

学位論文

**Evaluation of postoperative complications for PDA**

**in extremely low birth weight infants**

**(極低出生体重児における PDA 術後合併症の評価)**

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## 著者の宣言

本学位論文は、著者の責任において実験を遂行し、得られた真実の結果に基づいて正確に作成したものに相違ないことをここに宣言する。

## **Abstract**

### ***Background***

Patent ductus arteriosus (PDA), which disrupts the hemodynamics early after birth, causes intraventricular hemorrhage and neonatal necrotizing. Unlike medical treatment for hemodynamically significant PDA, there are disparities between institutions regarding the timing of surgery, considering the complications associated with surgery or access to surgery.

### ***Methods***

We aimed clarify the clinical picture of postoperative complications and examined whether there were risk factors regarding that indication of surgery for hemodynamically significant PDA from the point of postoperative complications associated with surgery.

### ***Results***

There were 36 cases of extremely low birth weight infants who required video-assisted thoracoscopic surgery for PDA (VATS-PDA). The median gestational age was 25.2 weeks, and the median birth weight was 699 g. The treatment indication of VATS-PDA was medical treatment resistance in 17 cases, relapsed PDA in 15 cases, and no additional administration of indomethacin because of severe side effects in four cases. Complications with VATS-PDA occurred in eight out of 36 cases. There were three cases of pneumothorax, two of thoracotomy transition, two of pulmonary hemorrhage, and four of post-ligation cardiac syndrome (PLCS). VATS-PDA-related death occurred in two cases because of PLCS. The

frequency of four or more times of indomethacin with or without postoperative complications was 88% vs. 39% (p=0.04), respectively.

### ***Conclusions***

All postoperative deaths were caused by PLCS, which had the highest risk of poor prognosis. VATS-PDA should be considered for unclosed PDA after one course of indomethacin administration.

***Keywords:*** Patent ductus arteriosus (PDA), video-assisted thoracoscopic surgery for patent ductus arteriosus (VATS-PDA), indomethacin, extremely low birth weight infants (ELBWI)

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## **Background**

In recent years, mortality rates for extremely low birth weight infants (ELBWI) have decreased, and neurological prognosis has also improved. However, a few ELBWI still die or have poor neurological prognosis even today. Patent ductus arteriosus (PDA), which disrupts the hemodynamics early after birth, causes intraventricular hemorrhage and neonatal necrotizing.<sup>1)2)</sup> The prevalence of PDA is higher for earlier gestational age and lower birth weight infants. These infants are also resistant to treatment with cyclooxygenase inhibitors such as indomethacin or ibuprofen and often have severe side effects. Surgery or catheter treatment<sup>3)</sup> is indicated for such cases who often experience difficulties in postoperative as well as preoperative management. Unlike medical treatment for hemodynamically significant PDA, there are disparities between institutions in the timing of surgery, considering the complications associated with surgery or access to surgery. Past reports did not reveal clear criteria for surgery for hemodynamically significant PDA. We aimed to clarify the clinical picture of postoperative complications and examined whether there were risk factors regarding the indication of surgery for hemodynamically significant PDA from the point of postoperative complications associated with surgery.

## **Methods**

We enrolled ELBWI who required surgical treatment for hemodynamically significant PDA in our institution between January 2013 and January 2020. All clinical data were obtained retrospectively from

electronic medical records in our institution. The requirement for informed consent was waived owing to the retrospective nature of the study. The management guidelines of our institution indicate prophylactic administration of indomethacin for preventing intraventricular hemorrhage at less than 26 weeks of gestation since August 2018. At birth and at least every 24 hours, neonatologists perform echocardiography. If hemodynamically significant PDA (increased pulmonary blood flow and decreased peripheral blood flow) is observed during prophylactic administration, indomethacin is administered as treatment. The administration interval is three times every 12 hours. Echocardiography is performed prior to indomethacin administration. An additional dose is not administered when the PDA is closed. In the case of re-administration after the end of one course, indomethacin administration is repeated at intervals longer than 24 hours apart. The first choice of surgery at our institution is thoracoscopic PDA closure (video-assisted thoracoscopic surgery for PDA: VATS-PDA). Based on past reports,<sup>4)5)6)7)</sup> this is the most suitable option for ELBWI because it does not involve a thoracotomy, the incisional wound is small, and we have noted few complications using it in our institution. Exclusion criteria in this study were ELBWI who underwent PDA closure with thoracotomy to prevent confounding by complications caused by surgical procedures. There are three indications for the VATS-PDA: resistance to medical treatment, reopened PDA, and cases where additional administration could not be performed because of severe side effects of indomethacin. Nine complication of VATS-PDA were considered: pneumothorax, infection, atelectasis,

arrhythmia, pleural fluid, clip dropout, recurrent nerve paralysis, post-ligation cardiac syndrome (PLCS), and transition to open chest. PLCS was defined as circulatory failure (decrease in preload and decrease in left ventricular ejection fraction) after hemodynamically significant PDA closure with surgery and need for intervention (use of blood transfusion or of catecholamine or vasodilators). We classified patients into two groups, with or without complications of VATS-PDA, and analyzed their risk factors.

### **Statistical analyses**

We used EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), for all statistical analyses.

EZR is a modified version of the R Commander that adds statistical functions frequently used in biostatistics. Descriptive statistics are shown as medians (interquartile range [IQR]). The Mann–Whitney U test was performed to compare continuous variables between the two groups and nominal variables were compared using Fisher's exact test. A P value <0.05 was considered statistically significant.

### **Ethical approval**

The study design complied with all the relevant national regulations and institutional policies, was in accordance with the tenets of the Helsinki Declaration, and was approved by the Committee of Medical Ethics of our institution (approval number; B20-166).

### **Results**

### ***Study population***

Figure 1 shows the flowchart of surgery for hemodynamically significant PDA in ELBWI. There were 38 cases of ELBWI who required surgery. Among them, one case underwent open-ended PDA ligation in another institution and 37 cases underwent surgery in our institution. One case had PDA clipping under thoracotomy for pneumothorax treatment before surgery, and VATS-PDA was performed for the remaining 36 cases. Complications with VATS-PDA occurred in eight out of 36 cases. Two infants died of PLCS. The treatment indication of VATS-PDA was medical treatment resistance in 17 cases, relapsed PDA in 15 cases, and no additional administration of indomethacin because of severe side effects in four cases.

### ***Maternal and neonatal background***

Table 1 shows the background of the newborns and mothers. The median gestational age was 25.2 weeks, and the median birth weight was 699 g. There was no significant difference in the neonatal background (gestational age, birth weight, Apgar score, sex, antenatal steroid use, clinical chorioamnionitis, and umbilical cord pH) between the two groups.

### ***Preoperative indomethacin administration and echocardiography findings with and without***

#### ***VATS-PDA-related complications***

Table 2 shows the details. The median total number of preoperative indomethacin administrations was four.

In the group with complications, the rate of indomethacin four times or more was higher. (Table 2)

Preoperative echocardiography showed no significant differences between the two groups.

### *Intraoperative findings with and without VATS-PDA-related complications*

Table 3 shows the details of the intraoperative findings with and without VATS-PDA-related complications.

The median age of VATS- PDA was day 25. There was a significant difference in the operation time (24 mins vs 33 mins,  $P < 0.01$ ) between the two groups.

### *VATS-PDA-related complications in eight cases*

Table 4 shows the details of eight cases of VATS-PDA complications. All VATS-PDA procedures were performed by the same surgeon, and there were no cases of emergency surgery. There were four cases of PLCS, three cases of pneumothorax, two cases of thoracotomy transition, and two cases of pulmonary hemorrhage. There were four cases of postoperative chest drain placement. Most of the cases were complicated by generalized edema. VATS-PDA-related death was noted in two cases attributable to PLCS. One was an ELBWI born at 344 g. The clip did not fit and transition to thoracotomy was required because of insufficient body development. The infant died of PLCS due to severe cardiac pump failure and poor response to the inotrope agent. The other infant had severe renal failure (serum creatinine 2.4 mg/dL at surgery requiring continuous intravenous administration of furosemide and mannitol). Both ELBWI who died had additional severe complications.

## **Discussion**

This study focused on the optimal therapeutic interventions for ELBWI with hemodynamically significant PDA. PLCS had the poorest prognosis for postoperative complications, and administration of indomethacin four times or more was found to be a risk factor for postoperative complications in this study.

The first choice of medical treatment for hemodynamically significant PDA is cyclooxygenase inhibitors.

ELBWI who are immature in terms of all functions show increased likelihood of medical treatment resistance and a high incidence of side effects such as renal failure, hypoglycemia, and intestinal perforation. Surgery is performed on such cases. In our institution, VATS-PDA is the first choice as the procedure most suitable for ELBWI because it is minimally invasive and has a short operation time. <sup>4)8)</sup>

Laborde et al. first reported VATS-PDA in 1993, <sup>9)</sup> and past reports revealed that postoperative complications mainly include pneumothorax, infections, atelectasis, arrhythmia, pleural effusion, dropout of the clip, recurrent nerve paralysis, PLCS, and transition to thoracotomy. <sup>5)10)11)12)13)</sup> Based on these

reports, the above nine were defined as complication associated with VATS-PDA in this study. The uncomplicated group had larger diameter ductus arteriosus and shorter operative time than the complicated group. We consider that this was attributable to the following two factors. One is that larger diameter ductus arteriosus did not affect the development of postoperative complications because the birth weight and body weight at the time of surgery in the complicated group were higher than those in the uncomplicated group.

Another is that two of the eight infants who developed complications underwent transition to thoracotomy

during surgery, which affected the operative time. As shown in Table 4, the complications were pneumothorax, pulmonary hemorrhage, PLCS, and transition to thoracotomy, and no recurrent nerve palsy, chylothorax, or dropout of the clip was observed. ELBWI who required thoracotomy had a large PDA diameter and blood flow through the ductus arteriosus remained even after clipping. The complication and mortality rates with VATS-PDA were not higher than those in previous reports (morbidity for VATS-PDA in infants who weighed less than 1500 g was pneumothorax in 6% and vocal cord paralysis in 5% <sup>10</sup>), mortality and morbidity for both VATS-PDA and thoracotomy were 26% in infants who weighed less than 750 g <sup>6</sup>), mortality and morbidity for VATS-PDA were 18% in low birth weight infants <sup>7</sup>), mortality and morbidity for thoracotomy were 1.8% and 4.8%, respectively, in ELBWI <sup>13</sup>). There were some postoperative complications of pneumothorax and pulmonary hemorrhage, but they recovered spontaneously and did not affect the prognosis of the patients. Conversely, PLCS had the highest risk of poor prognosis. Both deaths were caused by PLCS, and the infants who died had additional severe complications. Although there are no disparities among institutions in the criteria for medical treatment for hemodynamically significant PDA, there are marked differences regarding surgery among institutions because the treatment policies differ greatly according to the access to surgery at each institution. <sup>15</sup>)

Some previous reports examined the relationship between the surgical treatment criteria and the age at surgery. One of these reports revealed that the age at surgery (comparison of approximately 14 days of age

and approximately 21 days of age) was not associated with mortality and the complication rates.<sup>16)</sup> Another report also revealed that the age at surgery (comparison of younger than 14 days of age and older than 14 days of age) was not associated with mortality and the complications rates.<sup>17)</sup>

Therefore, in this study, we examined the risk factors from the viewpoint of complications caused by surgery and considered whether these risk factors should be considered in the criteria for surgery. We focused on medical treatment, that is, total number of indomethacin administrations, rather than the age at surgery. There was a significant difference in the risk factors for postoperative complications when indomethacin was administered more four times in the univariate analysis. Hemodynamically significant PDA causes pulmonary congestion, which is progressing because of increase in pulmonary blood flow, peripheral organ blood flow decrease, and prerenal renal failure. In addition, as the administration of indomethacin increases, the renal parenchyma is impaired and renal failure is also implicated.<sup>18)19)</sup> This series of exacerbations of renal impairment also causes symptoms such as decreased urine output and generalized edema and those findings were observed. Such findings are observed intraoperatively. In other words, it is important to perform surgery before exacerbation of edema, as edema complicates the surgical procedure. We should consider the indication of surgery when hemodynamically significant PDA does not close after one course of indomethacin administration.

### ***Limitations***

First, this was a single-institutional study, and very few ELBWI require surgery. In addition, VATS-PDA is performed in very few institutions in Japan, while most use thoracotomy. It is unclear whether this has affected our results. Second, we could only perform univariate analysis because of the small sample size.

## **Conclusions**

All postoperative deaths were due to PLCS, which had the highest risk of poor prognosis. VATS-PDA should be considered for unclosed PDA after one course of indomethacin administration because four or more doses of indomethacin increase the risk of postoperative complications.

## ***Acknowledgments***

Dr. Kagami Miyaji performed the VATS-PDA and provided us with valuable information regarding the surgical treatment.

## ***Disclosure***

None declared.

## **Author Contribution**

S.I., A.Y., and M.O. conceptualized the manuscript; S.I. wrote the original draft; S.I. performed the data collection; M.K. and H.N. critically reviewed the manuscript and supervised the entire study process. All authors read and approved the final manuscript.

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## Tables and Figure legends

Table 1. Maternal and neonatal background with or without VATS-PDA related complications

	Overall N=36	No complications N=28	With complications N=8	<i>P value</i>
gestational age (week)	25.2(24.7,26)	25.2(24.7,26)	25.0(24.5,25.6)	0.53
birth weight (g)	699(607,797)	712(639,838)	597(518,765)	0.15
Apgar score 1min	4(2,5)	4(2,5)	5(4,6)	0.22
Apgar score 5min	6(5,7)	6(5,7)	7(6,8)	0.21
gender (male) (N [%])	22(61)	16(57)	6(75)	0.44
Antenatal steroid (N [%])	22(61)	18(64)	4(50)	0.68
Clinical CAM (N [%])	7(19)	7(12)	0(0)	0.31
umbilical cord blood pH	7.37(7.33,7.40)	7.36(7.32,7.38)	7.39(7.37,7.43)	0.11

Median (25%,75%)

Abbreviations: VATS-PDA, video-assisted thoracoscopic surgery for patent ductus arteriosus; CAM, chorioamnionitis

Table 2. Preoperative IND administration and echo findings with and without VATS-PDA-related complications

	Overall N=36	No complications N=28	With complications N=8	<i>P value</i>
Day of first dose of IND	1 (1, 2)	1 (1, 2)	1 (1, 2)	0.75
IND administration (doses)	4 (3, 6)	4 (3, 6)	5 (5, 6)	0.07
IND > 4 doses n (%)	18 (82)	11 (39)	7 (88)	0.04
Serum Cr (mg/dL)	1.2 (0.7, 1.4)	1.2 (0.7, 1.4)	1.3 (0.8, 1.9)	0.46
Echocardiography				
LA/Ao	1.5 (1.3, 1.7)	1.5 (1.3, 1.7)	1.7 (1.4, 1.8)	0.37
LPA dia Vp (cm/s)	16 (11, 25)	16 (11, 25)	18 (13, 24)	0.63

Median (25%, 75%)

Abbreviations: VATS-PDA, video-assisted thoracoscopic surgery for patent ductus arteriosus; IND, indomethacin; Cr, creatinine; LA, left atrium; Ao, aorta; LPA, left pulmonary artery; dia Vp, diastolic flow velocity

Table 3. Details of intraoperative findings with and without VATS-PDA related complications

	Overall N=36	No complications N=28	With complications N=8	<i>P value</i>
The age of the VATS-PDA	25(22,35.8)	25(22,38)	27(24,35)	0.86
Weight at the time of surgery (g)	755(708,851)	776(713,860)	697(548,760)	0.10
Operation time (min)	25(20,28.3)	24(20,26)	33(28,46)	<0.01
PDA diameter (mm)	3.5(3,4)	3.5(3,4)	3.0(2.9,3.3)	0.24
Clip size (mm)	5(3.6,5)	5(4.4,5.3)	4.1(3.6,5)	0.15
Median (25%,75%)				

Abbreviations: VATS-PDA, video-assisted thoracoscopic surgery for patent ductus arteriosus

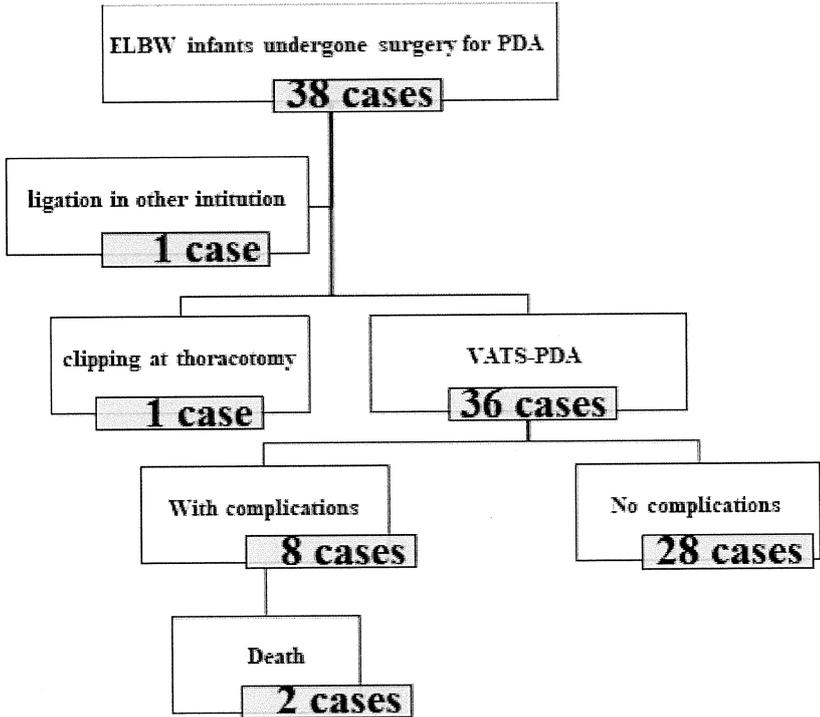
Table 4. Details of VATS-PDA-related complications in eight cases

Gestational age (week)	Birth weight (g)	Age at the surgery (days)	Weight at the surgery (g)	Total number of indomethacin administration	Date between the last dose and the surgery (days)	Urine (ml/kg/h)	Serum Cr at surgery (mg/dL)	Complications	Clinical picture
26	520	30	550	5	15	8.0	2.40	Death from PLCS	Increase in preload after PDA surgery.
				ns		/			
25	758	24	820	9	3	3.6	2.12	Pneumothorax	Chest drain placement and removal three days after operation.
						/			
24	784	19	724	7	13	4.8	1.29	Pulmonary hemorrhage	spontaneous remission.
						/			
24	648	35	670	6	29	3.7	0.94	Transition to thoracotomy	Because of hypotension and bradycardia during surgery.
						/			

26	510	35	740	5	19	Intravenous furosemide	5.0	0.42	Pulmonary hemorrhage, pneumothorax	Chest drain placement and removal one days after operation.
							/			
24	344	39	490	5	20	Intravenous furosemide	3.6	0.60	Transition to thoracotomy, death from PLCS	Because PDA diameter could not be clipped thickly and died of circulatory failure due to PLCS.
							/			
23	546	24	540	5	6	Intravenous furosemide	4.2	1.25	PLCS	Decrease in LVEF after PDA surgery.
							/			
25	813	23	930	3	15	Intravenous furosemide	2.5	1.76	Pneumothorax, pleural effusion, PLCS	Chest drain placement and removal two days after operation and decrease in LVEF after PDA surgery.
							/			
						Intravenous furosemide				

Abbreviations: VATS-PDA, video-assisted thoracoscopic surgery for patent ductus arteriosus; Cr, Creatinine; PLCS, post-ligation cardiac syndrome; LVEF, left ventricular ejection fraction

Fig.1 Flowchart of surgery treatment for hemodynamic significant PDA in extremely low birth weight infants



PDA; patent ductus arteriosus