47% recurrence rate, similar to our population, following standard indomethacin first course.[38] It is reasonable to speculate that the burden of exposure for patients requiring several courses of medical therapy is different among patients with a relapsing remitting course as compared to those with a refractory ductus that remains significant throughout the course of medical therapy. Patients in both categories may eventually require interventional closure, but the burden of shunt and therefore the impact on outcomes may be less in the former relapsing/remitting group.

The literature linking BPD and hsPDA is mixed; however, it is crucial to note that the 22^{+0}-23^{+0} week population is rarely accounted for in either observational or randomized studies despite being, arguably, the sub-population at the greatest risk as highlighted by a recent study.[10] Most randomized trials and commentaries have failed to acknowledge this omission, yet conclusions and practice changes have been extrapolated accordingly. A secular change in practice from an aggressive to a permissive approach to hsPDA has been associated with a 31% increase in the incidence of the composite of death/BPD among infants <26 weeks' gestation with no change in more mature patients.[10] Additionally, although it has been suggested that exposure to a hsPDA for at least 7 days increased risk of BPD or death in one study, important factors, such as timing, duration and magnitude of exposure are often not considered.[3,39] Even a short duration of early exposure may be relevant, as suggested by Clyman *et al*. Their group evaluated a cohort of infants born <28 weeks GA and suggested that 7-13 days of exposure was sufficient to increase the burden of BPD/death.[39] Over time, PDA attributable biological contributors to lung injury accumulate, which may be of relevance to periviable infants with the most immature antioxidant defense system.[8] Hyperoxia has been shown in animal models to worsen lung injury, particularly when combined with hyperventilation[40] Unlike the systemic circulation, which adapts to increased flow by dilating to normalize sheer stress[41] and upregulating expression of nitric oxide synthase[42], the pulmonary circulation reacts negatively to excessive blood flow. Neonatal lambs exposed to a prolonged shunt demonstrate uncoupling of endothelial nitric oxide synthase which has the downstream effect of a shift from NO generation to the production of superoxide which, in turn, binds available NO to make peroxinitrite.[43] Exposure to even 24h of hyperoxia has been shown in preterm lambs to be associated with lung injury and inflammation, particularly when combined with hyperventilation.[44] Infants with a diagnosis of PDA in the HS epoch had lower burden of PDA exposure, which may have contributed to lower likelihood of BPD. In addition, the lower rate of need for interventional PDA closure is also noteworthy, as infants with post-ligation cardiac syndrome are at greater risk of BPD.[45] For all of the above reasons, the reduction in both duration of shunt exposure and interventional PDA closure demonstrated in our study are important reasons to consider early HS and hsPDA treatment.

A secondary benefit of the availability of early comprehensive TnECHO is the ability to serially evaluate patients with disturbed pulmonary or systemic hemodynamics. Although all neonates were evaluated at 12-18h, approximately one quarter of the patients required early evaluation for clinical concern. This resulted in early identification of a variety of pathologies. Of interest, there were 6 patients who presented with hsPDA prior to 12h of age, with the earliest being 4h after birth. It is possible that immaturity is a contributing factor to the timing and magnitude of clinical symptoms of hsPDA; specifically, the extremely immature neonate is at greatest risk of either delay in or failure to augment cardiac output to compensate for shunt. This relates to the fact that the developing fetal myocardium is made up of myofibrils which are small, randomly oriented, peripherally located and disorganized with relatively few sarcomeres in each segment.[46] Mitochondria are present but few in number, and instead glycogen is available in large pools between the myofibrils. Together, this results in a myocardium with an abundance of non-contractile tissue and an inefficient energy source which contribute to the limited ability of the preterm to augment contractility. Early clinical consequences of PDA include metabolic acidosis and hypotension[47], are related to impaired post-ductal cardiac output; yet, clinicians may oftentimes

provide treatments directed at resolution of these symptoms (e.g., vasopressors, base) rather than diagnostic ascertainment. The reduction in vasopressor use in the HS epoch is therefore noteworthy and likely related to early identification and management of shunt, both with strategies to raise pulmonary vascular resistance (e.g., lower target oxygen saturations, permissive hypercapnia) and ductal closure strategies (e.g. acetaminophen, indomethacin). Unlike the disease-targeted therapy provided in the HS epoch, patients in the HC epoch were treated symptomatically for hypotension with dopamine because echocardiography was performed only at the end of the first postnatal week and the physiological diagnosis was unknown. The reduction in severe IVH and NEC may also be related to mitigation of ischemia and ischemia-reperfusion. As it pertains to IVH, systemic hypotension related to hsPDA results in impaired systemic blood flow. Treatment with dopamine, a vasoconstrictor, may improve blood pressure while paradoxically reducing cardiac output[48,49] and has been associated with loss of cerebral autoregulation.[50] Similarly, impaired systemic blood flow followed by an increase in superior mesenteric artery resistance, also associated with dopamine use in preterm infants[48], may predispose vulnerable neonates to NEC. Through reducing the risk of postductal hypotension, and subsequent need for non-specific vasopressors, the compounding effects of systemic vasoconstriction and increased end-organ resistance in the setting of PDA-driven systemic hypoperfusion are avoided.

Limitations

The major limitation of our study is the lack of standardization in the diagnosis of hsPDA and timing of echocardiography after day 7 in the HC epoch. Fortunately, however, echocardiograms were frequent, particularly when a hsPDA had been identified. Importantly, the institutional culture was one of aggressive PDA treatment, thus the current study is essentially evaluating the impact of more standardized PDA evaluation and earlier medical treatment beginning on day 0 vs day 7. Also different in the HS epoch was the use of acetaminophen; although unlikely, it is possible that acetaminophen itself may have positively modulated the likelihood of BPD independent of PDA closure. Important to the interpretation of this study was the increase in peri-natal optimization (e.g., magnesium sulfate, DCC) and concurrent increase in maternal morbidity (e.g. obesity, SSRI use). Although HS was independently associated with survival free of severe BPD on logistic regression, further studies are needed to evaluate the relationship of HS to other neonatal morbidities after adjusting for these potential confounders. A final limitation is in the lack of data surrounding the incidence of chronic pulmonary hypertension. Although we anticipate that there was a reduction in the incidence of chronic pulmonary hypertension proportional to the reduction in severe BPD, based on the emerging literature that non-intervention for PDA is associated with an increased risk, screening echocardiography was not performed consistently in the historical epoch to perform a meaningful comparison.

Conclusion

Among neonates born 22^{+0}-23^{+6} weeks gestation, early hsPDA diagnosis and physiology-targeted treatment was associated with a reduced risk of the composite primary outcome of death before 36 weeks or severe BPD as compared to HC patients. These extremely immature neonates may present with a variety of cardiovascular pathologies in the first 24h, of which hsPDA is one of the most frequent. Given the extreme paucity of literature on hsPDA in the <24 weeks gestation population, it is important that developmental and physiological first principles are considered. These neonates may be particularly disadvantaged due to extreme immaturity, thus magnifying the impact of shunt physiology on pulmonary and other systemic outcomes. It is important for readers to recognize, that effects seen in our center may not be easily generalizable to other centers. Further study in this population is warranted and will be increasingly possible as these extremely preterm infants are more widely resuscitated.

Declaration of Competing Interest

The authors report no potential conflicts of interest.

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