Spontaneous Closure of Patent Ductus Arteriosus in Infants ≤1500 g

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abstract

OBJECTIVES: Patent ductus arteriosus (PDA) remains a challenging issue in very low birth weight (VLBW) infants, and its management varies widely. Our aim in this study was to document the natural course of ductus arteriosus in a cohort of VLBW infants who underwent conservative PDA management with no medical or surgical intervention.

METHODS: A retrospective cohort study conducted in 2 European level-3 neonatal units.

RESULTS: A total of 368 VLBW infants were born within the study period. Two hundred and ninety-seven infants were free of congenital malformations or heart defects and survived to hospital discharge. Out of those, 280 infants received truly conservative PDA management. In 237 (85%) of nontreated infants, the PDA closed before hospital discharge. The Kaplan-Meier model was used to document the incidence proportion of PDA closure over time for different gestational age groups. The median time to ductal closure was 71, 13, 8, and 6 days in <26+0, 26+0 to 27+6, 28+0 to 29+6, and ≥30 weeks, respectively. For different birth weight groups, the median was 48, 22, 9, and 8 days in infants weighing <750, 750 to 999, 1000 to 1249, and 1250 to 1500 g, respectively. No statistically significant relationship was found between PDA closure before hospital discharge and neonatal morbidities.

CONCLUSIONS: The likelihood of PDA spontaneous closure in VLBW infants is extremely high. We provide in our findings a platform for future placebo-controlled trials focused on the smallest and youngest infants.

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WHAT'S KNOWN ON THIS SUBJECT: The management of patent ductus arteriosus in very low birth weight infants remains controversial. Spontaneous closure occurs frequently, and therefore many infants might receive unnecessary treatment. Data from small cohort studies suggest that noninterventional management is a feasible option.

WHAT THIS STUDY ADDS: Spontaneous closure of ductus arteriosus is extremely prevalent in very low birth weight infants. Infants born before 26 weeks and <750 g have significantly higher rates of patent ductus arteriosus at hospital discharge. Future studies should focus on this population.

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Patent ductus arteriosus (PDA) is a common issue in preterm neonates. It has been associated with an increased risk of short- and long-term complications, mainly bronchopulmonary dysplasia (BPD), chronic lung disease (CLD), and necrotizing enterocolitis (NEC).[1] However, the causality of this relationship has never been established.[2] Practices in PDA management vary greatly among institutions,[3] ranging widely from universal prophylactic treatment through selective treatment on the basis of different criteria to no treatment at all.

Despite the physiologic plausibility of PDA adverse effects (such as pulmonary overcirculation and systemic hypoperfusion), researchers on PDA medical treatment have failed to show a significant decrease in PDA-associated complications or any long-term benefit apart from the PDA closure itself.[4–6] The only beneficial treatment strategy seems to be prophylactic indomethacin, which decreases the rate of intraventricular hemorrhage (IVH) and severe early pulmonary hemorrhage, although this also has not translated into the improvement of long-term outcomes.[7,8] Such an approach exposes a large number of infants to unnecessary medication and carries the risk of adverse effects, especially if given together with steroids.[9–11] Surgical PDA ligation does not carry any long-term benefits either,[2] and it has been associated with adverse outcomes.[12,13] Early targeted treatment according to echocardiographic criteria within the first hours of life seems to be a promising approach. This method reduces pulmonary hemorrhages and trends toward IVH reduction without exposing the entire population to the treatment.[14]

Evidence exists that some infants might theoretically benefit from PDA closure[14]; however, the indication and mode of such treatment is uncertain at the moment. Also, spontaneous PDA closure occurs in a significant number of premature infants.[15,16] Therefore, a noninterventional, conservative approach to PDA management seems to be one of the options.[17,18] Until further evidence for treatment type, timing, and initiation criteria is available, we have adopted such an approach with a high threshold for any type of treatment and regular point-of-care echocardiography (ECHO) follow-up.

Our aim is to present the data on the "natural" course of PDA before hospital discharge in a large retrospective cohort of very low birth weight (VLBW) infants with a birth weight (BW) ≤1500 g who underwent conservative PDA management. A secondary outcome of this study is the comparison of selected neonatal morbidities between patients with closed and permanent PDA.

METHODS

Study Design

We have retrospectively analyzed data from a routine serial-targeted ECHO follow-up of VLBW infants admitted to 2 European level-3 NICUs: the Institute for the Care of Mother and Child, Prague, Czech Republic (center 1), and the Coombe Women and Infants University Hospital, Dublin, Ireland (center 2). PDA-targeted point-of-care ECHO follow-up had been in place in both units before the start of the data collection. Data from the period of February 2012–June 2013 in center 1 and June 2013–June 2014 in center 2 were analyzed. The respective research ethics committees approved the use of the data in each institution. Informed consent was not required because of the retrospective nature of the study.

Participating units have similar policies and philosophies with regards to ventilation, nutrition, hemodynamic management, and indications for hospital discharge. The units also share the same conservative approach to PDA, with a high threshold for treatment.

All VLBW infants without congenital malformations or chromosomal anomalies were eligible. Infants with congenital heart disease other than PDA and/or patent foramen ovale were excluded, as well as infants with acquired heart disease not related to PDA (such as infectious endocarditis, myocardial infarction, and twin-to-twin transfusion syndrome) and infants with incomplete inpatient follow-up. Infants who died during the study period were excluded from the primary analysis.

Functional ECHO and PDA Treatment

Targeted ECHO was performed within the first week of life followed by serial examinations in 1 to 2 weekly intervals until documented ductal closure or hospital discharge. All the clinicians performing the point-of-care ECHO assessment underwent appropriate training and were experienced with the technique. In both centers, the ultrasound assessment was performed by using a Phillips CX50 Ultrasound System with S8-3 broadband sector array or S12-4 sector array transducer (Phillips, Andover, MA).

The first ECHO examination focused not only on the ductal parameters but also on the heart anatomy. Follow-up scans were focused mainly on the PDA presence and the parameters of ductal significance, which included diameter, flow pattern, maximum and minimum flow velocities, left atrium-to-aorta ratio, presence of mitral insufficiency, flow in the abdominal aorta or celiac artery, and end-diastolic flow in the left pulmonary artery.[19,20] Ductal closure was defined as an absence of identifiable flow in the ductus arteriosus (DA) by using color Doppler. DA closure was always reaffirmed after 2 weeks. All

of the parameters were recorded into the infant's documentation and were available for clinical decisions. For the purpose of this article, only the information on ductal patency was used.

The decision to treat and the mode of therapy remained at the discretion of the attending physician and were based on the clinical and echocardiographic features attributable to the PDA.

Data Collection

The following demographic information was collected for every infant: gestation at birth, BW, sex, antenatal steroid (ANS) exposure, multiple gestation, and documented intrauterine growth restriction (IUGR) (BW <10th percentile). Clinical outcome data included survival to hospital discharge, PDA medical treatment, surgical ligation or catheter device closure, BPD (defined as oxygen requirement at 36 weeks postmenstrual age), IVH grades III and IV, periventricular leucomalacia (PVL), NEC grades ≥IIb, and retinopathy of prematurity (ROP) stages ≥III. The diagnoses were defined according to the Vermont Oxford Network.[21] The definition of early- and late-onset sepsis was based on the criteria proposed by Chiesa et al,[22] which is that neonates with positive blood culture results and clinical signs of infection, and/or neonates with negative blood culture results, clinical signs of infection, and a positive laboratory sepsis screen were considered as having sepsis.

Clinical data on infants discharged from the hospital with an open PDA focused on further management, which included ligation, device closure, and a follow-up plan. The data were gathered up to 12 months of age and sourced from the infant's general practitioner and/or cardiologist.

Outcomes

The primary outcome was the documentation of the time of the closure or permanent patency of the PDA in a large cohort of VLBW infants who did not receive medical or surgical treatment and therefore document the "natural history" of PDA. The secondary outcome was the comparison of the demographics and the outcomes of infants who achieved spontaneous PDA closure during the hospital stay with those who did not.

Statistical Analysis

Data were analyzed by using a Mann–Whitney *U* test, a χ^2, or a Fisher's exact test as appropriate. The incidence proportion of ductal patency was analyzed with the Kaplan-Meier model for different gestational age (GA) and weight groups. The Bonferroni correction was used for multiple comparisons among the groups. We used forward stepwise Cox regression to examine variables predictive of PDA patency; the tested variables were GA, BW, sex, multiple pregnancy, ANS, and IUGR. Cox regression is a method for investigating the effect of several variables on the time it takes for a specified event to happen (in our study, PDA patency at discharge from the hospital). The hazard ratio yielded from Cox regression is then expressing the ratio of hazard (probability) rates that are 1 U apart (eg, 1 gestational week). Infants who received medical or surgical treatment were not included in the Kaplan-Meier model or in the regression analysis. Statistical analysis was executed by using the IBM SPSS Statistics 24.0.0.0 software (IBM Corp, Armonk, NY).

RESULTS

In total, 368 VLBW infants were born within the study periods; 242 in center 1 and 126 in center 2. Seventy-one infants were excluded (Fig 1). Data on 297 VLBW infants (study group) were eligible for analysis. The mean weight and GA in the study group were 1112 ± 269 g and 29 ± 2 weeks, respectively. Forty-eight percent were boys, 42% were from multiple pregnancies, 17% were small for GA, and 89% were partially or fully exposed to ANSs.

PDA-Treated Patients

Out of the 297 infants in the study group, 17 infants received PDA treatment, 14 received medical treatment, 1 had PDA ligation performed later, and 3 additional infants were selected for PDA ligation without previous medical therapy. PDA closed in 6 infants receiving medical treatment, but remained open in another 7 infants.

Conservative PDA Management

Two hundred and eighty infants continued to be managed in a truly conservative manner. In 237 (85%) of them, PDA closed before hospital discharge. The Kaplan-Meier model revealed the incidence proportion of PDA closure over time for different GAs. For this group, the median (95% confidence interval [CI]) was 71 (51–91) days in <26+0 GA, 13 (0–34) days in 26+0 to 27+6 GA, 8 (7–9) days in 28+0 to 29+6 GA, and 6 (4–8) days in ≥30 GA. For BW groups, the median (95% CI) was 48 (9–87) days in <750 g; 22 (6–38) days in 750 to 999 g; 9 (6–12) days in 1000 to 1249 g; and 8 (7–9) days in 1250 to 1500 g (Figs 2 and 3). A statistically significant difference was found between the medians of ductal closure among infants born <27+6 and >28+0 GA and among infants <1250 g and >1250 g (Table 1).

Forward stepwise Cox regression revealed that the GA was the only significant predictor of ductus closure ($P < .0001$, hazard ratio 1.28, 95% CI 1.20–1.36) when all variables in the model were used. However, because GA and BW were significantly correlating and collinear ($r^2 = 0.54$, $P < .0001$), we tested

for GA and BW separately with the following additional tested variables: sex, multiple pregnancy, ANSs, and IUGR. Without including GA, BW became a statistically significant predictor of the ductus closure ($P < .0001$, hazard ratio 1.002, 95% CI 1.001–1.002). In the model excluding the BW, GA was the only statistically significant predictor of the ductus closure ($P < .0001$, hazard ratio 1.29, 95% CI 1.21–1.38), as expected. Sex, multiple pregnancy, ANSs, and IUGR were not statistically significant predictors in either model.

Comparison of Infants With Closed and Open PDA at Hospital Discharge

In conducting the univariate analysis, we found no statistically significant difference in severe neonatal morbidities (BPD, IVH grades III and IV, PVL, NEC grades ≥IIb, and ROP stages ≥III) between the infants who achieved spontaneous PDA closure and those whose PDA remained open in the truly conservative group (Table 2).

However, when infants who underwent treatment were included in the comparison, a statistically significant difference was found not only between the GA and the BW but also in the incidence of severe IVH: 2 (1%) infants in the PDA closure group vs 4 infants (8%) in the PDA nonclosure group ($P = .008$).

Follow-up After Hospital Discharge

Spontaneous PDA closure occurred in 24 (56%) out of 43 patients discharged from the hospital with ductus patency without previous medical treatment. Six patients were lost to outpatient follow-up. We cross-checked data for these 6 patients with the only cardiothoracic or cardiac center in each country (Our Ladies Children's Hospital, Crumlin, Dublin, Ireland, and University Hospital Motol, Prague, Czech Republic), and none of them underwent surgical intervention or presented with cardiac failure. Only 2 infants underwent artificial postdischarge closure, 1 by surgical ligation and 1 by percutaneous catheter device closure. In 11 infants, PDA remained open but nonsignificant 1 year after hospital discharge. Seven infants were discharged from the hospital with open PDA after failed medical treatment. Out of those, 2 experienced spontaneous postdischarge closure, 1 underwent surgical ligation, and 1 underwent percutaneous catheter device closure; PDA remained open in 3 of them after 1 year postdischarge. Overall, PDA was closed in 261 infants (93%) at the age of 12 months.

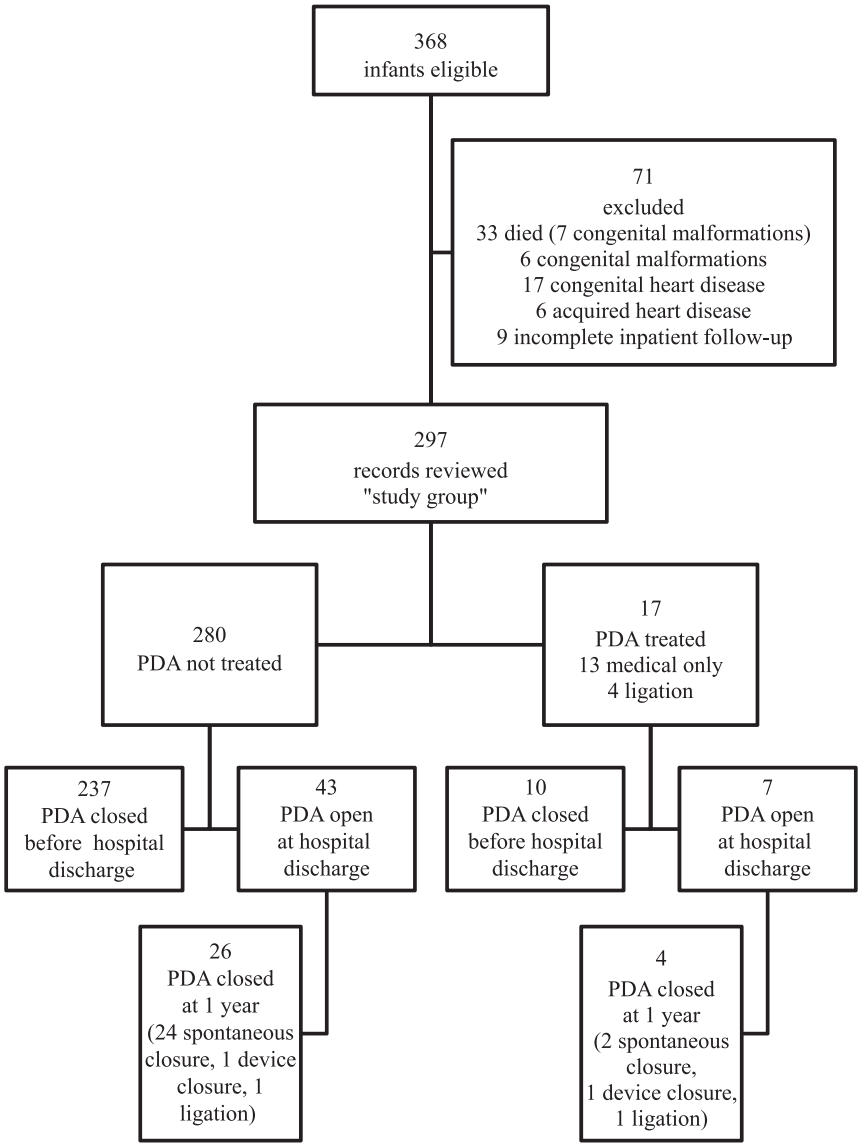

FIGURE 1
Overall number of eligible infants identified with subsequent flowchart of the study.

Neonatal Mortality

The overall mortality among infants eligible for the study was 9% (33 out of 368). Seven patients died because of serious congenital malformations. Twenty-six remaining infants died before hospital discharge; 19 died within the first 7 days, and 7 died later. The mean weight and GA were significantly lower than the study

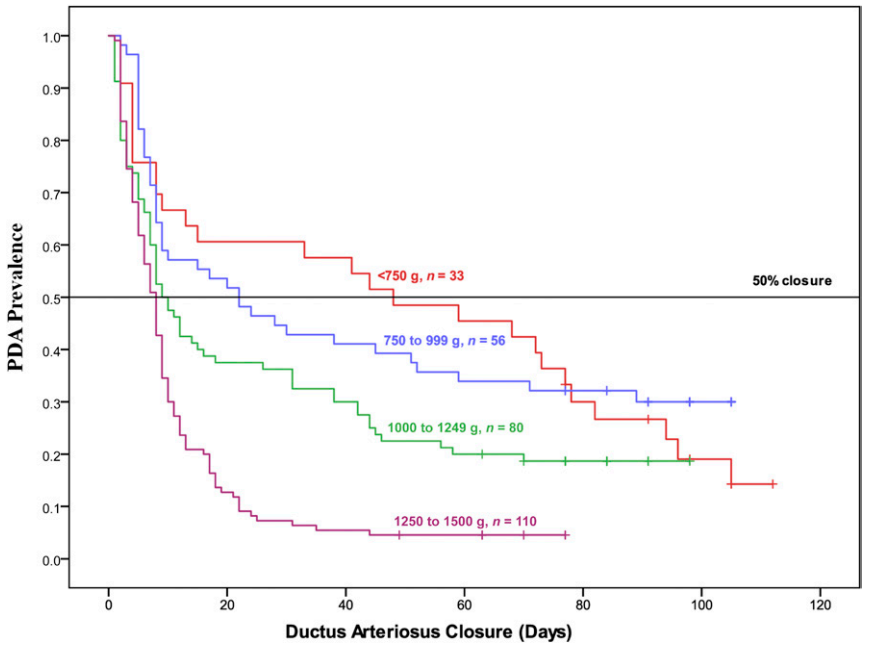

FIGURE 2

Prevalence of ductal patency stratified by BW over time before hospital discharge. The horizontal line represents 50% closure. The plus sign signifies censored patients who were discharged from the hospital before closure.

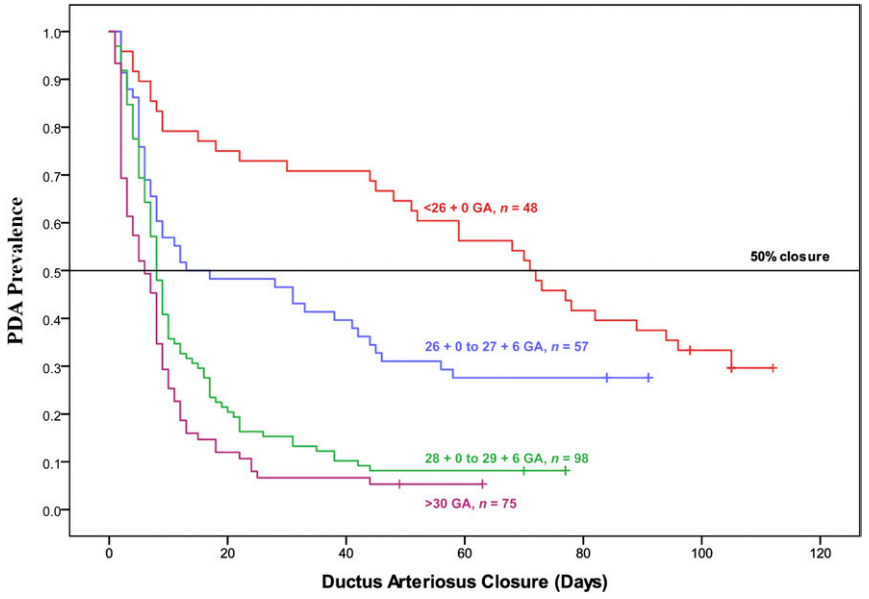

FIGURE 3

Prevalence of ductal patency stratified by GA over time before hospital discharge. The horizontal line represents 50% closure. The plus sign signifies censored patients who were discharged from the hospital before closure.

group (789 ± 256 g and 25.5 ± 2 weeks, respectively, $P < .0001$). The incidence of IVH and NEC was also significantly higher in comparison with survivors (52% vs 2% and 26% vs 1%, respectively, $P < .0001$). However, the main cause of death was early- or late-onset infection in 10 infants followed by severe IVH (which influenced further management of already critically ill infants) in 7 patients and NEC in 5 patients. Pulmonary hemorrhage occurred in 4 infants, and in 1 infant it was stated to be the main cause of death. Ten out of 19 infants who died before 7 days of age had a point-of-care ECHO done, and all of them had documented PDA. None of them was medically treated. Out of 7 infants who died after day 7, 3 of them had NEC stated as the cause of death. Six out of these 7 infants died with open PDA, and 2 of them were previously medically treated for the same without any positive result.

The overall results of the infants eligible for the study in comparison with the data from the Vermont Oxford Network are available in Table 3.

DISCUSSION

The data represent the true "natural history" of PDA derived from a robust retrospective cohort of VLBW infants who underwent noninterventional, conservative management. The likelihood of spontaneous closure before hospital discharge is age- and weight-dependent as documented in the Kaplan-Meier figures. Although the rate of spontaneous closure differs significantly among some of the weight and GA categories, spontaneous closure before hospital discharge occurs in the majority of even the youngest and smallest infants, specifically those with a GA <26 weeks' gestation (68%) and a BW <750 g (76%).

We have excluded the deceased infants from the analysis. However, out of 26 infants who died, 16 had a recorded cause of death that could be potentially related to PDA: IVH ($n = 7$), NEC ($n = 5$), and pulmonary hemorrhage either associated with IVH or alone ($n = 4$). Ten infants who died before 7 days of age had point-of-care ECHO done, and all of them had documented PDA; none of them were medically treated for PDA. We could speculate that the outcome of some deceased infants could be

influenced by early PDA treatment. However, the criteria for such treatment remain currently unclear.

There were no differences in morbidities in nontreated infants. The absence of a statistically significant difference between the groups may just be a consequence of a sample size insufficient to detect differences in those low-incidence morbidities, but it may also be that as morbidity rates have declined in recent years, these conditions may have become dissociated from historical risk indicators such as PDA. When including the treated infants in our study group in the univariate analysis, a significant difference in the incidence of severe IVH becomes apparent between the infants whose PDA closed and those whose remained open until hospital discharge. We suppose that the failed treatment itself has no causal relationship to the severe IVH because no infant received early treatment; all treatments were administered beyond day 3 of life. This result could reflect the fact that the overall "sickest" infants would have persistent PDA despite treatment.

Our data are in agreement with other published studies presenting conservative PDA management.[17,18] The mean closure date in our group of infants <26 weeks GA occurred later than in the cohort recently presented by Sung et al,[18] and the rate of infants discharged from the hospital with open PDA was higher in our group (32% and 5%, respectively). This difference could probably be explained by different fluid management. Sung et al[18] practiced significant fluid restriction with an average fluid intake of 107 ± 20 to 115 ± 21 mL/kg per day between days 7 and 28. In our study, fluid restriction was not routinely applied and diuretics were not used in either participating center. However, the rate of CLD in infants of GA 23 to 26 weeks was similar in both cohorts (34.5% in our cohort as compared with 38%).[18]

TABLE 1 Comparison of Spontaneous DA Closure Time Among Different BW and GA Groups (Statistical Significance $P < .05$)

$N = 280$	Time to Ductal Closure (d), Median (95% CI) IQR [Q1, Q3] SE of the Median (Kaplan-Meier)	Pairwise Comparison Between the Groups, *P*, Mantel-Cox Log Rank Test	Adjusted *P* Value for Multiple Comparisons (Bonferroni Correction)
≤750 g[a]	48 (9–87)	—	—
	[8, 94]	.700[b]	>.999[b]
	20	.058[c]	.347[c]
		<.001[d]	<.001[d]
751–1000 g[b]	22 (6–38)	.700[a]	>.999[a]
	[7, NA]	—	—
	8	.042[c]	.255[c]
		<.001[d]	<.001[d]
1001–1250 g[c]	9 (6–12)	.058[a]	.347[a]
	[3, 44]	.042[b]	.255[b]
	2	—	—
		<.001[d]	.002[d]
1251–1500 g[d]	8 (7–9)	<.001[a]	<.001[a]
	[3, 12]	<.001[b]	<.001[b]
	1	<.001[c]	.002[c]
		—	—
<26+0 GA[e]	71 (51–91)	—	—
	[18, NA]	.028[f]	.169[f]
	10	<.001[g]	<.001[g]
		<.001[h]	<.001[h]
26+0–27+6 GA[f]	13 (0–34)	.028[e]	.169[e]
	[6, NA]	—	—
	11	.001[g]	.003[g]
		<.001[h]	<.001[h]
28+0–29+6 GA[g]	8 (7–9)	<.001[e]	<.001[e]
	[5, 17]	.001[f]	.003[f]
	1	—	—
		.027[h]	.164[h]
>30 GA[h]	9 (4–8)	<.001[e]	<.001[e]
	[2, 11]	<.001[f]	<.001[f]
	1	.027[g]	.164[g]
		—	—

P value is a result of comparison of the BW and GA groups labeled a, b, c, d and e, f, g, h, respectively. NA, not applicable (because Q3 was outside of the inpatient stay); IQR, interquartile range; Q1, 25th percentile; Q3, 75th percentile.

TABLE 2 Comparison of Demographics and Clinical Outcomes of VLBW Infants With and Without Spontaneous PDA Closure Before Hospital Discharge

	PDA Closure Group ($n = 237$)	PDA Nonclosure Group ($n = 43$)	*P*
GA, wk, mean ± SD	29.2 ± 2.3	27.5 ± 2.0	.0001
Birth wt, g, mean ± SD	1145 ± 264	1004 ± 239	.001
ANSs, *n* (%)	215 (91)	37 (86)	.404
Multiple pregnancy, *n* (%)	99 (42)	19 (45)	.867
Sex: M/F	50, 50	44, 56	.510
IUGR, *n* (%)	41 (17)	6 (14)	.665
Severe IVH (grade III and IV), *n* (%)	2 (1)	2 (5)	.113
PVL, *n* (%)	4 (2)	1 (2)	.573
BPD, *n* (%)	24 (10)	8 (19)	.123
NEC grade ≥IIb, *n* (%)	2 (1)	1 (2)	.395
ROP stage ≥III, *n* (%)	4 (2)	0 (0)	>.999

Infants with natural course of DA only, $n = 280$.

The overall mortality and the rate of significant neonatal morbidities in our cohort compare favorably to large databases, including centers with different PDA management policies. The results of this large

TABLE 3 Comparison of the Neonatal Outcomes of All the Infants Eligible for the Study (BW ≤1500 g) Including Deaths and Congenital Anomalies to the Vermont-Oxford Network (BW 401–1500 g or GA From 22 Weeks, 0 Days to 29 Weeks, 6 Days)

	Eligible Infants (n = 368)	Vermont-Oxford Network 2013 (n = 60 562)
Mortality (%) [Q1, Q3]	9.0	14.6 [9.0, 18.4]
CLD (%) [Q1, Q3]	14.6	24.5 [10.5, 30.7]
Severe IVH (grade III and IV) (%) [Q1, Q3]	5.0	8.1 [3.5, 10.6]
PVL (%) [Q1, Q3]	2.4	2.9 [0.0, 4.1]
NEC ≥IIb (%) [Q1, Q3]	3.6	4.6 [0.0, 6.5]
Severe ROP (stage ≥III) (%) [Q1, Q3]	2.4	6.2 [0.0, 8.3]

cohort of infants who underwent truly noninterventional management might encourage further placebo-controlled studies by demonstrating the relative safety of the conservative approach.

Spontaneous PDA closure postdischarge in early infancy is frequently documented,[23] and our results are in agreement. In circumstances where cardiology feels that invasive closure is indicated, the occlusive device appears to be the modality of choice, as it is a much less invasive procedure than surgical ligation. Because a late medical PDA treatment is less effective[6] and indications for late PDA treatment are unclear, it might be beneficial to await early infancy before a closure decision.

The results need to be interpreted cautiously because of the retrospective nature of this study. We acknowledge other obvious limitations. Although the echocardiographic studies were conducted in the first week of life and then regularly in 1 to 2 weekly intervals, the days differ among the infants. The decision to treat was not uniform and sometimes difficult to retrospectively elucidate. The parameters of PDA echocardiographic or clinical significance were not accounted for in the data analysis. Also, the hospital discharge policy might differ significantly among institutions. We have therefore calculated the rate of PDA closure at 36 weeks postmenstrual age. The total closure rate in the truly conservative group of 280 infants at 36 weeks postmenstrual age was 83% as opposed to 85% at hospital discharge.

CONCLUSIONS

Spontaneous closure of the PDA is likely in VLBW infants, as demonstrated in a large cohort of infants who underwent truly noninterventional, conservative PDA management. The rate of permanent ductal patency at hospital discharge is inversely related to GA and BW. The results support the existing data on the feasibility of conservative management without an increase in neonatal morbidity and mortality. However, it is physiologically plausible that some infants might benefit from PDA treatment. The criteria for which infants will benefit from the treatment are not currently defined. Such criteria could be determined through randomised controlled trials and our data on infants managed conservatively provides a platform for future placebo-controlled research, as it has demonstrated the safety of the use of a placebo arm for such trials.

ABBREVIATIONS

ANS: antenatal steroid
BPD: bronchopulmonary dysplasia
BW: birth weight
CI: confidence interval
CLD: chronic lung disease
DA: ductus arteriosus
ECHO: echocardiography
GA: gestational age
IUGR: intrauterine growth restriction
IVH: intraventricular hemorrhage
NEC: necrotizing enterocolitis
PDA: patent ductus arteriosus
PVL: periventricular leucomalacia
ROP: retinopathy of prematurity
VLBW: very low birth weight

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