Original Article

Early Surgical Closure of Patent Ductus Arteriosus Improves Respiratory Outcome in Symptomatic Preterm Neonates

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Background: Surgical intervention to treat patent ductus arteriosus (PDA) is required when pharmacological treatment is contra-indicated or fails; however, the optimal time to perform surgery remains unclear. We evaluated the clinical outcome of surgical closure of PDA on symptomatic preterm neonates according to the timing of the operation.

Methods: We retrospectively evaluated 117 symptomatic preterm neonates who underwent surgical correction of PDA between April 2010 and December 2016.

Results: Morbidity and mortality rates were compared based on the timing of surgery. The early occlusion group was associated with significantly lower incidences of bronchopulmonary dysplasia (BPD) (odds ratio [OR] 0.298, $p=0.011$) and pneumonia (OR 0.874, $p=0.023$) than the late occlusion group. However, the former group had higher rates of mortality and intraventricular hemorrhage (IVH). Early occlusion was performed principally on neonates with primary occlusions. The morbidity rate of the secondary occlusion group did not vary by surgical timing.

Conclusions: Delayed PDA closure after medical treatment failure in neonates was associated with a higher incidence of BPD. Early primary PDA closure may improve the respiratory outcomes of preterm neonates, with acceptable safety.

Keywords: patent ductus arteriosus, preterm, neonates, congenital heart disease

Introduction

In preterm neonates, patent ductus arteriosus (PDA) is associated with heart failure, respiratory distress, necrotizing enterocolitis (NEC), and retinopathy. Surgical intervention is usually performed when pharmacological treatment is contraindicated or fails. Although some reports of postoperative morbidity have appeared, surgical occlusion is an effective and safe method of PDA closure, reducing the risks of bronchopulmonary dysplasia (BPD) and mortality.[1–3] Two randomized controlled trials performed a few decades ago revealed improvements in respiratory outcomes after surgical PDA closure.[4, 5] Vida et al. described the benefits of early closure of the PDA after two cycles of medical treatment in premature infants.[6] However, the optimal time to perform surgery remains unclear. To the best of our knowledge, no studies have enrolled only symptomatic preterm neonates. Surgical closure of clinically significant PDA may be associated with less morbidity than prophylactic surgical closure in asymptomatic neonates. Thus, we analyzed the surgical outcomes of symptomatic preterm neonates who underwent PDA occlusion, and sought to identify the optimal timing of closure.

Methods

Patients

We retrospectively evaluated 117 symptomatic

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preterm neonates who underwent surgery to treat PDA at Seoul National University Children's Hospital between April 2010 and December 2016. Neonates with congenital intracardiac anomalies were excluded.

In our hospital, preterm neonates (<35 weeks) are routinely admitted to neonatal intensive care units. Whenever clinical parameters imply symptomatic PDA, echocardiography is performed. The clinical parameters used to define symptomatic PDA include worsening blood gas values, cardiomegaly or pulmonary congestion evident radiologically, and hypotension, in agreement with the suggestions made by Limrungsikul.[7]

In cases with symptomatic or hemodynamically significant PDA, intravenous ibuprofen is started if not contraindicated. Follow-up echocardiography is performed to assess any change in the PDA after the first ibuprofen cycle. A second ibuprofen cycle is given if follow-up imaging reveals persistent PDA. Then, depending on their response to medical treatment, cardiologists refer the neonates to surgeons. All patients in the present study underwent surgical intervention because medical treatment was contraindicated (such as NEC or acute kidney injury, IVH, or other evidence of bleeding; primary group) or failed (secondary group).

To evaluate the effect of surgical timing on outcomes, we divided all patients into two groups by surgical timing. The early group consisted of patients who were <10 days of age at the time of surgery and the late group consisted of all other patients. In other studies, the mean age after completion of the second cycle of ibuprofen was 9 to 10 days.[6, 8] In comparison, the median age of the subjects in our cohort was 10 days. Therefore, we defined 10 days as the criterion for the timing of the surgery. As the characteristics of the infants in the two groups differed, we divided each group into two subgroups by prescription of preoperative ibuprofen, to form primary and secondary subgroups.

We recorded gestational age, birth weight, Apgar scores at 1 and 5 min, any history of respiratory distress syndrome, use of surfactants, maternal pre-eclampsia status, and delivery mode (vaginal or cesarean). Preoperative data included age at operation; size of the PDA as revealed by echocardiography; the use of preoperative ibuprofen; co-morbidities such as congenital diaphragmatic hernia (CDH) or NEC (Bell's classification≥II)[9]; any pulmonary hemorrhage; hypotension; and acute kidney injury (AKI), BPD, intraventricular hemorrhage (IVH), sepsis, pneumonia, and pulmonary hypertension status. Postoperative complications included vocal cord palsy, re-operation because of coarctation of the aorta, chylothorax, pneumothorax, and bleeding. The outcomes included mortality; necrotizing enterocolitis (Bell's classification≥II); AKI (serum creatinine concentration≥1.5 mg/dL or urine output <1 mL/kg/h after the first 48 h); IVH (≥ grade III), BPD; and pneumonia.

Surgical Procedure

Under general anesthesia, the PDA was approached via a thoracotomy (usually through the third or fourth intercostal space). In approximately half of the cases (n=55), both ends of the PDA were ligated and then divided; double ligation of the duct was performed in the remaining cases. Most of the operations were performed at the bedside in the neonatal intensive care unit, especially when the baby weighed less than 2 kg.

Statistics

Perioperative data were compared between the groups. Demographic characteristics were compared using the *t*-test, chi-square test, and Fisher's exact test, as appropriate. The chi-square and Fisher's exact test were used to compare morbidity and mortality rates. Predictors of mortality were sought by univariate and multivariate logistic regression. For subgroup analysis, we divided each group into a primary occlusion subgroup who underwent surgery without prior medical treatment and a secondary occlusion subgroup who underwent surgery after medical failure. All statistical analyses were performed with the aid of SPSS software (ver. 20.0; SPSS, Chicago, IL, USA). A p-value <0.05 was considered to reflect significance.

The study was approved by the institutional review board of Seoul National University Hospital (IRB no. 1706-072-859).

Results

Demographic Data and Preoperative Characteristics

Demographic characteristics, and preoperative and postoperative details, are described in Table 1. Twenty-eight patients had significant comorbidities, including congenital diaphragmatic hernias (n=2; one patient in the early group), a chromosomal abnormality (n=1;

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the late group), and an ileostomy or colostomy status due to bowel perforation (n=25; 14 patients in the early group). Mean age at operation was 14 days. The early group contained 56 patients; the late group had 61 patients. Fifty-four neonates underwent primary closure because of contra-indications to ibuprofen (primary closure) and sixty-three underwent occlusion after medical failure (secondary closure).

Demographic characteristics and preoperative outcomes were compared between the groups. The early and late groups did not differ significantly in terms of baseline characteristics except for age at operation (4.9 vs. 23.3 days; $p<0.001$) (Table 1). In terms of preoperative conditions, the early group had a lower incidence of sepsis (9 vs. 26; $p=0.0002$) and a higher incidence of pulmonary hemorrhage. Compared with the early group, the late group tended to have a higher incidence of NEC.

Postoperative Outcomes

No operative death was noted. One patient underwent re-operation to treat coarctation of the aorta that developed after PDA ligation. The patient is currently doing well and no residual coarctations have been

Table 1 Demographic and clinical characteristics according to the timing of surgery and the preoperative Ibuprofen usage

	Total	Early (n=56)		Late (n=61)		*p* value (Early vs. late)
		Total	Primary (n=40)	Total	Primary (n=14)	
Age at operation (days)	14.5 (13.0)	4.9 (2.5)	4.22 (2.069)	23.3 (12.4)	23.1 (11.4)	0.000
Apgar score at 1 minute	3.1 (2.1)	2.8 (2.0)	2.2(1.7)	3.3 (2.2)	3.36 (2.5)	0.211
Apgar score at 5 minutes	5.31 (2.2)	5.3 (2.1)	5.0 (2.3)	5.3 (2.3)	5.50 (2.4)	0.882
Gestational Age (weeks)	26.73 (2.91)	26.6 (2.9)	27.2 (3.1)	26.8 (2.9)	26.5 (3.4)	0.768
Maternal Preeclampsia	12 (10.3%)	6	5	6	0	0.876
Body weight (g)	956.8 (565.7)	986.8 (677.3)	1051.3 (775.7)	929.2 (443.3)	996.4 (644.3)	0.584
Caesarean section	66 (56.9%)	33	26	33	6	0.669
Respiratory distress Syndrome	95 (81.2%)	45	34	50	12	0.824
Use of Surfactants	93 (79.5%)	44	33	49	11	0.814
〈**Preoperative status**〉						
Bronchopulmonary dysplasia	9 (7.7%)	2	1	7	1	0.166
Acute kidney injury	50 (42.7%)	26	19	24	6	0.439
Necrotizing enterocolitis	18 (15.4%)	5	5	13	9	0.064
Intraventricular hemorrhage	3	0	3	0	0	0.067
Sepsis	35 (29.9%)	9	6	26	9	0.002
Hypotension	65 (55.6%)	35	26	30	12	0.148
Pneumonia	4 (%)	0	0	4	2	0.120
Pulmonary hemorrhage	22 (18.8%)	16	13	6	1	0.010
Pulmonary hypertension	32 (28.3%)	12	12	20	6	0.169

Values in parentheses: standard deviation.

Table 2 Postoperative clinical outcomes according to the timing of surgery and the preoperative Ibuprofen usage

	Total	Early (n=56)		Late (n=61)		OR	X^2	*p* value (Early vs. late)
Bronchopulmonary dysplasia	96 (82.1%)	41	25	55	12	3.354	5.696	0.017
Moderate to severe	71 (60.7%)	29	18	42	9	2.058	3.564	0.059
Use of Steroid	19 (16.2%)	3	0	16	3	6.281	9.351	0.002
Acute kidney injury	16 (13.7%)	9	8	7	2	0.677	0.522	0.470
Necrotizing enterocolitis	31 (26.5%)	11	4	3	1	0.212	6.010	0.014
Intraventricular hemorrhage	24 (20.5%)	15	14	9	3	0.473	2.592	0.107
Sepsis	37 (31.6%)	21	15	16	4	0.593	1.715	0.190
Retinopathy of prematurity	54 (46.2%)	22	14	32	9	1.705	2.039	0.153
Hypotension	26 (22.3%)	16	14	10	3	0.490	2.505	0.113
Pneumonia	10 (8.5%)	2	0	8	3	4.075	3.402	0.065
Pulmonary hypertension	34 (29.3%)	19	15	15	4	0.618	1.383	0.240
Mortality	19 (16.2%)	13	12	6	3	0.361	3.842	0.050

Values in parentheses: standard deviation. OR: odd ratios

found. No other complications related to the operation were observed. There were 19 in-hospital deaths after PDA closure: 13 in the early group and 6 in the late group (Table 2). The late group experienced significantly lower mortality (odds ratio [OR] 0.36, $p = 0.05$; Table 2). Twelve of thirteen deaths in the early group were in the primary closure subgroup. The causes of death were associated with prematurity (sepsis, pulmonary hemorrhage, etc.).

The late group had a significantly higher incidence of BPD (OR 3.354, $p = 0.017$) and tended to have a greater incidence of pneumonia (OR 4.075, $p = 0.065$). Within each group, we compared subgroups by preoperative medical treatment (yes or no). On subgroup analysis, early primary surgical closure was significantly associated with lower incidences of BPD (OR 1.600, $p = 0.004$) and pneumonia (OR 1.143, $p = 0.023$; Table 3).

Table 3 Odds ratios for the risk of postoperative morbidity and mortality according to the preoperative ibuprofen usage in the early group

Primary vs. Secondary in the Early group	OR	X^2	*p* value
Bronchopulmonary dysplasia	1.600	8.195	0.004
Moderate to Severe	2.689	2.582	0.108
Use of Steroid	1.231	7.925	0.020
Acute kidney injury	0.267	1.602	0.206
Necrotizing enterocolitis	7.000	8.247	0.004
Intraventricular hemorrhage	0.124	4.817	0.028
Sepsis	1	0.000	1.000
Retinopathy of prematurity	1.857	1.078	0.299
Hypotension	0.265	2.845	0.092
Pneumonia	1.143	5.185	0.023
Pulmonary hypertension	0.533	0.909	0.340
Mortality	0.156	3.616	0.082

OR: odd ratios

Table 4 Prognostic factors of survival accepted in the forward model and all other clinical parameters analyzed and not regarded as explanatory

Postoperative outcomes	β	OR	*p* value
Pneumonia	3.1	22.4 (2.4–206.8)	0.006
Hypotension	1.9	6.38 (1.4–28.2)	0.014
Pulmonary hypertension	1.9	6.5 (1.3–33.1)	0.025
Bronchopulmonary dysplasia	3.4	28.6 (5.3–166.7)	0.000
Sepsis	1.8	6.0 (1.2–30.3)	0.031
Variables not significant			
Acute kidney injury	—	—	0.256
Mean age at operation (S.D.)	—	—	0.818
Gestational age	—	—	0.683
Body weight	—	—	0.239
Early surgical occlusion	—	—	0.917
Primary occlusion	—	—	0.583

OR: odd ratios

Factors Prognostic of Mortality

BPD and pneumonia were significantly associated with an increased risk of mortality. No other variable (including gestational age and body weight) was significant in this context. Although the early group experienced a higher level of mortality, the timing of surgery was not a significant predictor of survival (Table 4).

Discussion

Our experience shows that PDA closure in preterm neonates is effective and safe; there was no perioperative mortality. The 5% in-hospital mortality and 5–10% morbidity are similar to those of previous studies showing that PDA ligation was relatively safe.[10–12] Although previous studies discussed the optimal timing of surgical intervention in preterm neonates, the results are controversial. The studies targeted preterm infants regardless of their symptoms or extent of hemodynamic compromise. We focused on the perioperative outcomes of symptomatic preterm neonates. Although some studies[11, 13, 14] have found that PDA closure in infants with cardiorespiratory complications or neural impairment is detrimental, Jaillard et al.[15] showed that early surgical closure was associated with improved lung compliance and nutrition. We found that early closure was associated with reductions in respiratory complications, such as BPD and pneumonia. Consistent with other studies,[16–18] we found that early surgery for symptomatic preterm neonates improved respiratory status.

We are the first to subject both the timing of surgery and preoperative medical treatment to subgroup analysis. We found that the timing of surgery per se was associated with the extent of preoperative medical treatment. This finding differs from those of other studies, possibly because of heterogeneity among the early surgical groups. Thus, as neonates who underwent early occlusion tended to undergo primary occlusion, we divided each group into two subgroups to evaluate the effect of preoperative medication on perioperative outcomes. Although the early group was at an increased risk of mortality, age at operation was not per se a significant predictor of mortality. The early and primary groups included neonates with contraindications for medical therapy and who tended to be hemodynamically unstable; these preoperative characteristics explain their sus-

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ceptibility. As mentioned in previous studies,[19] neonates who require early surgery tend to be at higher risk of morbidity and mortality. The early group in our cohort tended to include those with significant comorbidities, such as a congenital diaphragmatic hernia or previous ileostomy or jejunostomy due to bowel perforation. Moreover, outborn neonates contributed significantly to the higher mortality in the early group. These findings may explain why babies who had contraindications for medical treatment had higher mortality.

On subgroup analysis, early primary surgical closure was associated with a lower incidence of NEC. One explanation for this result is that prolonged ibuprofen usage by preterm neonates with medically retractable symptomatic PDA may be associated with a higher incidence of NEC, even in the early surgery group. However, this result should be interpreted with caution. Our surgical outcomes included new-onset NEC. As the early primary surgery group included patients already suffering from NEC, subgroup analysis may make it appear that the secondary closure group exhibited a higher incidence of NEC. Thus, further randomized controlled studies on the association between NEC and PDA closure are required.

The late group was at higher risk of sepsis and NEC, implying that delayed PDA closure may be associated with more morbidity. Some studies found that prolonged medical therapy may increase the risk of morbidity.[6, 20]Delayed PDA closure is associated with pulmonary complications such as chronic lung disease and the need for prolonged ventilator support.[15, 21] Some authors have suggested that early closure can prevent long-term cardiorespiratory compromise.[11] However, the details of the association between PDA and respiratory complications remain unknown. Multivariate analysis revealed that BPD and pneumonia were significantly prognostic of mortality. Little et al.[21] found that early PDA closure was beneficial and acceptably safe for preterm neonates. Moreover, in line with our results, Tschuppert et al.[22] found that early closure seemed to be associated with improved pulmonary function. However, some previous studies[23, 24] found that early PDA closure was no more beneficial than late closure; the cited studies enrolled all preterm neonates including those without symptoms.

Our study was limited by its retrospective nature; this was not a randomized controlled trial exploring the effect of timing of PDA closure on the long-term outcomes of symptomatic preterm neonates. In addition, as Limrungsikul et al.[7] pointed out, the diagnoses of symptomatic or hemodynamically significant PDA vary. Our institution uses in-house criteria to identify PDAs requiring intervention. As preterm neonates usually have comorbidities related to prematurity per se, decisions on PDA treatment will vary among neonatologists.

Conclusion

PDA closure is safe in preterm neonates, and early surgery seems to reduce respiratory complications. To reduce morbidity, symptomatic preterm neonates with PDA should be considered for prompt PDA closure as soon as medical therapy fails or contraindications to medical therapy are identified. A future randomized controlled trial is required to confirm the optimal timing of PDA closure in symptomatic neonates.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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