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Serial Echocardiography in Very Preterm Infants: A Pilot Randomized Trial

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Abstract

Aim—To determine whether routine echocardiography increases diagnosis and treatment of patent ductus arteriosus (PDA) and whether randomized non-disclosure is a feasible strategy for studying PDA management.

Methods—2 center pilot randomized, controlled trial. 88 infants with birth weights 1250 grams and gestational ages 30 weeks were randomized to disclosure or non-disclosure of serial echocardiogram findings. Echocardiograms were performed at 3–5 and 7–10 days of life. The primary outcome was time to regain birth weight.

Results—100% of echocardiograms in the disclosure group were disclosed; 16% (echocardiogram #1) and 29% (echocardiogram #2) were disclosed in the non-disclosure group. There was a statistically non-significant decrease in drug therapy for PDA in the non-disclosure group (adjusted odds ratio [AOR] 0.56, 95% confidence interval [CI] 0.24–1.34). There was no difference in time to regain birth weight or in other important neonatal outcomes. However, infants in the non-disclosure group were more likely to demonstrate appropriate weight loss and then regain birth weight within 7–14 days (AOR 2.64, 95% CI 1.08–6.44).

Conclusion—Randomized non-disclosure of echocardiograms is a feasible strategy for evaluation of approaches to PDA management in very preterm infants. Avoidance of routine echocardiography may reduce drug therapy for PDA without adverse clinical effects.

Keywords

Echocardiogram; Echocardiography; Patent ductus arteriosus; Very low birth weight infant; Very premature infant

INTRODUCTION

The normal process of constriction and obliteration of the ductus arteriosus is delayed or does not occur in up to 70% of very preterm infants.(1–3) Patent ductus arteriosus (PDA) is associated with increased risks of bronchopulmonary dysplasia and of necrotizing enterocolitis (NEC), but the frequently observed association between PDA and these

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common neonatal morbidities may not be a causal relationship.(4–8) Early closure of PDA with indomethacin does not reduce the incidence of NEC or of bronchopulmonary dysplasia, despite reduction of symptomatic PDA.(9–12)

Echocardiography is required to definitively diagnose the presence or absence of PDA in very preterm infants.(3, 13–15) Neonatal intensive care units have different protocols for screening for PDA in very preterm infants, ranging from universal screening to no routine echocardiography.(3) Higher rates of screening may be associated with a higher likelihood of diagnosis and treatment of PDA, even though the benefit of routine therapy remains unproven and many of these PDAs might eventually close spontaneously.(11, 16, 17) Early and potentially unnecessary medical and surgical treatments for PDA may have harmful side effects.(2, 4, 5, 7, 18–21) Enteral feedings are often withheld during PDA treatment, thus increasing the risk for poor nutrition and slow growth. Importantly, loss of weight after birth followed by adequate growth is independently associated with improved neurodevelopmental outcomes in very preterm infants.(22–24)

We conducted this randomized pilot trial of disclosure versus non-disclosure of the results of serial screening echocardiograms to evaluate how echocardiography influences clinical management and outcomes in very preterm infants. Our secondary objective was to demonstrate the feasibility of randomized non-disclosure as a strategy for use in future research on PDA management.

PATIENTS AND METHODS

Study Infants

This study was a two-center, randomized pilot trial. Written, informed consent was obtained from the parent or guardian of each study patient. Participants were enrolled between October 2009 and April 2011 in the neonatal intensive care units at the Hospital of the University of Pennsylvania and Pennsylvania Hospital and followed until hospital discharge.

Eligible infants were born with both birth weights $\geq$ 1250 grams and gestational ages $\geq$ 30 weeks, and had postnatal ages $\leq$ 72 hours. The exclusion criteria were: infant not considered viable, dysmorphic features or congenital malformations that could adversely affect growth, and known or suspected congenital heart disease other than PDA. There were no exclusions based on race, gender, or language. Infants who received prophylactic indomethacin were initially excluded. However, even though infants who had received prophylaxis were less likely to have PDA, the question of whether or not to screen remained relevant in this population. Thus, this exclusion was dropped after the first patient was enrolled.

Randomization

Participants were randomly allocated to disclosure or non-disclosure of serial echocardiograms in a 1:1 ratio, stratified by center. Allocation was determined in advance by a statistician not otherwise involved in the trial, using a computer-based random number generator and incorporating variable block sizes. To ensure allocation concealment, group assignments were placed in sequentially numbered sealed opaque envelopes which were opened immediately before the first echocardiogram was performed.

Study Interventions

The first echocardiogram was a standard complete study performed at 3–5 days of life to evaluate cardiac anatomy and characteristics of the PDA, if present.(25) A second limited echo was performed to re-evaluate the status of the PDA at 7–10 days of life. During each echocardiogram, the PDA diameter in millimeters, presence or absence of flow, direction of

flow, peak velocity across the PDA and left atrium-to-aorta ratio were noted. During all studies, the ultrasound monitor was concealed behind screens so that clinicians in the unit could not see the study as it was performed. Studies were performed with either a Philips IE33 (Andover, MA) or Siemens Sequoia (Bothell, WA) echocardiogram machine and appropriately sized transducers. All studies were performed by technologists and interpreted by a single pediatric cardiologist with special expertise in echocardiography (MSC).

For infants randomized to disclosure, the study coordinator distributed the echocardiogram results to the clinical team as soon as possible and within 24 hours. Results of studies on infants randomized to non-disclosure were unavailable to all clinicians and study staff (other than MSC) until the infant had undergone both study echocardiograms and achieved the primary endpoint. Decisions to pursue medical or surgical closure of the PDA were made by the primary physician, and were not dictated by study protocol. No PDAs were treated based on clinical signs alone.

We did not wish to prevent echocardiography and treatment of PDA in patients who were thought to have signs strongly suggestive of potential complications of a PDA, such as pulmonary hemorrhage. Therefore, the protocol included specific procedures for unblinding. Within 24 hours of a study echocardiogram, the attending physician was permitted to request disclosure if he or she felt strongly that the patient might have a PDA requiring treatment. Because ductal size may change quickly over time, clinically indicated echocardiograms were performed if >24 hours had elapsed since the study echocardiogram. Unless clearly indicated by the participant's clinical status, unblinding and non-study echocardiograms were strongly discouraged by means of monitoring and discussion with the clinicians, to avoid contamination and inappropriate co-interventions. Fluid management and feeding practices were not dictated by protocol or unit policy during the time that the study was conducted.

Outcomes

The primary outcome was the number of days between birth and the day that the patient regained birth weight. Secondary outcomes included PDA treatment with medicine (indomethacin or ibuprofen) or surgery, confirmed NEC (x-ray findings of pneumatosis or free air or at surgery) or >48 hours of NPO for suspected NEC, number of days to full enteral feedings (120 milliliters/kilogram/day), number of days on the ventilator, number of days of positive airway pressure (>2 liters/minute of oxygen by nasal cannula or any other noninvasive respiratory support), number of days with any respiratory support, number of days to death or discharge, intraventricular hemorrhage or periventricular leukomalacia, confirmed sepsis (positive blood culture), and highest stage of retinopathy of prematurity.

Statistics

Based on data from our hospitals, we expected enrolled infants to require 10 ± 5 days to regain their birth weight. Most neonatologists would consider a 3 day difference in time to regain birth weight to be clinically important. To detect a 3 day difference with 80% power and 2-sided $\alpha = 0.05$, we planned to enroll 88 patients in this pilot trial.

Standard descriptive statistics were used to summarize all variables. Groups were compared using t-tests or Mann-Whitney tests for continuous data and χ^2 tests or Fisher's exact tests for dichotomous data. We used Poisson regression, adjusted for center, to further evaluate differences in the primary outcome. We then adjusted for potential confounders because small sample size may lead to imbalances of prognostic characteristics despite randomization. We used logistic and Poisson regression for adjusted comparison of

dichotomous secondary outcomes and outcomes measured by counts, respectively. All randomized subjects were included in the analyses.

We used the same methods to perform post-hoc analyses of additional important outcomes. To further evaluate differences in the patterns of weight loss and gain, we defined any loss of weight, with return to the birth weight in 7–14 days, as normal. Conversely, we considered failure to lose weight or regain in <7 or >14 days abnormal.^(22, 24) We used logistic regression to compare the incidence of abnormal weight loss and gain.

To ensure safety, a statistician reviewed the data (with allocations masked) in one interim analysis. The institutional review board of the University of Pennsylvania approved the study.

RESULTS

Study Infants

Consent was obtained from the parents/guardians of 89 infants. One infant died before randomization and 44 patients were randomized to each group. Baseline characteristics and status at randomization including diagnosis of PDA, exposure to prophylactic indomethacin, and respiratory support, were similar in the groups (Supplementary Material, available online).

Study Procedures

Both study echocardiograms were performed in 84 participants. Echocardiogram 1 was performed in 86 infants; echocardiogram 2 was performed in 86 infants (Table 1). Four echocardiograms were not performed because of death (n=1), clinical instability (n=1), or protocol violation (n=2). Premature disclosure of blinded echocardiogram results occurred 19 times in 14 patients. The circumstances of these disclosures were: clinical concern for symptomatic PDA requiring treatment (n=16), follow-up of a patient with history of pulmonary hemorrhage requiring transfusion (n=1) and protocol violation (n=2). Of the 16 echocardiogram reports disclosed per protocol for clinical reasons, 12 (75%) revealed a PDA and were followed by drug or surgical therapy. The two protocol violations occurred when reports were placed accidentally in patient charts but not actually reviewed by the clinicians.

A non-study echocardiogram was obtained before study enrollment in 9 patients. A clinical echocardiogram was obtained between the two study echocardiograms in 9 patients randomized to disclosure and 7 patients randomized to non-disclosure. Clinicians were aware of the results of significantly more echocardiograms in patients randomized to disclosure (Table 1). This indicates successful implementation of the study intervention.

No safety concerns were raised during the interim analysis and no adverse events were reported.

Outcomes

Four patients in the disclosure group and one in the non-disclosure group failed to lose any weight after birth. Therefore, these patients could not be included in the primary analysis. Neither a bivariate comparison nor the pre-planned Poisson analysis of the primary outcome demonstrated a difference between the groups in time to regain birth weight (Table 2).

There were no statistical differences between the groups in the pre-planned secondary outcomes (Table 2). The results were unchanged when potential confounders (sex, gestational age, antenatal steroid exposure, and multiple gestation) were included in the

analyses. Additional post-hoc analyses to further evaluate differences between the groups revealed a non-significant decrease in the number of doses of drug for treatment of PDA administered to infants in the non-disclosure group (incidence rate ratio adjusted for center 0.69, 95% confidence interval (CI) 0.42–1.16, $p=0.24$). There was also an insignificantly lower rate of surgical NEC in the non-disclosure group (odds ratio adjusted for center 0.29, 95% CI 0.07–1.25, $p=0.10$).

Although the *a priori* analysis of the primary outcome did not reveal a difference between the groups, further evaluation of the data revealed important differences in the patterns of postnatal weight loss and gain. We observed a normal pattern of initial weight loss and subsequent regain of birth weight within 7–14 days in 70% of patients in the non-disclosure group but in only 48% of patients in the disclosure group. The non-disclosure group had significantly better odds of normal weight loss and gain (odds ratio adjusted for center 2.64, 95% CI 1.08–6.44, $p=0.03$). This result was unchanged when also adjusted for sex, gestational age, antenatal steroid exposure and multiple gestation.

DISCUSSION

We performed this randomized pilot trial to demonstrate the feasibility of randomized non-disclosure of diagnosis of PDA as a means to further understand PDA management in this population and to evaluate the role of serial echocardiography in the diagnosis and treatment of PDA in very preterm infants. A strategy of randomized non-disclosure has been used in similar situations in perinatal research, when it is unclear whether increased diagnostic information leads to improved outcomes.(26–28) We have demonstrated that clinicians can care for patients without always knowing the status of the PDA. There was good distinction between the two groups, with 100% disclosure of results in the disclosure group and only 16% (echocardiogram #1) and 29% (echocardiogram #2) disclosure in the non-disclosure group. Clinicians never had any echocardiogram information for 14 patients in the non-disclosure group. Randomized non-disclosure is feasible and may be a useful strategy for future, larger studies of PDA management.

The clinicians were aware of the results of significantly more echocardiograms in the disclosure group and there was a statistically non-significant reduction in the incidence of drug therapy of the PDA in the non-disclosure group. The small size of this pilot study precludes firm conclusions about whether nondisclosure influences the use of medicine or surgery to close the PDA. The clinicians' knowledge of the echocardiogram results, which provided opportunities for more aggressive PDA treatment, did not appear to improve outcomes. Moreover, our results suggest potentially worse outcomes including longer length of stay, higher rates of NEC, and more retinopathy of prematurity among infants in the disclosure group. These observations are consistent with a recent trial by Sosenko, who reported no improvement in outcomes with “early” versus “expectant” treatment of symptomatic PDA in very preterm infants.(29)

Nearly all infants lose weight after birth. Both postnatal weight loss and subsequent weight gain are important prognostic factors for long-term outcomes in preterm infants.(22, 24) We selected regaining birth weight as the primary outcome for this pilot trial because PDA treatment strongly influences fluid and nutrition management. However, infants who experience fluid retention and poor nutrition after birth because of early drug therapy for PDA may regain birth weight at a similar time as infants who lose weight appropriately after birth and then regain it because of good nutrition. The distribution of weight loss and gain in the current study may be confounded by drug-induced fluid retention. More patients in the disclosure group failed to lose any weight or regained birth weight within a few days. This observation led to our post-hoc analyses, which revealed that patients in the non-disclosure

group were significantly more likely to lose weight after birth and then regain this weight in 7–14 days.

PDA management in very preterm infants has long been a challenge for neonatologists. The current trend among some experts is to discourage routine early treatment of PDA, yet this guidance is of little help to the practitioner who is weighing the risks and benefits of diagnosis and treatment.(21, 30) While echocardiography remains the gold standard method of diagnosis of PDA, this pilot trial does not provide evidence that it is necessary to perform echocardiography in *all* very preterm infants. Instead, it may be equally appropriate or perhaps better to reserve the test for patients who are thought to have significant signs of symptomatic PDA, and in whom the benefit of the diagnostic information is likely to outweigh potential risk. Despite our limitations of sample size, this pilot study has led to important observations that will aid the design of future studies in this area. We have demonstrated that randomized non-disclosure is a feasible strategy for research comparing aggressive and conservative approaches to PDA management. In future studies that build upon these results, it will be important to further elucidate which patients benefit from the diagnostic information provided by echocardiography and evaluate whether echocardiographic signs might predict later clinically significant PDA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATION LIST

AOR	adjusted odds ratio
CI	confidence interval
IQR	interquartile range
IVH	intraventricular hemorrhage
NEC	necrotizing enterocolitis
NPO	nil per os
PDA	patent ductus arteriosus
PVL	periventricular leukomalacia
ROP	retinopathy or prematurity
SD	standard deviation

References

1. Koch J, Hensley G, Roy L, Brown S, Ramaciotti C, Rosenfeld CR. Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 grams or less. *Pediatrics*. 2006; 117:1113–21. [PubMed: 16585305]

2. Madan JC, Kendrick D, Hagadorn JI, Frantz ID. Patent ductus arteriosus therapy: impact on neonatal and 18-month outcome. *Pediatrics*. 2009; 123:674–81. [PubMed: 19171637]
3. O'Rourke DJ, El-Khuffash A, Moody C, Walsh K, Molloy EJ. Patent ductus arteriosus evaluation by serial echocardiography in preterm infants. *Acta Paediatr*. 2008; 97:574–8. [PubMed: 18394102]
4. Laughon MM, Simmons MA, Bose CL. Patency of the ductus arteriosus in the premature infant: is it pathologic? Should it be treated? *Curr Opin Pediatr*. 2004; 16:146–51. [PubMed: 15021192]
5. Bose CL, Laughon MM. Patent ductus arteriosus: lack of evidence for common treatments. *Arch Dis Child Fetal Neonatal Ed*. 2007; 92:F498–502. [PubMed: 17951552]
6. Knight DB. The treatment of patent ductus arteriosus in preterm infants. A review and overview of randomized trials. *Semin Neonatol*. 2001; 6:63–73. [PubMed: 11162286]
7. Schmidt B, Roberts RS, Fanaroff A, Davis P, Kirpalani HM, Nwaesei C, et al. Indomethacin prophylaxis, patent ductus arteriosus, and the risk of bronchopulmonary dysplasia: further analyses from the Trial of Indomethacin Prophylaxis in Preterms (TIPP). *J Pediatr*. 2006; 148:730–4. [PubMed: 16769377]
8. Fowlie PW, Davis PG. Prophylactic indomethacin for preterm infants: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed*. 2003; 88:F464–6. [PubMed: 14602691]
9. Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *N Engl J Med*. 2001; 344:1966–72. [PubMed: 11430325]
10. Fowlie PW, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. *Cochrane Database Syst Rev*. 2010:CD000174. [PubMed: 20614421]
11. Cooke L, Steer P, Woodgate P. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. *Cochrane Database Syst Rev*. 2003:CD003745. [PubMed: 12804488]
12. Hammerman C, Strates E, Komar K, Bui K. Failure of prophylactic indomethacin to improve the outcome of the very low birth weight infant. *Dev Pharmacol Ther*. 1987; 10:393–404. [PubMed: 3677969]
13. Davis P, Turner-Gomes S, Cunningham K, Way C, Roberts R, Schmidt B. Precision and accuracy of clinical and radiological signs in premature infants at risk of patent ductus arteriosus. *Arch Pediatr Adolesc Med*. 1995; 149:1136–41. [PubMed: 7550818]
14. Skelton R, Evans N, Smythe J. A blinded comparison of clinical and echocardiographic evaluation of the preterm infant for patent ductus arteriosus. *J Paediatr Child Health*. 1994; 30:406–11. [PubMed: 7833075]
15. Alagarsamy S, Chhabra M, Gudavalli M, Nadroo AM, Sutija VG, Yugrakh D. Comparison of clinical criteria with echocardiographic findings in diagnosing PDA in preterm infants. *J Perinat Med*. 2005; 33:161–4. [PubMed: 15843268]
16. Vanhaesebrouck S, Zonnenberg I, Vandervoort P, Bruneel E, Van Hoestenbergh MR, Theyskens C. Conservative treatment for patent ductus arteriosus in the preterm. *Arch Dis Child Fetal Neonatal Ed*. 2007; 92:F244–7. [PubMed: 17213270]
17. Herrman K, Bose C, Lewis K, Laughon M. Spontaneous closure of the patent ductus arteriosus in very low birth weight infants following discharge from the neonatal unit. *Arch Dis Child Fetal Neonatal Ed*. 2009; 94:F48–50. [PubMed: 18450808]
18. Brooks JM, Travadi JN, Patole SK, Doherty DA, Simmer K. Is surgical ligation of patent ductus arteriosus necessary? The Western Australian experience of conservative management. *Arch Dis Child Fetal Neonatal Ed*. 2005; 90:F235–9. [PubMed: 15846015]
19. Chorne N, Leonard C, Piecuch R, Clyman RI. Patent ductus arteriosus and its treatment as risk factors for neonatal and neurodevelopmental morbidity. *Pediatrics*. 2007; 119:1165–74. [PubMed: 17545385]
20. Kabra NS, Schmidt B, Roberts RS, Doyle LW, Papile L, Fanaroff A. Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants: results from the Trial of Indomethacin Prophylaxis in Preterms. *J Pediatr*. 2007; 150:229–34. [PubMed: 17307535]
21. Clyman RI, Couto J, Murphy GM. Patent ductus arteriosus: are current neonatal treatment options better or worse than no treatment at all? *Semin Perinatol*. 2012; 36:123–9. [PubMed: 22414883]

22. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. *Pediatrics*. 2006; 117:1253–61. [PubMed: 16585322]
23. Cheong JL, Hunt RW, Anderson PJ, Howard K, Thompson DK, Wang HX, et al. Head growth in preterm infants: correlation with magnetic resonance imaging and neurodevelopmental outcome. *Pediatrics*. 2008; 121:e1534–40. [PubMed: 18519457]
24. Wadhawan R, Oh W, Perritt R, Lupton AR, Poole K, Wright LL, et al. Association between early postnatal weight loss and death or BPD in small and appropriate for gestational age extremely low-birth-weight infants. *J Perinatol*. 2007; 27:359–64. [PubMed: 17443198]
25. Lai WW, Geva T, Shirali GS, Frommelt PC, Humes RA, Brook MM, et al. Guidelines and standards for performance of a pediatric echocardiogram: a report from the Task Force of the Pediatric Council of the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2006; 19:1413–30. [PubMed: 17138024]
26. Nienhuis SJ, Vles JS, Gerver WJ, Hoogland HJ. Doppler ultrasonography in suspected intrauterine growth retardation: a randomized clinical trial. *Ultrasound Obstet Gynecol*. 1997; 9:6–13. [PubMed: 9060122]
27. Bloom SL, Spong CY, Thom E, Varner MW, Rouse DJ, Weininger S, et al. Fetal pulse oximetry and cesarean delivery. *N Engl J Med*. 2006; 355:2195–202. [PubMed: 17124017]
28. Lawrence R, Mathur A, Nguyen The Tich S, Zempel J, Inder T. A pilot study of continuous limited-channel aEEG in term infants with encephalopathy. *J Pediatr*. 2009; 154:835–41. e1. [PubMed: 19230897]
29. Sosenko IR, Florencia Fajardo M, Claire N, Bancalari E. Timing of Patent Ductus Arteriosus Treatment and Respiratory Outcome in Premature Infants: A Double-Blind Randomized Controlled Trial. *J Pediatr*. 2012; 160:929–35. e1. [PubMed: 22284563]
30. Benitz WE. Patent ductus arteriosus: to treat or not to treat? *Arch Dis Child Fetal Neonatal Ed*. 2012; 97:F80–2. [PubMed: 22174019]

KEY NOTES

- Randomized non-disclosure of the results of serial echocardiograms is a safe and feasible strategy for research about the diagnosis and management of patent ductus arteriosus.
- There is not a clear benefit to performing routine echocardiography for diagnosis of patent ductus arteriosus in all very preterm infants.
- Avoidance of routine echocardiography may reduce drug therapy for PDA without adverse clinical effects.

Figure 1.

Study flow diagram indicating the numbers of infants who were eligible for and enrolled in the study and reasons for exclusion.

* Prophylactic indomethacin was eliminated as an exclusion after one patient was enrolled.

Table 1

Numbers of clinical and study echocardiograms performed, disclosure status, and PDA findings

	Disclosure Group (n=44)	Non-Disclosure Group (n=44)	P-value ¹
Study Echocardiogram #1			
Number performed	43	43	1.00
Number disclosed – n (%)	43 (100%)	7 (16%)	<0.001
Day of life performed – mean +/- SD	4.5 +/- 0.8	4.2 +/- 0.9	0.11
PDA present – n (%) ²	26 (63%)	27 (63%)	0.95
Size of PDA if present, in millimeters – mean +/- SD ²	1.7 +/- 0.7	1.7 +/- 0.8	0.74
Study Echocardiogram #2			
Number performed	44	42	0.49
Number disclosed – n (%)	44 (100%)	12 (29%)	<0.001
Day of life performed – mean +/- SD	8.9 +/- 1.3	9.0 +/- 1.2	0.94
PDA present – n (%) ²	17 (40%)	18 (43%)	0.76
Size of PDA if present, in millimeters – mean +/- SD ²	1.4 +/- 0.6	1.3 +/- 0.6	0.79
Total number of echocardiogram reports known to the clinicians – median [IQR] ³	3 [2, 6]	2 [0, 4]	<0.001

¹ Comparison of disclosure versus non-disclosure group via Fisher's exact, χ^2 , t-tests, or Mann-Whitney tests.

² The presence or absence of a duct could not be determined in either study echocardiogram for 1 patient in the disclosure group and in the first study echocardiogram for 1 patient in the disclosure group. These patients were excluded from this analysis.

³ The total number of echocardiogram reports is the sum of all disclosed study echocardiograms plus any additional echocardiograms requested by the clinical team at any time during the hospitalization.

Table 2

Primary and Secondary Outcomes

	Disclosure (n=44)	Non-Disclosure (n=44)		
	median [IQR]	median [IQR]	Incidence Rate Ratio Adjusted for Center (95% CI)	Incidence Rate Ratio Adjusted for Center and Patient Characteristics ¹ (95% CI)
PRIMARY OUTCOME				
Days to regain birth weight ²	10 [7.5–14.5]	10 [8–12]	0.92 (0.77–1.09)	0.94 (0.80–1.11)
SECONDARY OUTCOMES				
Days on ventilator	7 [2–25]	8 [1–31]	0.93 (0.53–1.67)	1.22 (0.78–1.93)
Days of noninvasive positive airway pressure	36 [20.5–48]	29.5 [9–47.5]	0.99 (0.76–1.28)	1.05 (0.84–1.32)
Days receiving any respiratory support	65 [35.5–96.5]	54.5 [27–86]	0.92 (0.72–1.17)	1.01 (0.84–1.21)
Days to full feeds	24 [15–36]	24 [15.5–31.5]	1.07 (0.78–1.48)	1.14 (0.84–1.55)
If alive, day of life discharged	97 [67–129]	84 [52–107]	0.90 (0.71–1.15)	1.00 (0.83–1.20)
	n (%)	n (%)	Odds Ratio Adjusted for Center (95% CI)	Odds Ratio Adjusted for Center and Patient Characteristics ¹ (95% CI)
Any PDA treatment after randomization	21 (48)	17 (39)	0.69 (0.30–1.63)	0.75 (0.29–1.93)
Drug treatment for PDA	20 (45)	14 (32)	0.56 (0.24–1.34)	0.61 (0.23–1.57)
Surgical treatment for PDA	6 (14)	8 (18)	1.43 (0.45–4.58)	2.56 (0.58–11.25)
Grade 3/4 IVH or PVL	5 (11)	7 (16)	1.46 (0.43–5.04)	2.01 (0.45–8.95)
ROP any stage ³	25 (58)	17 (41)	0.51 (0.21–1.21)	0.53 (0.18–1.59)
Confirmed or suspected NEC	18 (41)	11 (25)	0.47 (0.19–1.18)	0.53 (0.20–1.37)
Confirmed NEC	9 (20)	6 (14)	0.51 (0.16–1.60)	0.62 (0.18–2.15)
Sepsis	13 (30)	16 (36)	1.38 (0.56–3.39)	1.80 (0.64–5.08)
Died	4 (9)	5 (11)	1.25 (0.31–5.00)	1.01 (0.21–5.00)

¹ Incidence rate ratio or odds ratio for outcome occurring in disclosure vs. non-disclosure (reference) group, adjusted for center, sex, gestational age, antenatal steroid exposure, and multiple gestation

² This outcome is only reported for infants who lost weight after birth (disclosure n=40, nondisclosure n=43).

³ Retinal examinations were performed in 43 patients in the disclosure group and 41 patients in the non-disclosure group.