**Ductus Arteriosus and Failed Medical Therapy**

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**Abstract**

**Background**

Management of a patent ductus arteriosus (PDA) after pharmacological therapy failure in preterm neonates is controversial and shows marked practice variation. To evaluate which factors motivate the decision to ligate a PDA in clinical practice we examined several clinical and echocardiographic variables.

**Methods**

We conducted a retrospective single center cohort study. We included infants born less than 37 weeks of gestation, admitted to our neonatal intensive care between 01.01.2008 and 31.12.2015 with a PDA detected on echocardiography after two or three courses of medical therapy. Logistic regression analyses were used to predict surgical ligation for twelve clinical and nine echocardiographic variables separately. We used the multiple imputation technique for missing values.

**Results**

89 neonates were included of which forty (45%), underwent surgical ligation of their PDA. In our final multivariate regression model, invasive respiratory support (OR 3.6, 95% CI 1.29-10.03), left atrial/aortic root ratio (OR 5.48, 95% CI 1.66-18.11) and presence of ductal steal (OR 3.82, 95% CI 1.47-9.91) were significant predictors for surgical ligation. The prediction model using clinical and echocardiographic variables explained 9% and 24% of the variability to ligate respectively, indicating significant residual variation due to unmeasured factors.

**Conclusions**

Our results indicate that invasive respiratory support, increased left atrial/aortic root ratio and the presence of ductal steal were important predictors for surgical ligation in our center. However, this explained only a small proportion of the variability, which emphasizes the need for evidence-based guidelines in the management of preterm neonates after failed pharmacological therapy for a PDA.

**Key words:** Surgical ligation, preterm infants, echocardiography

**Abbreviations:** PDA= patent ductus arteriosus, BPD= bronchopulmonary dysplasia, NEC= necrotizing enterocolitis, IVH= intraventricular hemorrhage, NICU= neonatal intensive care unit, NSAIDs= non-steroidal anti-inflammatory drugs, DFLPA= diastolic forward flow in left pulmonary artery, LA/Ao= left atrial/aortic root, LVIDD= left ventricular internal end-diastolic diameter, MI= multiple imputation, MCAR= missing completely at random, OR= odds ratio, CI= confidence interval

# Introduction

A patent ductus arteriosus (PDA) is defined as the failure of the physiological closure of the ductus arteriosus, which normally occurs within one to five days after delivery in full-term newborns [1]. A PDA is especially common in preterm neonates with an incidence inversely correlated with gestational age and birth weight [2–4], occurring in approximately 70% of infants born before 28 weeks of gestation [5]. A PDA has been associated with several adverse clinical outcomes such as bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), intraventricular hemorrhage, (IVH) and death [6,7] due to increased pulmonary blood flow and redistribution of flow to other organs [7].

Treatment options for a PDA are conservative management, pharmacological therapy or surgical ligation, but the optimal treatment strategy remains a subject of debate [8–10]. In modern day practice the first-line therapy for a significant PDA is pharmacological closure with ibuprofen or indomethacin[11]. Unfortunately, successful closure of a PDA occurs in approximately 50% after the first course, with a further 29% closing after a second course[12,13]. Until now, little information is available to guide neonatologists and pediatric cardiologists on actions to take after failure of pharmacological therapy. Surgical ligation of a PDA may be performed in these cases [5,14–17], but there is still no convincing evidence of which infants would benefit most from surgical ligation[18]. The decision seems to be based upon personal preferences and past experience, and varies between institutions and caregivers [9]. Given this lack of consensus, we aimed to identify which clinical and echocardiographic factors guided the decision to surgically close a PDA after failure of pharmacological therapy in our Neonatal Intensive Care Unit (NICU). We hypothesized that ligation of a prolonged PDA is performed more frequently in neonates with a lower gestational age, longer ventilator dependency and more comorbidities (NEC, BPD).

# Patients and Methods

## Study population

We conducted a retrospective single-center cohort study in the NICU of the Amsterdam University Medical Center, location AMC. We included all infants less than 37 weeks gestation admitted to the NICU between 01.01.2008 and 31.12.2015 with a PDA still evident on an echocardiogram after two or three courses of medical therapy. We excluded neonates with other significant congenital heart disease, chromosomal abnormalities and with four or more missing values.

## Protocol

In our NICU, an echocardiogram is routinely performed in all infants born before 27 weeks of gestation on day three to five. In infants born after 27 weeks, an echocardiogram is only performed if there are clinical symptoms suggestive of a PDA, such as a heart murmur or in cases with unexplained pulmonary compromise. During the study period a hemodynamically significant PDA was treated with a course of non-steroidal anti-inflammatory drugs (NSAIDs), which could either be ibuprofen or indomethacin. A PDA was judged to be ‘hemodynamically significant’ based on the criteria of Skinner *et al.*[19], as shown in “Table S1”. Indomethacin was the first choice of treatment up until 2010. After a systematic review showing a reduced risk of NEC and transient renal insufficiency for ibuprofen when compared to indomethacin, the first choice of treatment became ibuprofen [20]. For ibuprofen the dosage was 10 mg/kg on day 1, followed by 5 mg/kg for day two and three. The dosage of indomethacin was 0.2 mg/kg as a loading dose, followed by 0.2mg/kg/day at 12-hour intervals for three days. After completion of the first course, the echocardiogram was repeated. If the ductus was still patent, a second three-day course of NSAIDs was given. In some patients a third course was given. If the ductus was still open after the second or third course of NSAIDs, as assessed by echocardiography, the options were surgical ligation or a conservative approach.

## Measurements

The following clinical variables were collected at the time the decision was taken to either ligate the PDA or pursue a conservative approach: gender, gestational age, birth weight, maternal use of antenatal steroids, delivery method (vaginal/caesarean), Apgar score at five minutes (<7/≥7), surfactant use, and the number of days between birth and start of the first course of pharmacological therapy. We also collected partial pressure of carbon dioxide (pCO2, <7kPa / ≥7kPa), the type of respiratory support (non-invasive/invasive), presence of tachypnoea (>60/min), pulse pressure (systolic blood pressure minus diastolic pressure), and presence of edema.

Echocardiographic variables collected included ductal diameter (in mm), diastolic forward flow into the left pulmonary artery (DFLPA, in cm/s), left atrial to aortic root ratio (LA/Ao ratio), left ventricular internal end-diastolic diameter (LVIDD, in % of normal), mitral valve regurgitation (yes/no), presence of abdominal steal (i.e., zero or negative diastolic flow in descending aorta or coeliac artery, yes/no), and peak flow velocity in the ductus (m/s). Since there are no Z-scores for postnatal ductal size, we adjusted ductal size for body weight at the time of the measurement for a better interpretation of ductal size. We also calculated the difference in velocity between systolic and diastolic flow (delta velocity in m/s) as a representation of the flow in the ductus. If there was a bi-directional shunt present, the delta velocity was equal to the peak flow velocity (as we calculated the difference between peak flow velocity and the baseline, which is zero). If no value was available within the first week after completion of NSAID therapy, it was stated to be missing.

## Multiple imputation

To maximize the inclusion rates for our analysis, we imputed missing data based on the multiple imputation (MI) method. The MI method replaces missing values with imputed ones based on more than one prediction model, therefore generating multiple complete datasets for analysis. The statistical reasoning is that the observed-data likelihood can be approximated by the average of the completed-data likelihood [21]. Our imputation method was the fully conditional specification. This is an iterative Markov chain Monte Carlo method that fits a univariate model using all the other available variables as predictors with 100 iterations. Logistic regression and predictive mean matching were used for dichotomous and numeric data, respectively. In our data, five imputation sets were used which should give an efficiency of 99% compared to using an infinite number of imputations [22]. All of our missing numerical variables were normally distributed. Little’s missing completely at random (MCAR) test was used for testing the assumption of randomization of missing data. For validation we compared data of the complete cases with the incomplete cases.

## Data analysis

Patients’ characteristics were described by mean value and standard deviation, median value and range or by rate and percentage, where appropriate. For group comparisons of continuous data, T-tests and Mann-Whitney U tests were used for normally and non-normally distributed data, respectively. Statistical testing of categorical variables was performed using chi-square test. First, a univariate logistic regression analysis was conducted to predict surgical ligation of a PDA using clinical and echocardiographic variables as predictors. Secondly, a multivariate final model was created using the relevant variables from the univariate analysis. Odds ratio (OR) and 95% confidence intervals (CI) were estimated. The Hosmer Lemeshow test was used to assess model goodness of fit and Nagelkerke’s R2 is reported as an indication of the variation in our outcome variable that is explained by our model.

SPSS (SPSS Inc., Chicago IL, USA, version 24) was used for the statistical analyses and a p-value less than 0.05 was considered to be significant.

# Results

A total of 89 neonates were included, 40 of whom underwent surgical ligation of their PDA. Gestational age ranged from 24 to 31.6 weeks with a mean of 26.7 weeks (SD 1.76). Median birth weight was 895 grams (range 560-1930). Twelve neonates (13%) received a third course of medical therapy. The type of medical treatment was missing in one patient. Of the remaining 88, 59 (67%) received ibuprofen, 27 (31%) indomethacin and two patients (2%) received both. A summary of the patients’ characteristics is shown in (Table 1) and a comparison between the conservative and surgical ligation groups is shown in (Table 2).

## Multiple Imputation

An overview of the differences between incomplete and complete cases is shown in “Table S2”. Little’s MCAR test was not significant (p=0.09), indicating that our data was missing at random. This allowed us to use the MI technique. Characteristics of patients with complete data were comparable to those with incomplete data (see “Table S2”). Complete data was achieved for 57 (64%) of the 89 patients. Of the remaining two patients, 16 (50%) had one value missing, 14 (44%) had two missing values and two (6%) had three missing values. Eight of the 21 variables included for analysis were incomplete. The incomplete variables and the percentage missing were as follows: Pulse pressure (17%), presence of steal (10%), mitral valve regurgitation (7%), pCO2 level (7%), LVIDD (6%), DFLPA (5%), peak flow velocity (2%) and edema (2%). In total 3% (49 out of 1820) of the values were missing.

## Logistic regression

An overview of the OR and 95% CI for the univariate and the final multivariate model is shown in “Tables 3 and 4” for the clinical and echocardiographic predictors, respectively. All results shown are the pooled results from the original and the five imputed datasets.

In our final model, the omnibus test for overall goodness of fit was significant (p= 0.01) meaning that there is a significantly better fit of the data in favor of the model with predictors. The Hosmer Lemeshow test could not be interpreted for our clinical model, as there were not enough subgroups available for adequate interpretation. For our echocardiographic model, the Hosmer Lemeshow test was not significant (p= 0.60-0.89) indicating that the model predicted outcomes did not significantly differ from the observed outcomes in the original data.

Our model with the clinical predictors predicted 64% of the outcomes, with surgical ligation as the dependent variable, correctly. Nagelkerke’s R2 indicated a relationship of 9% between the predictors and prediction. Our model with the echocardiographic variables predicted 69-70% correctly. Nagelkerke’s R2 was 23.3-25.2%. The low Nagelkerke’s R2 indicate that our model explained only a minor proportion of the variability to ligate the PDA.

# Discussion

In the present study we investigated the predictive value of clinical and echocardiographic parameters for the decision of surgical ligation after failure of pharmacological closure of a PDA in preterm neonates. Our results demonstrate that invasive respiratory support, a higher LA/Ao ratio and the presence of steal guided the decision for surgical ligation in our NICU.

Interestingly, in our first univariate analysis ductal diameter was not a significant predictor for surgical ligation. However, after adjustment for weight we found it to be of predictive value. We were not the first to adjust ductal diameter for weight as a better reflection of the dimension relative to subject size. El Hajjar *et al.*[23] and Visconti *et al.*[24] both found an inverse relationship between ductal diameter after adjusting the diameter for weight, and spontaneous closure. When looking into proposed staging systems, such as the Skinner criteria[19] or the one as proposed by McNamara *et al.*[25], the absolute ductal diameter is one of the criteria for a hemodynamically significant duct. Our finding suggests that weight adjusted ductal dimensions may be more valuable in clinical decision making than absolute ductal dimensions.

There were significantly more adverse outcomes in the surgical ligation group than in the conservative management group. A possible explanation could be the significantly lower birth weights in the ligation group. Also, surgical ligation seems to be reserved for those infants with a persistent significant PDA on clinical and echocardiographic grounds [16]. This could indicate that we tend to ligate PDAs in sicker infants, or that ligation is an independent risk factor for death. In our study, two out of nine deaths in the surgical ligation group occurred within the first week after PDA ligation, and five infants died within the first month. There was one infant who died before ligation could take place. The independent risks of the PDA and the added effect of ligation on adverse outcomes are difficult to establish and we have to be careful when interpreting results on adverse outcome after ligation [26].

Our prediction model with the clinical variables explained 9% of the variance to ligate a PDA, and a model with the echocardiographic variables explained 23-25%, indicating significant residual variation based on other, unmeasured factors. A possible explanation could be that clinicians’ individual preference or experience is an important predictor on the variation in PDA treatment, a finding that is confirmed in various studies [27,28].

## Strengths and weaknesses

For validation of our model we performed sensitivity analyses that demonstrated minimal differences between original and imputed data, confirming accurate use of statistical techniques. Also, even though missing data was present Little’s MCAR test indicated that no systematic differences in complete and incomplete cases existed and therefore selection bias was unlikely. Our study has several limitations. Firstly, there were some factors that could have introduced bias. Some of the neonates received a third course of medication and were included in the conservative group. For sensitivity analyses we excluded these neonates and we found the same results. Secondly, regression analysis tends be ‘overfitting’, meaning that our prediction model might be good at predicting the outcome in our data, but might be difficult to generalize to another population [29]. A third limitation is the relatively small sample size, which might not justify an immediate translation to clinical practice. Furthermore, intra and inter-physician variability in the evaluation of the PDAs over time cannot be excluded. Lastly, because of the long time period of this study and a potential changed approach over time, two PDAs of the same clinical significance in similar infants may not have been treated similarly during the period of the study. Indeed, we saw a PDA ligation rate reduce from 62% in 2008 to 13% in 2015. (The ligation rate for 2015 is hypothetical, as one infant died before the surgery could take place.) This is in line with the trend described by El-Khuffash *et al.*[16]. They proposed that the emergence of non-invasive positive-pressure ventilation modalities had led to earlier successful extubation of infants, facilitating conservative management after failure of pharmacological closure. Trying to adjust for this by stratification based on year of treatment was not possible due to the small number of patients in our cohort. Lastly, there is no consensus about the definition of a hemodynamic significant duct and the potential echocardiographic risk factors used are authority-based and not validated [30]. An important first step could be the recognition of those infants with PDAs that would benefit the most from surgical ligation. Until these issues are resolved, we realize that all decisions to ligate PDAs remain somewhat subjective.

# Conclusion

Our study indicates that invasive respiratory support, an increased LA/Ao ratio and the presence of steal significantly increased the chance of ligation over a conservative approach after pharmacological treatment failure of a PDA in preterm neonates in our NICU. Our model only explained a small amount of the variability, indicating that important factors that guide clinical decision making remain undetermined. Ultimately, evidence-based guidelines are necessary to facilitate risk-stratification of patients with a persistent PDA to ensure that the best treatment choices are made where possible. The first step in this process should be to assess which infants benefit most from surgical ligation.

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| Tables

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| Table 1: General population characteristics and demographics. Data are presented as mean (standard deviation), median{range} or n (%) |
| Number | 89 |
| Gestational Age (weeks) | 26.8 (1.76) |
| Birth weight (g)a | 895 {560-1930}  |
| Gender (male %) | 53 (60) |
| Antenatal steroids (%) | 71 (80) |
| Surfactant administered (%) | 52 (58) |
| Caesarean delivery (%) | 24 (27) |
| Apgar score at 5 min ≤ 6 (%) | 33 (37) |
| Time difference birth and start first course of medication (days)a | 7 (2-45) |
| Death (%) | 10 (11) |
| BPD (%) | 51 (57) |
| NEC (%) | 9 (10) |
| IVH (grade 3 or 4) (%) | 7 (8) |
| Surgical ligation (%) | 40 (45) |

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| aNon-normal distributionBPD= Bronchopulmonary dysplasia, NEC= Necrotizing enterocolitis, IVH= intraventricular hemorrhage,  |

Tables

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| Table 2: Comparison between conservative and surgical ligation groups in original data. Data are presented as mean (standard deviation), median (range) or n (%) |
|  | Conservative group (n=49) | Surgical ligation (n=40) | p |
| Gestational age (weeks) | 27.1 (1.56) | 26.3 (1.90) | 0.03 |
| Birth weight (g) | 960 (610-1930) | 823 (560-1500) | 0.004 |
| Gender (male %) | 30(61) | 23(58) | 0.72 |
| Use of antenatal steroids (%) | 36(73) | 35(88) | 0.10 |
| Caesarean delivery (%) | 17(35) | 7(18) | 0.07 |
| Apgar score at 5 min ≤ 6 (%)  | 19(39) | 14(35) | 0.71 |
| Surfactant use (%) | 26(53) | 26(65) | 0.26 |
| pCO2 ≥7 kPa(%) | 25(58)a | 29(73) | 0.17 |
| Time difference birth and start first course of medication (days) | 8 (3-45) | 6 (2-29) | 0.02b |
| Tachypnoea (%) | 19(39) | 14(35) | 0.71 |
| Pulse pressure (mmHg) | 30.1 (9.1)a | 27.2 (7.3)a | 0.15 |
| Oedema (%) | 13(27) | 15(39)a | 0.20 |
| Invasive respiratory support (%) | 7(14) | 15(38) | 0.01 |
| DFLPA (cm/s) | 24.8 (11.9)a | 31.7 (12.9)a | 0.01 |
| LA/Ao ratio (median, range) | 1.5(1.2-3.1) | 1.8(1.2-3.2) | 0.001b |
| MV regurgitation (%) | 15 (33)a | 16(42)a | 0.41 |
| Presence of steal (%) | 10 (23)a | 21(58)a | 0.001 |
| LVIDD (% of normal) | 120.2 (25.5)a | 127.7 (27.0)a | 0.20 |
| Ductal diameter (mm) | 1.8 (0.7) | 2.1 (0.8) | 0.02 |
| Ductal diameter adjusted for weight (mm/kg) | 1.5 (0.73) | 2.1 (0.89) | 0.001 |
| Peak flow velocity (m/s) | 2.6 (0.85) | 2.3 (0.79) | 0.06 |
| Delta velocity (m/s) | 1.28 (0.64) | 1.31 (0.45) | 0.80 |
| BPD (%) | 21(43) | 30 (77)a | 0.001 |
| NEC (%) | 3(6) | 6(15) | 0.17 |
| IVH (grade ≥3) (%) | 3(6) | 4(10) | 0.59 |
| Death (%) | 1(2) | 9(23) | 0.002 |
| Total adverse outcomes (%) | 26(53) | 35(92)a | <0.001 |
| aMissing data was present. The % is the correct reflection of the total number of patients.  |
| bMann-whitney U test |
| BPD= Bronchopulmonary dysplasia, DFLPA= diastolic forward flow into the left pulmonary artery, IVH= intraventricular hemorrhage, LA/Ao= left atrium/aortic root ratio, LVIDD= left ventricular internal diastolic diameter, MV= mitral valve, NEC= Necrotizing enterocolitis |

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| Table 3. Regression analyses clinical variables.  |
| Variables | Univariate analysisOdds ratio (95% CI) | Invasive respiratory support + modelAdjusted odds ratio (95% CI) |
| Invasive respiratory support | 3.6 (1.29-10.03) | - |
| Use of antenatal steroids | 2.53 (0.82-7.84) | 2.92 (0.88-9.68) |
| pCO2 ≥ 7 kPa | 1.98 (0.78-5.02) | 2.75 (0.84-9.00) |
| Oedema | 1.73 (0.70-4.30) | 1.48 (0.57-3.84) |
| Surfactant use | 1.64 (0.70-3.88) | 1.25 (0.50-3.11) |
| Apgar score at 5 min ≥ 7 | 1.18(0.49-2.80) | 1.35 (0.54-3.36) |
| Female | 1.17 (0.50-2.73) | 1.25 (0.52-3.03) |
| Birth weight (grams) | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) |
| Gestational age (weeks) | 0.96 (0.93-0.998) | 0.97 (0.94-1.01) |
| Pulse pressure | 0.96 (0.90-1.03) | 0.98 (0.92-1.05) |
| Tachypnoea | 0.85 (0.36-2.02) | 1.10 (0.44-2.77) |
| Caesarean delivery | 0.40 (0.15-1.09) | 0.47 (0.17-1.32) |

CI= confidence interval

Tables

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| Table 4. Regression analyses echocardiographic variables.  |
|  | Univariate analysesOdds ratio (95% CI) | LA/Ao ratio + modelAdjusted odds ratio (95% CI) | LA/Ao ratio + steal + modelAdjusted odds ratio (95% CI) |
| Variables  |
| LA/Ao ratio | 5.48 (1.66-18.11) | - | - |
| Presence of steal | 3.68 (1.48-9.16) | 3.82 (1.47-9.91) | - |
| DD/W (mm/kg) | 2.96 (1.49-5.87) | 2.32 (1.13-4.80) | 1.79 (0.85-3.80) |
| Ductal diameter (mm) | 1.98 (1.08-3.63) | 1.49 (0.77-2.86) | 1.06 (0.51-2.20) |
| MV regurgitation | 1.42 (0.59-3.42) | 1.35 (0.53-3.42) | 1.11 (0.41-2.99) |
| Delta velocity (m/sec) | 1.11 (0.52-2.35) | 1.10 (0.50-2.42) | 0.92 (0.39-2.17) |
| DFLPA (cm/sec) | 1.04 (1.00-1.08) | 1.03 (0.99-1.07) | 1.03 (0.99-1.08) |
| LVIDD (% of normal) | 1.01 (0.99-1.03) | 1.01 (0.99-1.02) | 1.00 (0.98-1.02) |
| Peak flow velocity (m/sec) | 0.60 (0.35-1.03) | 0.64 (0.37-1.10) | 0.67 (0.37-1.19) |
| CI= confidence interval, DD/W= ductal diameter/weight, DFLPA= diastolic forward flow into the left pulmonary artery, LA/Ao= left atrium/aortic root, LVIDD= left ventricular internal diastolic diameter, MV= mitral valve  |

Supplementary table

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| Table S1. Skinner Criteria for hemodynamic significance of a patent ductus arteriosus |
|  | Small left-to-right shunt | Moderate left-to-right shunt | Large left-to-right shunt |
| Ductus diameter (mm) | <1.6 | 1.6-2.0 | >2.0 |
| Flow pattern in ductus | Closing | Growing/pulsatile | Pulsatile |
| DFLPA (m/s) | <0.20 | 0.20-0.40 | >0.40 |
| Flow in descending aorta  | Antegrade flow | None or some reversed flow | Reversed flow |
| Flow velocity in ductus (m/s) | >2.0 | 1.0-2.0 | <1.0 |
| LA/Ao ratio | <1.4 | 1.4-1.6 | >1.6 |
| For hemodynamic significance at least 2 indicators for a large left-to-right shunt or 1 indicator for large and at least 2 indicators for moderate were necessary. |
| DFLPA= diastolic forward flow into the left pulmonary artery, LA/Ao= left atrium/aortic root  |

Supplementary table

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| Table S2. Comparison between complete cases (CC) and incomplete cases (IC). Data are presented as mean (standard deviation), median (range) or n (%) |
|  | CC (n=57) | IC (n varies per variable) | p |
| Gestational age (weeks) | 26.5 (1.6) | 27.3 (1.9) (n=32) | 0.04 |
| Birth weight (g) | 895(560-1930) | 880(610-1500) |  |
| Gender (male %) | 37(65) | 16(50) | 0.17 |
| Use of antenatal steroids (%) | 47(82) | 24(75) | 0.40 |
| Caesarean delivery (%) | 15 (26) | 9 (28) | 0.85 |
| Apgar score at 5 min ≤ 6 (%) | 21(37) | 12 (38) | 0.95 |
| Surfactant use (%) | 34(60) | 18 (56) | 0.76 |
| pCO2 ≥7 kPa (%) | 37(65) | 17 (65) | 0.97 |
| Tachypnea (%) | 18(32) | 15 (47) | 0.15 |
| Pulse pressure (mmHg) | 28.3 (8.1) | 31.0 (9.4) (n=17) | 0.25 |
| Edema (%) | 17(30) | 11 (37) | 0.52 |
| Invasive respiratory support (%)  | 11(19) | 11 (34) | 0.11 |
| DFLPA (cm/s) | 28.3 (12.5) | 26.9 (13.4) (n=28) | 0.64 |
| LA/Ao (median, range) | 1.7(1.2-3.2) | 1.68(1.2-2.8) | 0.79a |
| MV regurgitation (%) | 19 (33) | 12 (46) | 0.26 |
| Presence of steal (%) | 25 (44) | 6 (26) | 0.14 |
| LVIDD (% of normal) | 123.6 (27.6) | 124.1 (24.0) (n=27) | 0.94 |
| Ductal diameter (mm) | 1.89 (0.73) | 2.02 (0.81)(n=32) | 0.42 |
| Delta velocity (m/s) | 1.3 (0.49) | 1.29 (0.67) (n=32) | 0.96 |
| Systolic velocity (m/s) | 2.5 (0.79) | 2.42 (0.93) (n=30) | 0.72 |
| Weight during echogram (kg) | 1.2 (0.54) | 1.1 (0.30) (n=32) | 0.62 |
| BPD (%) | 37(65) | 14 (45) | 0.07 |
| NEC (%) | 5(9) | 4 (13) | 0.58 |
| IVH(grade ≥3) (%) | 4(7) | 3 (9) | 0.82 |
| Death (%) | 8(14) | 2 (6) | 0.26 |
| Total adverse outcomes (%) | 42(75) | 19(61) | 0.18 |
| Surgical ligation (%) | 27(47) | 13(41) | 0.54 |
| a Mann-whitney U test |
| BPD= bronchopulmonary dysplasia, DFLPA= diastolic forward flow into the left pulmonary artery, IVH= intraventricular hemorrhage LA/Ao= left atrium/aortic root ratio, LVIDD= left ventricular internal diastolic diameter, MV= mitral valve, NEC= necrotizing enterocolitis |