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ORIGINAL ARTICLE

Acetaminophen to avoid surgical ligation in extremely low gestational age neonates with persistent hemodynamically significant patent ductus arteriosus

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OBJECTIVE: The objective of this study was to evaluate the effectiveness of rescue oral acetaminophen in improving echocardiography (echo) indices of patent ductus arteriosus (PDA) shunt volume and avoiding surgical ligation in extremely low gestational age (GA) neonates (ELGANs, <28 weeks) with persistent PDA.

STUDY DESIGN: Retrospective cohort study of ELGANs with moderate or severe PDA at risk for ligation after a practice change introducing oral acetaminophen (60 mg kg^{-1} day^{-1} for 3 to 7 days) to facilitate ductal constriction after indomethacin failure.

RESULTS: Twenty-six infants (median GA 24.4 weeks at birth) with persistent PDA under consideration for surgical ligation were treated with oral acetaminophen at a mean of 27 days of life. Echo indices of shunt volume improved in 12 (46%) infants (3 closed and 9 reduced to mild shunt), all of whom avoided ligation. There was no echo improvement in 14 (54%) infants, of which 8/14 underwent ligation, and ligation was deferred in 6/14 infants, mostly owing to improvement in respiratory stability. Fewer responders than non-responders underwent ligation (0% vs 57%, $P<0.01$), though there were no differences in other neonatal outcomes.

CONCLUSIONS: In ELGANs with persistent significant PDA, rescue therapy with oral acetaminophen was associated with improvement in echo indices of shunt volume and avoidance of ligation in nearly half of infants.

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INTRODUCTION

Observational studies have associated patent ductus arteriosus (PDA) ligation with increased bronchopulmonary dysplasia, severe retinopathy of prematurity and neurodevelopmental impairment in early childhood.[1–3] Although the precise causal mechanism remains uncertain, the administration of general anesthesia or surgical complications such as pneumothorax, left vocal cord paresis or postoperative cardiorespiratory instability may contribute to increased morbidity.[4]

The association of PDA surgery, especially early routine ligation,[5] with adverse neonatal and neurodevelopmental outcomes has resulted in a secular trend toward avoiding or delaying PDA surgery.[6] Extremely preterm infants with a hemodynamically significant PDA now typically undergo a period of conservative management after failure of pharmacotherapeutic closure, with the goal of facilitating spontaneous ductal closure and avoiding surgical ligation.[7] However, persistence of a PDA beyond the first week of life has itself been associated with increased mortality and bronchopulmonary dysplasia, with increased markers of ductal shunting associated with poorer outcomes.[8–10]

An alternative late therapy to achieve PDA closure or restriction would be a valuable tool to avoid ligation and simultaneously reduce an infant's exposure to the circulatory consequences of a large ductal shunt. Randomized trials support the administration of acetaminophen for early PDA closure in preterm infants.[11,12] However, a limited number of studies have evaluated the effectiveness of acetaminophen as salvage therapy to avoid surgical ligation in extremely low gestational age neonates (ELGANs, <28 weeks).[13–15] Studies to date have also predominantly focused on achieving complete ductal closure, an approach that inadequately considers that clinical improvement and avoidance of ligation may be achieved with a reduction of shunt volume (owing to ductal restriction).

The objective of this study was to evaluate the effectiveness of rescue oral acetaminophen treatment in facilitating ductal closure in ELGANs with persistent moderate or severe PDA being considered for surgical ligation.

METHODS

We conducted a retrospective cohort study of ELGANs with persistent moderate or severe PDA being referred for ligation following a clinical practice change introducing oral acetaminophen treatment to facilitate ductal constriction and avoid surgical closure after failure of, or contraindication to, indomethacin.

The neonatal intensive care unit at Sunnybrook Health Sciences Centre is a tertiary perinatal center that admits approximately 160 ELGANs annually. Infants with clinically symptomatic PDA are evaluated in consultation by a neonatologist with expertise in targeted neonatal echocardiography. Infants also undergo an anatomical evaluation by a pediatric cardiologist, both at the time of initial diagnosis of PDA and again prior to surgical ligation. Up to two courses of indomethacin therapy are

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administered to facilitate ductal closure in infants with clinically and echocardiographically significant PDA. Infants with persistent significant PDA after failure of pharmacological and/or conservative management are considered for surgical ligation, a decision made by the attending neonatologist in consultation with the targeted neonatal echocardiography specialist. Conservative management comprises ventilator strategies such as the judicious use of positive end-expiratory pressure to mitigate alveolar edema and permissive hypercapnia with mild acidosis (pH 7.25 to 7.30, $PaCO_2$ (partial pressure of carbon dioxide) 50 to 60 mmHg) to modulate pulmonary vascular resistance and ductal shunting.[16] Fluid restriction and changes in SpO_2 (pulse oximetry) targets are not utilized in our unit owing to limited evidence of efficacy for PDA treatment.[17]

The clinical criteria for surgical ligation include signs of a large ductal shunt (for example, murmur, radiographic cardiomegaly and pulmonary edema) with concomitant respiratory insufficiency and/or end-organ hypoperfusion. Only infants who are dependent on invasive mechanical ventilation or persistent high-level non-invasive respiratory support (that is, non-invasive positive pressure ventilation or non-invasive high frequency oscillatory ventilation with high mean airway pressure or FiO_2 (fraction of inspired oxygen) and inability to wean) are considered candidates for ligation. After being referred for ligation, infants are triaged according to clinical and echocardiographic severity[18] and subsequently transported to our local quaternary surgical referral center for the procedure.

Reports of PDA closure associated with acetaminophen treatment[19,20] led to a clinical practice change in July 2012 whereby infants being considered for surgical ligation were treated with oral acetaminophen (15 mg kg^{-1} $dose^{-1}$ every 6 h for 3 to 7 days) with the goal of effecting ductal closure and avoiding PDA surgery. All infants treated with acetaminophen underwent a comprehensive echocardiography ('echo') evaluation before and within 3 days after the treatment course. Hepatic enzyme monitoring was performed at the discretion of the attending neonatologist.[15,21] Infants who did not show demonstrable improvement in the clinical signs and/or echo indices of PDA shunt volume were referred for surgical ligation.

Eligible infants were identified using the local echocardiography database, as all patients being considered for PDA ligation undergo serial echocardiography. Infants were excluded if they had chromosomal abnormalities or congenital heart disease (other than small or moderate secundum atrial septal defect or small ventricular septal defect).

Two neonatologists with expertise in echocardiography (DEW, FM) and blinded to patient outcomes independently reviewed each (pre- and post-acetaminophen) echocardiogram. Echo indices of PDA hemodynamic significance were measured offline (EchoPAC, GE, Wisconsin USA). For each echo parameter, measurements were performed in triplicate and averaged; each echo parameter was classified as 'mild', 'moderate' or 'severe' (Table 1). The overall echocardiographic hemodynamic significance was summarized as 'mild', 'moderate' or 'severe', based on the majority category among all of the individual echo parameters. Demographic, preoperative and postoperative clinical and outcome data were subsequently collected by a single investigator (DEW).

The primary outcome was the frequency of infants who demonstrated both significant improvement in echo indices of shunt volume (moving from a moderate or severe to a mild or closed ductal shunt) and avoidance of PDA ligation after acetaminophen treatment. Secondary outcomes included mortality, necrotizing enterocolitis stage $\geqslant 2$ (according to the modified Bell's staging[22]), severe retinopathy of prematurity (defined as stage $\geqslant 3$ or stage 2 with disease requiring treatment) and moderate–severe bronchopulmonary dysplasia, which was defined as the need for supplementary oxygen or positive pressure ventilation at 36 weeks corrected GA. Descriptive statistics were used to summarize perinatal and pretreatment and posttreatment characteristics for all study infants. Mean (s.d.) and median (interquartile range (IQR)) were used to characterize normally distributed and skewed data, respectively. The characteristics of acetaminophen responders and non-responders were compared using the chi-square test for categorical variables and Student's *t*-test or Wilcoxon rank-sum test for continuous variables. Pre- vs post-acetaminophen changes in echo indices of ductal shunt volume were evaluated using the Student's *t*-test or McNemar's test, as appropriate. Interobserver variability for the summary evaluation of ductal hemodynamic significance was evaluated using Cohen's kappa statistic.

This study was approved by the local hospital Research Ethics Board.

Table 1. Echocardiography parameters of ductal hemodynamic significance

Parameter	*Hemodynamic significance*		
	Mild	*Moderate*	*Severe*
Ductus arteriosus size and flow pattern			
PDA diameter			
2D diameter, mm	<1.5	1.5–3	>3
PDA:LPA ratio	<0.5	0.5–1	>1
PDA Doppler			
Peak systolic velocity (m/s)[a]	>2.5	1.5–2.5	<1.5
Peak systolic velocity: minimum diastolic velocity	<2	2–4	>4
Pulmonary overcirculation/left heart loading			
LV output (ml kg^{-1} min^{-1})	<300	300–400	>400
LV chamber size	*Z*-score $<+1.5$	$+1.5<Z<+2.5$	$+2.5<$ *Z*-score
LA hypertension			
LA:Ao	<1.5	1.5–2.0	>2.0
Mitral valve E:A ratio[b]	<1		>1
IVRT, ms	>45	30–45	<30
LPA Vmax diastole, m s^{-1}	<0.3	0.3–0.5	>0.5
Systemic steal			
Abdominal aorta	No diastolic reversal	Diastolic reversal	

Abbreviations: Ao, aorta; IVRT, isovolumic relaxation time; LA, left atrium; LPA, left pulmonary artery; LV, left ventricle; mitral valve E:A, early-to-late (atrial contraction) inflow ratio; PDA, patent ductus arteriosus. [a]Very large left to right ductal shunts may have higher peak systolic velocities (>1.5 m s^{-1}), indicating high shunt volume rather than flow restriction. [b]Mitral valve E:A ratio >1 is suggestive of left atrial pressure loading.

RESULTS

From 1 July 2012 to 31 December 2014, 401 ELGANs were admitted to the neonatal intensive care unit. Of these, 32 infants with persistent moderate or severe PDA were considered candidates for surgical ligation after failure of indomethacin treatment. Four infants were not treated with acetaminophen owing to co-morbid necrotizing enterocolitis and underwent surgical ligation. Of the 28 infants treated with oral acetaminophen, one infant died on the fifth day of therapy owing to septic shock, and one infant was excluded from the study owing to the presence of subaortic stenosis.

The remaining 26 infants (GA at birth 24.4 weeks (24.3 to 26.0), birth weight 700 g (633 to 910)) were treated with acetaminophen and were included in the analysis. Of the 26 treated infants, 88% received antenatal corticosteroids, 62% were singletons, 38% were male and 8% were outborn. The median 5-min Apgar score was 7 (5 to 8). Delivery room intubation occurred in 20 (81%) infants, of whom all but 1 was treated with exogenous surfactant. Nineteen of the 26 infants received indomethacin prophylaxis at birth.

Acetaminophen treatment commenced at 25 (±7) days of life at 28.6 weeks (27.6 to 29.8) corrected GA. At the time of the initiation of treatment, the median infant weight was 900 g (817 to 1179), 69% of infants were invasively ventilated and the mean airway pressure (invasive or non-invasive) was 10.4 (±2.9) cm H_2O. In total, infants had been invasively ventilated for 94% (50 to 100) of their neonatal intensive care unit course. In addition, 35% of infants had sustained grade 3 or 4 intraventricular hemorrhage and 23% had developed culture-positive sepsis prior to acetaminophen treatment. The median total indomethacin dose was

Table 2. Changes in echocardiographic indices of PDA hemodynamic significance in responders vs non-responders to oral acetaminophen treatment

Echocardiography parameter	*Acetaminophen responders* (n = *12*)			*Acetaminophen non-responders* (n = *14*)		
	Pre-acetaminophen	*Post-acetaminophen*	P-*value*[a]	*Pre-acetaminophen*	*Post-acetaminophen*	P-*value*[a]
PDA diameter (mm)	2.5 (0.5)	1.6 (0.2)	< 0.01	2.7 (0.5)	2.7 (0.5)	0.74
PDA:LPA ratio	0.82 (0.19)	0.56 (0.11)	< 0.01	0.92 (0.16)	0.84 (0.22)	0.07
PDA peak systolic velocity (m s^{-1})	2.4 (0.5)	2.9 (0.6)	0.01	2.1 (0.5)	2.3 (0.6)	0.01
PDA mean pressure gradient (mm Hg)	10.8 (5.4)	22.2 (7.8)	< 0.01	7.7 (4.2)	10.6 (6.9)	0.06
PDA systolic Vmax: diastolic Vmin ratio	3.4 (1.3)	1.7 (0.4)	< 0.01	3.8 (1.3)	3.7 (1.1)	0.81
Left ventricular output (ml kg^{-1} min^{-1})	415 (91)	279 (37)	< 0.01	419 (92)	432 (79)	0.34
LVIDd (mm kg^{-1})	16.9 (3.3)	14.3 (2.2)	< 0.01	16.9 (2.8)	17.0 (2.3)	0.77
LA:Ao ratio	2.0 (1.7–2.2)	1.4 (1.3–1.5)	0.01	2.1 (1.8–2.2)	2.0 (1.9–2.4)	0.42
Mitral valve E:A ratio	0.89 (0.78–0.95)	0.77 (0.7–0.81)	0.04	0.83 (0.74–0.90)	0.87 (0.72–0.9)	0.50
IVRT (ms)	28 (7)	46 (9)	< 0.01	30 (8)	28 (9)	0.55
LPA diastolic Vmax (m s^{-1})	0.54 (0.14)	0.27 (0.10)	< 0.01	0.50 (0.20)	0.55 (0.21)	0.13
Celiac artery absent/reverse EDF, *n* (%)	9 (75%)	1 (8%)	< 0.01	8 (62%)	12 (86%)	0.12
Abdominal aorta reverse EDF, *n* (%)	9 (81%)	1 (9%)	< 0.01	11 (79%)	13 (93%)	0.50

Abbreviations: EDF, end-diastolic flow; IVRT, isovolumic relaxation time; LPA, left pulmonary artery; LVIDd, left ventricle internal diameter in diastole; mitral valve E:A ratio, early-to-late (atrial contraction) inflow ratio; PDA, patent ductus arteriosus; Vmax, maximum velocity; Vmin, minimum velocity. Parameters are expressed as mean (s.d.) or median (interquartile range). [a]Paired *t*-test for continuous variables and McNemar's test for categorical variables.

1.45 mg kg^{-1} (IQR 0.9 to 1.5). Infants were treated with oral acetaminophen for a median of 7 days (IQR 7 to 7, range 3 to 7).

Echocardiography evaluation at the initiation of acetaminophen treatment revealed a PDA diameter of 2.6 (±0.5) mm, peak systolic velocity of 2.2 (±0.5) m s^{-1} and PDA peak systolic velocity to minimum diastolic velocity ratio of 3.6 (±1.3).[23] Left ventricular output was 417 (±89) ml kg^{-1} min^{-1} and LA:Ao ratio 2.1 (1.8 to 2.2). Diastolic flow reversal was present in the abdominal aorta of 80% of infants, and 68% had absent or reverse diastolic flow in the celiac artery.

Twelve infants (46%) had a significant improvement in echo indices of shunt volume (three closed and nine reduced to a mild shunt) and did not undergo ligation (Table 2). None of the 'responders' to acetaminophen required subsequent medical therapy for PDA prior to discharge. Fourteen infants (54%) did not have echo improvement, of which eight underwent surgical ligation. Of the 6/14 infants without echo improvement who did not undergo ligation, the procedure was deferred in 4 infants who experienced clinical improvement in ventilation support (1 later died owing to necrotizing enterocolitis, 3 survived with persistent PDA at discharge), 1 infant died after withdrawal of life support owing to severe intraventricular hemorrhage (which had occurred prior to acetaminophen) and 1 infant's PDA closed after a late course of indomethacin. Responders and non-responders had similar perinatal and pretreatment clinical and echocardiographic characteristics and neonatal morbidities (Table 3).

The interobserver agreement for the summary echocardiographic assessment of PDA shunt volume severity (moderate or severe vs mild or closed) was excellent (kappa = 0.92, 95% confidence interval 0.77 to 1.00).

Hepatic enzymes were monitored in 16 infants. Pre-treatment and post-treatment median serum alanine aminotransferase levels were 7 (5 to 9, range 4 to 19) IU l^{-1} and 12 (9 to 16, range 4 to 61) IU l^{-1}, respectively (reference range < 54 IU l^{-1}). Pre-treatment and post-treatment median serum aspartate aminotransferase were 25 (17 to 33, range 13 to 46) and 45 (23 to 53, range 17 to 114) IU l^{-1}, respectively (reference range 14 to 75 l^{-1}). One infant had elevated serum alanine aminotransferase (61 IU l^{-1}) and serum aspartate aminotransferase (114 IU l^{-1}) at the conclusion of acetaminophen treatment, though this coincided with the development of culture-positive sepsis and meningitis.

DISCUSSION

In this cohort of ELGANs with persistent moderate or severe PDA who were at high risk of surgical ligation, late rescue therapy with oral acetaminophen was associated with both temporal improvement in echo indices of shunt volume and avoidance of surgical ligation in nearly half of infants. These findings suggest that acetaminophen therapy may help bridge the current uncertainty regarding the management of infants with persistent hemodynamically significant PDA.

The optimal balance of the risks and timing of PDA surgery vs prolonged exposure to the ductal shunt is presently unknown. Paradoxically, some studies have favored a delayed, highly selective use of surgical ligation[5,7] while others have suggested that prolonged exposure to a significant PDA is detrimental and should be avoided.[8,10] Acetaminophen may provide an alternative option for attempted medical closure after failure of cyclooxygenase inhibitor therapy, in lieu of either a prolonged period of conservative management or immediate routine surgical ligation. The high rate of PDA closure or significant restriction in this study suggests that acetaminophen treatment may reduce the surgical ligation burden, including the incipient immediate risks of patient transfer and perioperative morbidity.

The use of rescue oral acetaminophen to facilitate late ductal closure in extremely preterm infants at risk of surgical ligation is supported by three previous small case series of ELGANs comprising a total of 27 infants, where 44% (12/27) of infants achieved ductal closure.[13–15] Although other small series[19,20,24] have reported higher rates of ductal closure with oral acetaminophen, their study populations comprised more mature preterm infants (⩾28 weeks) who uncommonly require ligation. A recent case series of 36 extremely preterm infants with persistent PDA reported that 89% had PDA closure or significant restriction after a course of intravenous acetaminophen; however, this formulation is not available in all jurisdictions.[25]

The mechanism of action of acetaminophen to effect PDA closure remains poorly understood. Acetaminophen inhibits the peroxidase moiety of prostaglandin H_2 synthetase complex, thereby reducing the production of prostaglandin E_2, known to contribute to early ductal patency. Although acetaminophen is known to mediate reductions in prostaglandin E_2 in the central nervous system, its potential peripheral circulatory effects are comparably novel.[26,27] Although limited observational and animal

Table 3. Clinical characteristics and neonatal outcomes of extremely low gestational age neonates treated with acetaminophen to avoid surgical ligation

	Acetaminophen responders (n = 12)	*Acetaminophen non-responders (n = 14)*	P-*value*[a]
Perinatal characteristics			
GA at birth (weeks)	24.4 (24.1–26.3)	24.5 (24.3–25.7)	0.83
Birth weight (g)	715 (623–965)	700 (633–795)	0.56
Any antenatal corticosteroids, *n* (%)	11 (92%)	12 (86%)	1.00
5-min Apgar <7, *n* (%)	6 (50%)	4 (29%)	0.42
Indomethacin prophylaxis, *n* (%)	7 (58%)	12 (86%)	0.19
Characteristics at the time of acetaminophen treatment			
GA (weeks)	29.0 (27.1–29.6)	27.9 (27.6–28.7)	0.43
Weight (g)	879 (758–1191)	876 (850–1009)	0.61
Total indomethacin dose (mg kg^{-1})	1.2 (0.75–1.5)	1.5 (1.1–1.5)	0.17
% of days invasively ventilated	84 (27–100)	100 (58–100)	0.30
Invasive ventilation, *n* (%)	7 (58%)	11 (79%)	0.26
Mean airway pressure (cm H_2O)	10.5 (6.5–12.5)	10.5 (9.0–13.8)	0.20
FiO_2	0.25 (0.21–0.36)	0.30 (0.28–0.35)	0.25
Serum pH	7.33 (7.27–7.35)	7.30 (7.28–7.33)	0.31
Base deficit (mmol l^{-1})	−2 (−5 to +1.5)	−1 (−4 to 0)	1.00
Grade 3 or 4 IVH, *n* (%)	4 (33%)	5 (36%)	1.00
Culture-positive sepsis, *n* (%)	1 (8%)	5 (36%)	0.10
Characteristics at the conclusion of acetaminophen treatment			
Invasive ventilation, *n* (%)	4 (33%)	8 (57%)	0.22
Mean airway pressure (cm H_2O)	7.5 (5.5–11.3)	10.0 (9.0–14.0)	0.10
FiO_2	0.30 (0.21–0.38)	0.31 (0.28–0.35)	0.60
Serum pH	7.32 (7.29–7.38)	7.32 (7.31–7.35)	1.00
Base deficit (mmol l^{-1})	−5 (−9 to −1)	−3 (−5 to −3)	0.55
Neonatal outcomes			
Surgical PDA ligation, *n* (%)	0 (0%)	8 (57%)	<0.01
Death or moderate–severe bronchopulmonary dysplasia, *n* (%)	7 (58%)	9 (64%)	0.75
Death prior to discharge, *n* (%)	0 (0%)	2 (14%)	0.17
Moderate–severe bronchopulmonary dysplasia, *n* (%)	7 (58%)	7 (50%)	0.67
Severe ROP requiring treatment, *n* (%)	0 (0%)	0 (0%)	1.00
Necrotizing enterocolitis $\geqslant 2$, *n* (%)	1 (8%)	1 (7%)	1.00

Abbreviations: FiO_2, fraction of inspired oxygen; GA, gestational age; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity. Continuous variables are presented as median (interquartile range) or mean (s.d.). [a]Chi-square or Fisher's Exact test for categorical variables and Student's *t*-test or Wilcoxon rank-sum test for continuous variables.

studies have suggested that the ductal constriction effect of acetaminophen may be dose-dependent and that a prolonged course may improve PDA closure rates,[15] the optimal dose and duration of treatment requires further study. No controlled studies have evaluated the efficacy of acetaminophen as late rescue therapy for persistent PDA in infants being considered for surgical ligation.

The strengths of this study are that this represents the largest case series to date of rescue oral acetaminophen therapy in infants with persistent PDA being referred for surgical ligation. In addition, echocardiography determination of ductal hemodynamic significance was performed uniformly, reliably and using a comprehensive set of individually validated indices representing ductal size, shunt restriction, left heart volume loading and pulmonary overcirculation and systemic arterial diastolic flow reversal. Finally, the patients included in this study represent the most immature preterm infants (median GA at birth 24 weeks) and comprise the population known to be empirically at highest risk of surgical ligation.

This study has several limitations: First, the lack of a control population of untreated infants means that this study cannot differentiate between the effect of acetaminophen and the possibility of spontaneous ductal closure during the treatment course. A recent cohort study of extremely preterm infants reported 73% spontaneous ductal closure rate for infants with PDA on the third day of life. However, the rate of spontaneous closure or diminution of the PDA in the subgroup of infants comparable to our study (with prolonged persistence of the PDA beyond the first 2 to 3 weeks of life) was not reported.[28] Although the possibility of spontaneous ductal closure in our study cannot be excluded, our data provide an observational benchmark for comparison with future studies and supports a randomized placebo-controlled trial of rescue oral acetaminophen therapy in infants being referred for surgical ligation.

Second, while the primary outcome of this study was the combination of ductal closure/restriction and avoidance of surgical ligation, any benefit of this approach should be measured against its effects on neonatal and neurodevelopmental outcomes. Although there was no clear evidence of immediate harm, it is not possible to exclude a contribution of the persistent PDA or acetaminophen therapy on mortality in infants who died during or after their treatment course. Although the rate of mortality (7.7%) and bronchopulmonary dysplasia (54%) in this cohort of ELGANs with prolonged persistent PDA was similar to other published data,[8,10] this study lacked a control group and thus the broader impact of this practice change on clinical outcomes requires further study.

Finally, our summary classification of PDA shunt volume as mild/moderate/severe was based on a novel, unweighted aggregation of echo markers, which has not been validated against

clinical outcomes. However, individual components (for example, diastolic flow reversal in the abdominal aorta, left ventricular output) have been previously validated as reliable markers of a high volume shunt or shown to correlate with neonatal outcomes.[29–31] This summary classification represents our current practice of incorporating a standard set of echo parameters to provide a robust sonographic evaluation of PDA hemodynamic significance that minimizes the effect of measurement error in individual parameters. The high interobserver agreement in this study supports its reliability as a summation of the PDA echocardiography assessment.

CONCLUSION

Late rescue therapy with oral acetaminophen for persistent moderate or severe PDA was associated with significant temporal improvement in echocardiography indices of shunt volume and avoidance of surgical ligation in nearly half of infants. Additional controlled studies are needed to evaluate the effect of acetaminophen treatment on neonatal and neurodevelopmental outcomes in this high-risk population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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