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Original

Management of preterm infants and incidence of patent ductus arteriosus

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Abstract

The effect of different methods of perinatal management for patent ductus arteriosus (PDA) occurrence is unknown. Therefore, we compared methods of perinatal management and PDA incidence in preterm infants before and after the introduction of early aggressive nutrition (EAN) in our institution. Infants (gestational age < 34 weeks) who were admitted as inpatients between 2006 and 2008 (no EAN, period A) and between 2012 and 2014 (EAN, period B) were assessed. Maternal and neonatal factors affecting PDA incidence were investigated. Compared to period A, infant immaturity was more severe and the PDA incidence was higher in period B. More severe immaturity and a higher rate of concomitant respiratory distress syndrome (RDS) were noted in infants who developed PDA, both in periods A and B. Multiple logistic regression analysis showed that PDA onset was associated with the presence or absence of RDS, gestational age, and echocardiographic indicators immediately after birth. Despite changes in our institution's perinatal management, the incidence of PDA was unaffected, with infant immaturity being the most important PDA risk factor. Our results indicate that echocardiographic indicators immediately after birth could be used to predict PDA onset in preterm infants with a low gestational age and RDS.

Key words : *patent ductus arteriosus, serum osmolality, respiratory distress syndrome, left atrium/aortic root ratio, left pulmonary artery mean diastolic velocity/peak systolic velocity ratio*

I. Introduction

In Japan, the methods used for perinatal management changed significantly during the late 2000s, including the introduction of insurance coverage for magnesium sulfate ($MgSO_4$) [1] and steroid [2] administration in mothers expected to give birth preterm; changes in target value of oxygen saturation (SpO_2) and blood pressure in preterm infants [3, 4]; and introduction of early aggressive nutrition (EAN) for the purpose of improving neurological prognosis [5-6]. Ductus arteriosus function and structure are immature in

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preterm infants, and the hemodynamically significant patent ductus arteriosus (PDA) tends to develop in these patients [7]. Cyclooxygenase (COX) inhibitors are used to treat patients with PDA, but surgical ligation is required if they are resistant to COX inhibitors. Various risk factors for PDA and COX inhibitor resistance [8-12], as well as a link between high serum osmolality and PDA have been reported in preterm infants [13]. However, the impact of changes in perinatal management and echocardiography immediately after birth on significant PDA remains unknown. Echocardiography is noninvasive and useful for the diagnosis of PDA onset, but there are no established echocardiographic indices to predict the onset of PDA from the early postnatal period in preterm infants.

The present study investigated the relationship between changes in maternal and neonatal management at our hospital, along with PDA onset, as well as the role of echocardiography in the prediction of PDA onset.

II. Materials and Methods

1. Subjects

We selected preterm infants born before 34 weeks of gestation who were inpatients at our neonatal intensive care unit (NICU) before our hospital introduced EAN (2006 to 2008, period A) and after our hospital introduced EAN (2012 to 2014, period B). In period B, we conducted intravenous nutrition with 0.5 to 2.5 g/kg /day of amino acid preparation, glucose of caloric nitrogen ratio > 300 to 400, and fat preparation of 0.5 to 1.5 g/ kg/ day. Infants with congenital or chromosomal abnormalities, who died within 24 hours of birth, or who were born outside our hospital were excluded from this study. This study was conducted after obtaining the approval of the Iwate Medical University ethics committee (H28-198).

Table 1. Maternal factors

1. Age
2. Multiple births
3. Hypertensive disorder of pregnancy
4. Gestational diabetes mellitus
5. Chorioamnionitis
6. Ritodrine hydrochloride
7. Magnesium sulfate
8. Antenatal steroids

2. Criteria for PDA treatment intervention

The criteria for PDA treatment were as follows: 1) there were two or more echocardiography findings from among (a) pulmonary arterial-side ductus arteriosus diameter > 1.5 mm [14, 15], (b) left atrium/ aortic root ratio (LA/Ao) > 1.5 [14, 15], (c) left pulmonary artery mean diastolic velocity/ peak systolic velocity ratio (LPA d/s) > 0.3 [16], and (d) M-shaped or pulsatile PDA flow pattern [16]; 2) one or more echocardiography findings were fulfilled, with a cardiovascular dysfunction score of 3 points or higher [17]; and 3) the above criteria were not met but echocardiography findings revealed a trend to exacerbation, and PDA onset was predicted. LPA d/s was only used for infants in period B.

3. PDA and non-PDA groups

Patients who fulfilled the treatment intervention criteria by 168 hours after birth and received COX-inhibitor therapy were included in the PDA group. All other patients were included in the non-PDA group. Indomethacin was the COX inhibitor used in all patients.

Table 2. Neonatal factors

1. Gestational age	20. Total water quantity
2. Birth weight	21. Serum osmolality
3. Sex	22. Serum sodium
4. Cesarean delivery	23. Serum potassium
5. Apgar score at 1/5 min	24. Glucose
6. Small for gestational age	25. Blood urea nitrogen
7. Death	26. Serum magnesium
8. Congenital infection	27. Cardiothoracic ratio
9. Heart rate	28. Glucose insulin therapy
10. Mean blood pressure	29. Amino acids
11. Pulse pressure	30. Glucose infusion rate
12. SpO_2	31. Lipids
13. FiO_2	32. Initiation of PDA treatment
14. Mechanical ventilation	33. Age at medical closure of PDA
15. Respiratory distress syndrome	34. Age at surgical ligation of PDA
16. Nitric oxide	35. Diameter of the ductus arteriosus
17. Catecholamine	36. LA/Ao
18. Diuretics	37. LPA d/s
19. Bicarbonate	

PDA, patent ductus arteriosus; LA/Ao, left atrium/aortic root ratio;
LPA d/s, left pulmonary artery mean diastolic velocity/peak systolic velocity ratio

4. Maternal and neonatal factors (Tables 1 and 2)

Maternal factors comprised 8 items including age, pregnancy complications, and drug therapy. A total of 37 items were extracted as neonatal factors, including perinatal period information, complications, vital signs until postnatal day 4, blood biochemistry findings, drug therapy, and echocardiography findings. Serum osmolality was calculated using the formula [blood osmolality = 2 (Na^+ + K^+) + blood glucose level/1.8 + blood urea nitrogen/2.8] [13]. Congenital infection was defined as IgM > 20 mg/dL at birth or a culture-positive aseptic site.

5. Statistical analysis

Maternal and neonatal factors were compared in preterm infants with a gestational age below 34 weeks in periods A and B. Maternal and neonatal factors were then compared between the PDA and non-PDA groups for each period.

Continuous data were compared using the Mann-Whitney U-test and discrete data were compared using the chi-squared test. Values are presented as median (interquartile range) or numbers (percentages). An analysis of PDA risk factors was performed using multiple logistic regression analysis, with the presence or absence of PDA as a dependent variable and study periods and maternal/neonatal factors (including use of EAN) as independent variables. LPA d/s was used only in period B. Factors with multicollinearity (birth weight, Apgar score at 5 min, and mechanical ventilation) were excluded. As the time to PDA onset differed among patients, the

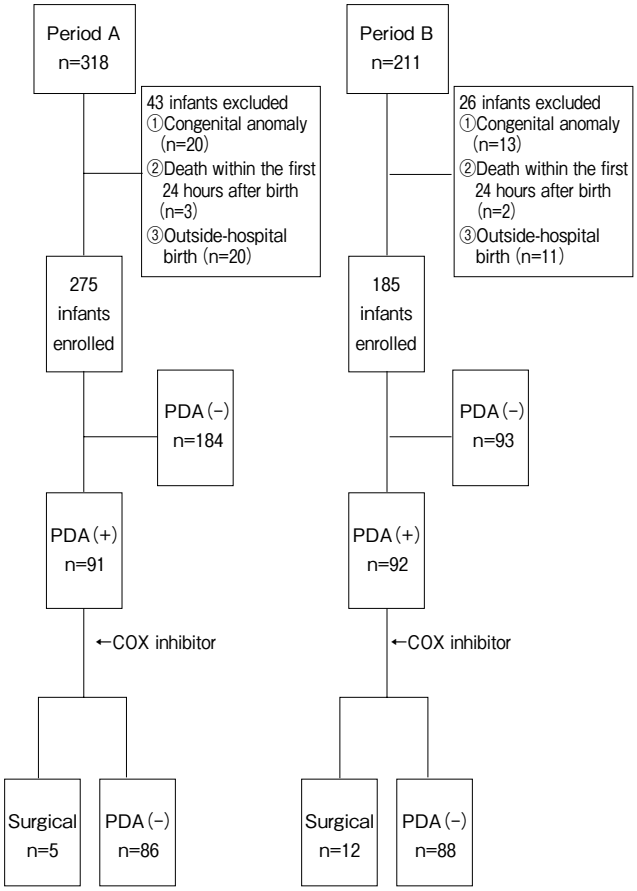

Fig. 1. Study cohort
PDA, patent ductus arteriosus; COX, cyclooxygenase

analysis of PDA risk factors was performed using only values measured before treatment immediately after birth for the following independent variables: vital signs, blood biochemistry findings, total water quantity, glucose infusion rate, echocardiography findings, and drug therapy.

PDA prediction ability was calculated as the area under the curve (AUC) after factors that were revealed by multiple logistic regression analysis were adjusted based on gestational age, birth weight, and small-for-gestational-age (SGA) status. In order to validate our PDA prediction models, of the 460 patients identified in both periods A and B, we randomly selected two thirds 309 of these patients for the derivation cohort; the remaining one third 151 were used for our internal validation cohort. Since LPA d/s was only used for 185 infants in period B, we randomly selected two thirds 121 of these patients for the derivation cohort; the remaining one third 64 were used for our internal validation cohort. Statistical analysis was performed using SPSS (ver. 23. IBM, Tokyo, Japan) and JMP® 14 (SAS Institute Inc., Cary, NC, USA), and the significance level was set at $p < 0.05$ (two-tailed test).

III. Results

1. Study cohort (Fig. 1)

Among 318 inpatients born before 34 weeks of gestation during period A, 275 were

Table 3. Demographic and clinical parameters of infants in periods A and B

	<34 weeks of gestational age		
	Period A (n = 275)	Period B (n = 185)	p-value
Gestational age, weeks	29.9 (27.0–32.0)	28.6 (26.6–31.1)	0.002
Birth weight, g	1212 (848–1549)	1076 (766–1394)	0.006
Apgar score at 1 min	6 (4–8)	4 (3–6)	<0.001
Apgar score at 5 min	8 (7–9)	7 (6–8)	<0.001
Female	135 (49.1%)	75 (40.5%)	0.071
Cesarean delivery	261 (94.9%)	176 (95.1%)	0.913
Congenital infection	18 (6.5%)	26 (14.1%)	0.007
Mechanical ventilation	211 (76.7%)	144 (77.8%)	0.781
Respiratory distress syndrome	173 (62.9%)	123 (66.5%)	0.432
Death	13 (4.7%)	6 (3.2%)	0.433
Maternal age, years	30 (27–34)	32 (28–36)	0.077
Multiple births	81 (29.5%)	44 (23.8%)	0.180
Hypertensive disorder of pregnancy	42 (15.3%)	32 (17.3%)	0.562
Gestational diabetes mellitus	5 (1.8%)	4 (2.2%)	0.523
Chorioamnionitis	83 (30.2%)	71 (38.4%)	0.068
Ritodrine hydrochloride	216 (78.5%)	150 (81.1%)	0.508
Magnesium sulfate	68 (24.7%)	88 (47.6%)	<0.001
Antenatal steroids	200 (72.7%)	172 (93.0%)	<0.001
PDA	91 (33.1%)	92 (49.7%)	<0.001
Initiation of PDA treatment, hours	26 (22–41)	30 (21–41)	0.953
Age at medical closure of PDA, hours	75 (55–95)	66 (45–96)	0.154
Surgical ligation of PDA	5 (1.8%)	12 (6.5%)	<0.001

Values are presented as median (interquartile range) or numbers (percentage).
PDA, patent ductus arteriosus

included in the study after the exclusion of 20 patients with congenital anomalies and chromosomal abnormalities, 3 patients who died within 24 hours after birth, and 20 patients born outside our hospital. Among 211 inpatients born before 34 weeks of gestation during period B, 185 were included in the study after the exclusion of 13 patients with congenital anomalies and chromosomal abnormalities, 2 patients who died within 24 hours after birth, and 11 patients born outside our hospital (Fig. 1).

In period A, 91 patients (33.1%) had PDA and 5 patients (1.8%) underwent surgical intervention. In period B, 92 patients (49.7%) had PDA and 12 patients (6.5%) underwent surgical intervention (Fig. 1). Significantly more patients had PDA ($p < 0.001$), and significantly more patients in the PDA group underwent surgical intervention ($p = 0.009$) in period B than in period A. The median time to therapeutic intervention in the PDA group was 26 hours (22–41) during period A and 30 hours (21–41) during period B, with no significant difference between the two periods.

2. Infant demographics and clinical parameters in period A and B (Table 3)

Infants in period B had a lower gestational

Table 3. Demographic and clinical parameters of infants in periods A and B

	Period A			Period B		
	PDA (+) (n=91)	PDA (−) (n=184)	p-value	PDA (+) (n=92)	PDA (−) (n=93)	p-value
Gestational age, weeks	27.0 (25.2–29.7)	31.0 (28.7–32.4)	<0.001	27.6 (25.0–28.9)	30.1 (28.0–32.3)	<0.001
Birth weight, g	868 (679–1226)	1402 (1019–1619)	<0.001	980 (690–1172)	1254 (886–1524)	<0.001
Apgar score at 1 min	5 (3–6)	7 (5–8)	<0.001	4 (3–5)	5 (3–7)	<0.001
Apgar score at 5 min	7 (6–8)	8 (7–9)	<0.001	7 (6–8)	8 (6–9)	<0.001
Female	53 (58.2%)	83 (45.1%)	0.060	36 (39.1%)	40 (43.0%)	0.698
Cesarean delivery	89 (97.8%)	172 (93.5%)	0.103	90 (97.8%)	86 (92.5%)	0.087
Congenital infection	9 (9.9%)	9 (4.9%)	0.115	15 (16.3%)	11 (11.8%)	0.381
Mechanical ventilation	88 (96.7%)	123 (66.8%)	<0.001	86 (83.5%)	58 (62.4%)	<0.001
Respiratory distress syndrome	82 (90.1%)	91 (49.5%)	<0.001	77 (83.7%)	46 (49.5%)	<0.001
Death	10 (11.0%)	3 (1.6%)	0.001	5 (5.4%)	1 (1.1%)	0.103
Maternal age, years	29 (27–34)	31 (28–34)	0.253	33 (29–36)	31 (27–34)	0.083
Multiple births	27 (29.7%)	54 (29.3%)	0.956	26 (28.3%)	18 (19.4%)	0.155
Hypertensive disorder of pregnancy	8 (8.8%)	34 (18.5%)	0.036	11 (12.0%)	21 (22.6%)	0.056
Gestational diabetes mellitus	1 (1.1%)	4 (2.2%)	0.465	2 (2.2%)	2 (2.2%)	0.685
Chorioamnionitis	33 (36.3%)	50 (27.2%)	0.122	38 (41.3%)	33 (35.5%)	0.416
Ritodrine hydrochloride	76 (83.5%)	140 (76.1%)	0.158	80 (87.0%)	70 (75.3%)	0.042
Magnesium sulfate	21 (23.1%)	47 (25.5%)	0.656	38 (41.3%)	50 (53.8%)	0.090
Antenatal steroids	78 (85.7%)	122 (66.3%)	0.001	86 (93.5%)	86 (92.5%)	0.789

Values are presented as median (interquartile range) or numbers (percentage).
PDA, patent ductus arteriosus

age ($p = 0.002$), smaller birth weight ($p < 0.01$), and lower Apgar score ($p < 0.001$). Congenital infections were also more common during period B ($p = 0.007$), and magnesium sulfate ($MgSO_4$) and steroid therapy were administered to more mothers of infants in period B ($MgSO_4$: $p < 0.001$, steroid: $p < 0.001$).

Infants in period A had a higher total water quantity during days 3 and 4 after birth ($p = 0.038$ and 0.009, respectively), and more infants in period A received catecholamine therapy ($p < 0.001$), while infants in period B received a higher glucose infusion rate on days 2–4 after birth ($p = 0.003$, < 0.001, and < 0.001, respectively). The mean blood pressure, SpO_2, and FiO_2 were higher in period A ($p < 0.001$) and blood glucose levels were higher in period B ($p < 0.001$), but all were within normal limits. Serum osmolality was high on days 2–4 after birth among infants in period B ($p < 0.001$, < 0.001, and $= 0.001$, respectively).

3. Demographics of infants with and without PDA in periods A and B (Table 4)

In both periods A and B, infants in the PDA group had a lower gestational age, smaller birth weight, and lower Apgar score compared to infants in the non-PDA group (gestational age: $p < 0.001$, birth weight: $p < 0.001$, Apgar score: $p < 0.001$, in A and B, respectively). In period B, ritodrine hydrochloride therapy was more common among infants with PDA ($p = 0.042$) (Table 4).

During both periods A and B, a higher

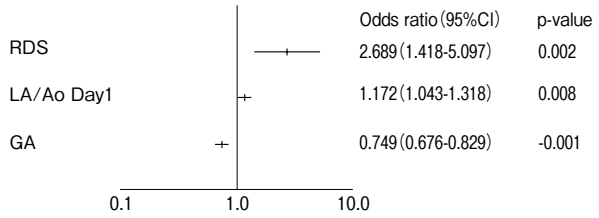

Fig. 2. Multiple logistic regression analysis of RDS, GA and LA/Ao on day 1
RDS, respiratory distress syndrome; GA, gestational age; CI, confidence interval; LA/Ao, left atrium/aortic root ratio

proportion of infants in the PDA group developed respiratory distress syndrome (RDS) ($p < 0.001$), and the use of mechanical ventilation was more common ($p < 0.001$). During periods A and B, LA/Ao on days 2 and 3 after birth was larger in the PDA group (LA/Ao on day 2: $p < 0.001$, LA/Ao on day 3: $p < 0.001$, in A and B, respectively). During period B, LPA d/s on days 2 and 3 after birth was larger in the PDA group ($p = 0.001$ and 0.006, respectively). Blood glucose levels were high on days 2–4 after birth in the PDA group during period A ($p = 0.030$, 0.020, and < 0.001, respectively), and high on days 2 and 4 after birth in the PDA group during period B ($p = 0.009$ and 0.001, respectively). Serum osmolality was high on days 2–4 after birth in the PDA group during both periods A ($p = 0.001$, 0.001, and <0.001, respectively) and B ($p = 0.008$, 0.034, and 0.003, respectively).

4. Multiple logistic regression analysis (Fig. 2)

Only significant factors were noted in the multiple logistic regression analysis. Multiple logistic regression analysis revealed that the presence or absence of RDS, gestational age, and LA/Ao immediately after birth were associated with PDA. During period B, LPA d/s immediately after birth were associated with PDA ($p = 0.035$, Odds ratio 1.043, 95% CI 1.003-1.084). Study period, blood glucose level, serum osmolality, and use of EAN were not associated with PDA (Fig. 2).

5. Receiver operating characteristic curve and model validation (Fig. 3)

In the derivation set, AUC were 0.764 and 0.821 for the gestational age and LA/Ao, respectively. When the gestational age and LA/Ao were applied to the internal validation

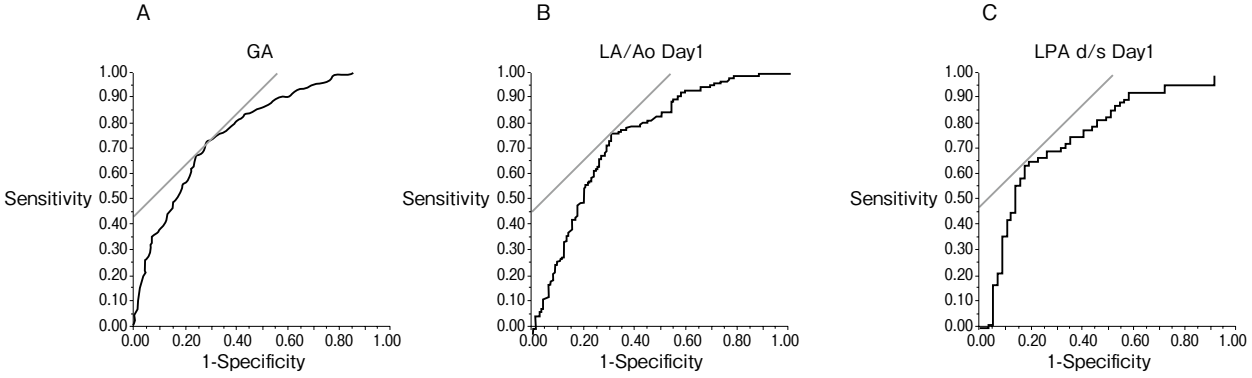

Fig. 3-A. Receiver operating characteristic curve of GA
B. Receiver operating characteristic curve of LA/Ao on day1
C. Receiver operating characteristic curve of Period B's LPA d/s on day1
GA, gestational age; LA/Ao, left atrium/aortic root ratio; LPA d/s, left pulmonary artery mean diastolic velocity/peak systolic velocity ratio

set, AUC were 0.763 and 0.816, respectively. Similarly, in the derivation set in period B, AUC was 0.746 for LPA d/s. When LPA d/s was applied to the internal validation set, AUC was 0.829.

IV. Discussion

Preterm infants in period B had a lower gestational age, smaller birth weight, and lower Apgar score compared to those in period A, showing that more infants with more severe immaturity were admitted to our NICU during period B than during period A. Congenital infections were also more common in period B, and infants with PDA requiring COX-inhibitor therapy or surgical intervention were more common during period B. The increase in infants with PDA requiring these treatments is consistent with the results of a national survey of infants born with a birth weight under 1,500 g between 2003 and 2008 [18].

Steroid therapy and $MgSO_4$ therapy for mothers expected to deliver preterm were included under Japan's national health insurance after a report that prenatal steroid therapy reduced the incidence of RDS, intraventricular hemorrhage, necrotizing enterocolitis, and mortality [19], and a report that increased blood Mg concentration suppressed uterine contraction [20], among other reports. Some reports suggest that prenatal steroid therapy reduces PDA incidence by inhibiting postnatal prostaglandin synthesis and reducing prostaglandin E_2 sensitivity in the muscular layer of the ductus arteriosus [21-23]. However, PDA incidence was higher during period B despite the blanket use of prenatal steroid therapy, and multivariate analysis also found no relationship between PDA onset and prenatal steroid therapy. Toyoshima et al. reported that $MgSO_4$ administered to rat embryos suppressed the constriction of the ductus arteriosus by increasing $MgSO_4$ concentration and enhancing antagonistic action against Ca^{2+} in postnatal pups [24]. In the present study, although $MgSO_4$ was administered to more mothers during period B, infants born of mothers that received $MgSO_4$ did not always have a high Mg concentration (data not shown), and multivariate analysis also found no relationship between $MgSO_4$ therapy and PDA onset.

Postnatal SpO_2 tended to be lower during period B. This was due to a change to the target SpO_2 level that was expected to prevent the onset of retinopathy of prematurity, chronic lung disease, and necrotizing enterocolitis, and to reduce mortality [25, 26]. Multivariate analysis did not reveal a relationship between SpO_2 and PDA onset, but based on the significantly higher FiO_2 in the PDA group, we deduced that severe respiratory disease has a more important influence in making infants susceptible to PDA onset compared to the need for a high concentration of oxygen.

A recent report noted that reduced postnatal serum osmolality stimulates ductus arteriosus constriction in rats, and that the risk of PDA onset is probably increased in human preterm infants with a gestational age under 28 weeks, because serum osmolality does not tend to decrease in these infants [13]. Additionally, it has been reported that intravenously administering high concentrations of glucose, amino acids, and fat formulations improves the neurological

prognosis of preterm infants.

In the present study, serum osmolality was compared before and after the introduction of EAN. At our hospital, EAN of high-concentration glucose and amino acids was introduced with the presumption that it would increase serum osmolality [5, 27]. Results showed that serum osmolality was significantly higher during period B after the introduction of EAN. Although high serum osmolality was observed in the PDA group during periods A and B, multiple logistic regression analysis did not demonstrate a relationship between PDA onset and high serum osmolality and EAN. Similarly, blood glucose levels were high in period B but within normal limits, and there was no relationship between blood glucose levels and PDA onset. The findings that immaturity was more severe in preterm inpatient infants during period B and that the presence and absence of RDS and gestational age were associated with PDA suggest that infant immaturity was a stronger influence on PDA onset than the intervention in the mother or infant.

At present, there are no established objective factors to predict PDA onset from the early postnatal period. Pereira et al. reported that gestational age was the only predictive factor of PDA onset in the early postnatal period in preterm infants with a gestational age under 29 weeks, and that PDA onset could not be predicted from echocardiographic findings [28]. Opinions vary on this subject, with Lee et al. reporting that echocardiography in the early postnatal period increased the rate of PDA diagnosis but did not lead to an improved survival rate [29], and Polat et al. reporting that ductus arteriosus length and morphology were useful for predicting cases of PDA that required treatment [30]. Multiple logistic regression analysis and AUC findings from the present study indicate that PDA onset may be predicted by echocardiography immediately after birth. Compared to the report of Toyoshima et al [31], in which AUC of LA/Ao was 0.919, AUC of LA/Ao immediately after birth in our study (0.757) was lower. However, their study used the LA/Ao just before PDA ligation, which was different from our study. AUC for the LPA d/s immediately after birth was comparable with those for gestational age and LA/Ao. To our knowledge, this is the first study to predict PDA in preterm infants using LPA d/s. We assume that in severely immature infants, from immediately after birth, LA/Ao and LPA d/s are sensitive indicators of volume overload from left-to-right shunt through the ductus arteriosus. However, different medical institutions have different echocardiography criteria for PDA treatment intervention, and echocardiography indicators are prone to interobserver variability. In the future, it will be important to standardize the techniques and establish echocardiography indicators that are not susceptible to interobserver variability.

One limitation of this study was its retrospective single-center design. Moreover, although the proportion of patients with PDA onset who underwent surgical intervention in this study was similar to those in other reports [18], it was insufficient for an analysis of factors associated with COX-inhibitor resistance. A prospective study at multiple study sites is needed to evaluate the effect of different methods of preterm infant

management on PDA onset, COX-inhibitor resistance, and long-term prognosis.

In conclusion, this study compared two periods of different treatment strategies and showed that preterm infant immaturity, illness severity, and increased PDA incidence were greater during the second period. The study also showed a substantial difference in vital signs and blood biochemistry findings between the two periods, although it found no association between these findings and PDA onset. With regard to predictive factors for PDA, we suggest that PDA onset can be predicted from immediately after birth by combining echocardiography findings with findings indicative of immaturity.

Conflicts of interest: The authors have no conflict of interest to declare.

References

1) **Watanabe T, Sawaki R, Matsudai T, et al.**: The clinical features of neonates with hypermagnesemia at our hospital. Jpn J Pediatr **67**, 1337-1341, 2014.
2) **Oozeki K, Takigawa I, Matsui S, et al.**: Prenatal steroid therapy and the prognosis of extremely immature infants. J Jpn Soc Perin Neon Med **48**, 840-844, 2013.
3) The STOP-ROP Multicenter Study Group: Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. Pediatrics **105**, 295-310, 2000.
4) **Schmidt B, Whyte RK, Asztalos EV, et al.**: Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. JAMA **309**, 2111-2120, 2013.
5) **Isaacs EB, Gadian DG, Sabatini S, et al.**: The effect of early human diet on caudate volumes and IQ. Pediatr Res **63**, 308-314, 2008
6) **Wilson DC, Cairns P, Halliday HL, et al.**: Randomised controlled trial of an aggressive nutritional regimen in sick very low birthweight infants. Arch Dis Child Fetal Neonatal Ed **77**, F4-11, 1977.
7) **Yokoyama U, Minamisawa S** and **Ishikawa Y**: Regulation of vascular tone and remodeling of the ductus arteriosus. J Smooth Muscle Res **46**, 77-87, 2010.
8) **Cotton RB, Lindstrom DP** and **Stahlman MT**: Early prediction of symptomatic patent ductus arteriosus from perinatal risk factors a discriminant analysis model. Acta Paediatr Scand **70**, 723-727, 1981.
9) **Nagashima T, Kobayashi M, Teramoto S, et al.**: Analysis of very low birth weight infants born at the Jikei University School of Medicine Women's and Children's Medical Center: focus on patent ductus arteriosus. Jikeikai Med J **54**, 1–9, 2007.
10) **Chen YY, Wang HP, Chang JT, et al.**: Perinatal factors in patent ductus arteriosus in very low-birthweight infants. Pediatr Int **56**, 72-76, 2014.
11) **Koch J, Hensley G, Roy L, et al.**: Rosenfeld CR. Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000g or less. Pediatrics **117**, 1113–1121, 2006.
12) **Kalis NN, Pieper C, van der Merwe PL, et al.**: Factors influencing successful closure with indomethacin of the patent ductus arteriosus in premature infants. Cardiovasc JS Afr **12**, 268–272, 2001.
13) **Aoki R, Yokoyama U, Ichikawa Y, et al.:** Decreased serum osmolality promotes ductus arteriosus constriction. Cardiovasc Res **104**, 326-336, 2014.
14) **Kluckow M** and **Evans N**: Early echocardiographic prediction of symptomatic patent ductus arteriosus in preterm infants undergoing mechanical ventilation. J Pediatr **127**, 774-779, 1995.
15) **Iyer P** and **Evans N**: Re-evaluation of the left atrial to aortic root ratio as a marker of patent ductus arteriosus. Arch Dis Child Fetal Neonatal Ed **70**, F112-F117, 1994.
16) **Toyoshima K, Kawataki M, Sato Y, et al.**: Serial echocardiographic assessment of mVcfc-ESWS relation in very low birth infant with perinatal complications. J Jpn Pediatr Soc Premature and Newborn Med **14**, 45-52, 2002.

17) **Yeh TF, Raval D, Luken J, et al.**: Clinical evaluation of premature infants with patent ductus arteriosus: a scoring system with echocardiogram, acid-base, and blood gas correlations. Crit Care Med **9**, 655-657, 1981.
18) **Kusuda S, Fujimura M, Uchiyama A, et al.**: Trend in morbidity and mortality among very-low-birth-weight infants from 2003 to 2008 in Japan. Pediatr Res **72**, 531-538, 2012.
19) **Brownfoot FC, Crowther CA** and **Middleton P**: Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev **8**, CD006764, 2008.
20) **Kawarabayashi T, Kishikawa T** and **Sugimori H**: Effects of external calcium, magnesium, and temperature on spontaneous contractions of pregnant human myometrium. Biol Reprod **40**, 942-948, 1989.
21) **Thibeault DW, Emmanouilides GC** and **Dodge ME**: Pulmonary and circulatory function in preterm lambs treated with hydrocortisone in utero. Biol Neonate **34**, 238–247, 1978.
22) **Clyman RI, Ballard PL, Sniderman S, et al.**: Prenatal administration of betamethasone for prevention of patient ductus arteriosus. J Pediatr **98**, 123-126, 1981.
23) **Amorim MM, Santos LC** and **Faúndes A**: Corticosteroid therapy for prevention of respiratory distress syndrome in severe preeclampsia. Am J Obstet Gynecol **180**, 1283-1288, 1999.
24) **Toyoshima K, Momma K** and **Nakanishi T**: Fetal reversed constrictive effect of indomethacin and postnatal delayed closure of the ductus arteriosus following administration of transplacental magnesium sulfate in rats. Neonatology **96**, 125-131, 2009.
25) The STOP-ROP Multicenter Study Group: Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. Pediatrics **105**, 295-310, 2000.
26) **Schmidt B, Whyte RK, Asztalos EV, et al.**: Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. JAMA **309**, 2111-2120, 2013.
27) **Wilson DC, Cairns P, Halliday HL, et al.**: Randomised controlled trial of an aggressive nutritional regimen in sick very low birthweight infants. Arch Dis Child Fetal Neonatal Ed **77**, F4-F, 1977.
28) **Pereira SS, Kempley ST, Shah DK, et al.**: Early echocardiography does not predict subsequent treatment of symptomatic patent ductus arteriosus in extremely preterm infants. Acta Paediatr **107**, 1909-1916, 2018.
29) **Lee JH, Greenberg RG, Quek BH, et al.**: Association between early echocardiography, therapy for patent ductus arteriosus, and outcomes in very low birth weight infants. Cardiol Young **27**, 1732-1739, 2017.
30) **Polat TB, Celik IH** and **Erdeve O**: Early predictive echocardiographic features of hemodynamically significant patent ductus arteriosus in preterm VLBW infants. Pediatr Int **58**, 589-594, 2016.
31) **Toyoshima K, Masutani S, Senzaki H, et al.**: Left atrial volume is superior to the ratio of the left atrium to aorta diameter for assessment of the severity of patent ductus arteriosus in extremely low birth weight infants. Circ J **78**, 1701-1709, 2014.

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早産児の管理方法の変化と早産児動脈管開存症の発症

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要旨

周産期の管理方法の変化が早産児動脈管開存症（patent ductus arteriosus, PDA）の発症に与える影響は明らかでない．early aggressive nutrition 導入前の2006 年から 2008 年（期間 A）と導入後の 2012 年から 2014 年（期間 B）に当院 NICU に入院した在胎 34 週未満の早産児を対象に，周産期管理方法と PDA 発症の頻度を比較し，母体・新生児因子で PDA 発症に関与する因子を抽出した．期間 A に比し期間 B で児の未熟性が強く，PDA 発症率が高かった．PDA 発症群と非発症群の比較では，両期間の発症群で児の未熟性が強く，新生児呼吸窮迫症候群（respiratory distress syndrome, RDS）を合併する割合が高かった．多重ロジスティック解析では RDS の有無や在胎週数，生直後の心臓超音波検査指標が PDA の発症に関連していた．周産期の管理方法は変化していたが，それらの変化は PDA の発症に関連せず，児の未熟性が最も重要な危険因子であった．在胎週数が短く，RDS 合併例では，出生直後の心臓超音波検査指標が PDA 発症の予測を補強できる可能性が示唆された．