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Surgical Ligation for Patent Ductus Arteriosus in Extremely Premature Infants: Strategy to Reduce their Risk of Neurodevelopmental Impairment

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Surgical ligation for patent ductus arteriosus (PDA) in extremely low birth weight infants (ELBWIs) has been shown a possible association with neurodevelopmental impairment (NDI) because of its invasiveness. However, we have undergone surgical ligation for ELBWIs immediately after cyclooxygenase inhibitor failed to close a hemodynamically significant PDA (hsPDA) to maintain proper systemic circulation. We aimed to determine the effect of surgical ligation for hsPDA on NDI in ELBWIs. In enrolled 71 ELBWIs, the clinical parameters, including the developmental quotient (DQ), were collected and compared among three groups that were divided by closure mode: spontaneous closure (n = 11), cyclooxygenase inhibitor therapy (n = 37) and surgical ligation (n = 23). No significant differences in DQ at the age of 36 months among the three groups were found: Median (interquartile range): 92.0 (31.0), 89.0 (22.0) and 92.0 (24.5), respectively. In a comparison between groups of DQ < 70 (n = 15) and DQ ≥ 70 (n = 56), a significant difference was found in the parameters related to prematurity ($p < 0.05$ for each): gestational age [23.9 (1.70) vs. 25.4 (2.50) weeks], birth weight [595 (183) vs. 714 (192) g], Apgar score < 5 (1 min) (67% vs. 36%), and laser photocoagulation for retinopathy of prematurity (73% vs. 43%), but there was no significant association with hsPDA. Therefore, we propose that surgical ligation for hsPDA in ELBWIs should be immediately carried out for preventing future neurodevelopmental deterioration if the cyclooxygenase inhibitor failed to close hsPDA.

Keywords: cyclooxygenase inhibitor; developmental quotient; hemodynamically significant patent ductus arteriosus; Kyoto scale of psychological development 2001; neurodevelopmental impairment
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Introduction

Premature infants tend to develop persistent patent ductus arteriosus (PDA), because spontaneous closure of the ductus arteriosus is delayed after birth (Reller et al. 1993). In these infants, increasing exposure to hemodynamically significant PDA (hsPDA) increases the risk of pulmonary congestion, reduced systemic blood flow and congestive heart failure (Clyman et al. 1987, 2012; Alpan et al. 1991; Clyman and Noori 2012; Noori and Seri 2015). Since many clinical studies have demonstrated strong association between the presence of hsPDA and chronic lung disease (CLD), necrotizing enterocolitis, retinopathy of prematurity (ROP), and neurodevelopmental retardation (Rheinlaender et al. 2010; Tauzin et al. 2012; Wickremasinghe et al. 2012; Janz-Robinson et al. 2015), hsPDA is a potential risk factor that seriously affects the long-term prognosis of premature infants.

Administration of a cyclooxygenase (COX) inhibitor, which inhibits the synthesis of prostaglandin E (PGE), has been the first-line therapy for hsPDA in premature infants because patency of the ductus arteriosus has been shown to strongly depend on the plasma PGE concentration in premature infants (Smith 1998; Irmesi et al. 2014; Oncel and Erdeve 2015). Surgical ligation is not considered a first-line therapy option for hsPDA in premature infants because of its possible invasiveness although it is the most reliable treatment for hsPDA. Clinical studies have also shown that surgical ligation of hsPDA in premature infants is associated with an increased risk of CLD, ROP and neurodevelopmental impairment (Kabra et al. 2007; Rheinlaender et al. 2010; Wickremasinghe et al. 2012). Therefore, surgical ligation is generally reserved for premature infants in whom COX inhibitor therapy is ineffective.

On the other hand, it has been reported that 16 to 32% of extremely low birth weight infants (ELBWIs) are resis-

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tant to treatment with a COX inhibitor (Van Overmeire et al. 2004; Rheinlaender et al. 2010; Wickremasinghe et al. 2012). Contraction of the smooth muscle in the wall of the ductus arteriosus and sufficient thickening of its intima are essential to achieve anatomic closure of the ductus arteriosus (Clyman 2006). Intimal thickening occurs continuously throughout the fetal period due to PGE2 stimulation of the EP4 receptors present in the smooth muscle cells in the ductus arteriosus (Yokoyama et al. 2010). Therefore, in ELBWIs, since the intima is not yet sufficiently thickened at birth due to immaturity, the ductus arteriosus is highly likely to show persistent patency. Furthermore, the COX inhibitor administered to cause contraction of the ductus arteriosus also reduces the production of PGE2, resulting in inhibition of the anatomic closure due to intima formation of the ductus arteriosus.

For these reasons, hsPDA in ELBWIs is likely to be resistant to COX inhibitor therapy and to eventually require treatment by surgical ligation. Furthermore, because the myocardial contractile and diastolic function is immature in ELBWIs (Friedman 1972), long-term exposure to hsPDA tends to cause multiple organ injury. Therefore, to minimize the exposure time of ELBWIs to hsPDA, in our institution, we have adopted a treatment policy of immediately performing surgical ligation as soon as hsPDA proves resistant to COX inhibitor therapy, and to avoid the repeated administration of COX inhibitors. The purpose of this study was to clarify whether surgical ligation for hsPDA is associated with a higher risk of complications or worse neurodevelopmental outcomes in ELBWIs, and thereby, to confirm the validity of our treatment policy.

Methods

This study was conducted with the approval of the ethics committee of the Tohoku University School of Medicine (No. 2010-249).

Patient enrollment

The study involved all ELBWIs (n = 111) born at the Center for Perinatal-Neonatal Medicine, Tohoku University Hospital, with an expected date of birth between June 2007 and March 2011.

All data were extracted retrospectively from the medical records. The clinical characteristics were compared between the enrolled (n = 71) and excluded groups (n = 40). The exclusion criteria were as follows: (1) lack of consent for the study, (2) death, (3) chromosomal aberrations or multiple malformations, (4) lack of consent for the developmental assessment at the corrected age of 36 months (hereinafter simply, “at the age of 36 months”), and (5) failure to carry out developmental assessment at the age of 36 months due to relocation or loss of contact information.

Clinical information and neurodevelopmental assessment

First, the enrolled subjects (n = 71) were divided into three groups according to the mode of closure of the ductus arteriosus: the spontaneous closure group (n = 11), the COX inhibitor group (n = 37), and the surgical ligation group (n = 23). To analyze the clinical parameters associated with the mode of closure of the ductus arteriosus, 17 perinatal clinical parameters and 9 hsPDA severity indices were compared among the three groups (Table 1). Next, to analyze the relationship between the mode of closure of the ductus arteriosus and the developmental prognosis, the developmental quotients (DQs) at the age of 36 months were compared among the three groups (Table 2). Third, the subjects (n = 71) were also divided into two groups according to the DQ at the age of 36 months, DQ ≥ 70 (n = 56) and DQ < 70 groups (n = 15), based on the Kyoto Scale of Psychological Development 2001, in which DQ < 70 has been generally defined as delayed (Kono et al. 2016). To analyze the relationship between the DQ at the age of 36 months and the clinical parameters, the perinatal clinical parameters, hsPDA severity indices, and mode of closure of the ductus arteriosus were compared between these two groups (Table 3).

Management of hsPDA

Circulatory management of ELBWIs in our institution during the study period was characterized as follows: (1) In cases of diagnosis of intrauterine inflammation or fetal growth retardation due to chronic hypoxia, betamethasone was not administered to the mother before delivery, in principle; (2) in cases of diagnosis of respiratory distress syndrome (RDS) at birth, an artificial lung surfactant was used to prevent its progression; (3) left heart failure was treated with sedatives and vasodilators; (4) only cardiogenic shock or septic shock was treated with dopamine to elevate the blood pressure; (5) in cases of increased vascular permeability with worsening anasarca, hydrocortisone was administered; (6) in cases diagnosed as hsPDA, a COX inhibitor (indomethacin) was immediately administered; (7) indomethacin was not administered preventively before a diagnosis of hsPDA; (8) the initial dose of indomethacin was 0.2 mg/kg, with subsequent dosing at 0.1 mg/kg for infants within 48 h of birth and 0.2 mg/kg for infants from 2 to 7 days after birth. In all cases, indomethacin was administered intravenously for 1 h up to 3 times according to its attached document of the Japan pharmaceutical reference; (9) In cases where the hsPDA was refractory to indomethacin, a surgical clip ligation was immediately performed without expecting or waiting for spontaneous closure of the PDA. This was usually done on the incubator bed in the neonatal intensive care unit to keep the patient at rest. (10) In the operative procedure, the ductus was approached through a left posterolateral thoracotomy in the third intercostal space. The mediastinal pleura was incised along the aorta and the ductus. After minimal dissection above and below the aortic side of the ductus, a medium-size hemoclip was placed around it to close its vascular lumen. The entire procedure usually took 15 to 20 min, and was performed by expert cardiovascular surgeons.

Definitions

The definitions and extraction methods of the perinatal clinical parameters and hsPDA severity indices in this study are described below. Antenatal mothers received intramuscular injections of 12.0 mg of betamethasone twice at an interval of 24 h. RDS was diagnosed based on the stable microbubble rating of amniotic fluid at birth (Chida and Fujiwara. 1993; Chida et al. 1993). Cerebral white matter injury (CWMI) was diagnosed by radiologists based on abnormal signals on magnetic resonance imaging (MRI) at the corrected age of 37 to 42 weeks, according to the definition of Baker or Maalouf (Baker et al. 1988; Maalouf et al. 1999). Intraventricular hemorrhage (IVH) was defined as grade II or more severe hemorrhage according to the classification of Papile et al. (1987): namely, hemorrhage in which the hematoma has progressed to the lateral ventricle. ROP was diagnosed

according to the international classification (American Academy of Pediatrics 1984), and patients with progressive, extraretinal fibrovascular proliferation (stage III) were treated by laser photocoagulation. Home oxygen use was prescribed when the patient could not maintain $SpO_2 \geq 90\%$ or $PaO_2 \geq 50$ torr in room air at the corrected age of 0 months. Cerebral palsy was diagnosed according to the definition of the Surveillance of Cerebral Palsy in Europe (Surveillance of Cerebral Palsy in Europe 2000). Low vision was defined as a corrected visual acuity of ≤ 0.3 in both eyes at 3 years of age. To numerically represent the cognitive abilities at the age of 36 months as DQ scores (total, posture-movement, cognition-adaptability and language-sociality), the patients were examined using the Kyoto Scale of Psychological Development 2001, which has been standardized for the Japanese population (Koyama et al. 2009).

HsPDA was diagnosed based on the presence of a continuous systolic heart murmur, tachycardia, increased pulse pressure, reduced systolic blood pressure, reduced oxygenation and ventilation, cardiomegaly and pulmonary congestion on the chest radiograph, continuous left-to-right shunting of blood through the PDA, and left atrial enlargement on the echocardiogram (Su et al. 1997). An ultrasonographic device (Sonos5500; Hewlett-Packard, Andover, USA) with a 7 MHz probe was used for the blood flow diagnosis. hsPDA refractory to indomethacin was defined as (1) no reduction in the diameter of the ductus arteriosus within 6 h of initial treatment with indomethacin, (2) continued hsPDA symptoms after the three doses of indomethacin, or (3) a relapse into hsPDA within 72 h of the initial dose. The closure of PDA was confirmed based on continuous cessation of its Doppler flow velocity in echocardiography, observed every 6 to 8 h for 72 h.

All of the hsPDA severity indices were calculated from the data recorded immediately before the closure of the ductus arteriosus (i.e., disappearance of the flow through the ductus arteriosus). The mean arterial pressure (MAP) was measured noninvasively (IntelliVue MP50 Neonatal Monitor; Philips, Boeblingen, Germany). The ventilatory index (VI) and ventilatory efficacy index (VEI) were calculated as respiratory indices reflecting pulmonary congestion: $VI = FiO_2$ MAP/PaO_2, $VEI = 3800$ / respiratory rate $\Delta P \times PaCO_2$ (Δpaw: difference in airway pressure). PaO_2 and $PaCO_2$ were substituted by values measured percutaneously (Percutaneous blood gas transducers M1918A; Philips, Stargard, Poland). The mean urine output (mL/h) during the 8 h period before the closure of the ductus arteriosus was calculated. Blood lactate levels were measured using a blood gas analyzer (Rapidlab860; Siemens, Boston, USA). Blood flow velocity waveforms of the anterior cerebral artery and renal artery were measured by the pulse Doppler method, and clear images obtained at an incident angle of ≤ 5 degrees were used. The resistive index (RI) was calculated using the following formula: RI = (maximum systolic velocity – end diastolic blood flow velocity)/maximum systolic velocity. The ratio of the left atrial to aortic diameter was measured using the M-mode method according to the recommendation of the American Society of Echocardiography (Sahn et al. 1978). Exposure time to hsPDA was defined as the time from the first administration of indomethacin to the ultrasonographic disappearance of the blood flow through the ductus arteriosus.

Statistical analysis

Continuous variables are represented by the median (the interquartile range) and categorical variables as the number of cases (%). The statistical analysis software, IBM® SPSS® Statistics Ver. 23 (IBM Co. Ltd., Armonk, USA), was used for the statistical analysis, with the level of significance set at $p < 0.05$.

In the comparison between the enrolled subjects and excluded patients, categorical variables were analyzed using the Fisher's exact test and continuous variables using the Mann-Whitney U test.

To analyze the relationship between the mode of closure of the ductus arteriosus and the clinical parameters (Tables 1 and 2), the perinatal clinical parameters, hsPDA severity indices, and DQ scores at 36 months of age were compared among the spontaneous closure, COX inhibitor, and surgical ligation groups. Categorical variables were analyzed using the chi-square test and continuous variables were analyzed using the Kruskal-Wallis test. Items showing significant differences were further analyzed by Scheffe's multiple comparisons.

To analyze the relationship between DQ scores at the age of 36 months and the clinical parameters (Table 3), the perinatal clinical parameters, hsPDA severity indices, and mode of closure of the ductus arteriosus were compared between the DQ ≥ 70 and DQ < 70 groups. Categorical variables were analyzed using Fisher's exact test and continuous variables using the Mann-Whitney U test.

Results

There were 111 ELBWIs who were born at our institution during the study period. Of these, 40 infants met the following exclusion criteria: (1) lack of consent for the study (6 cases), (2) death (11 cases), (3) chromosomal aberrations or multiple malformations (1 case), (4) lack of consent for the developmental assessment at 36 months of age (6 cases), (5) failure to carry out developmental assessment at 36 months of age due to relocation or loss of contact information (14 cases) and (6) others (2 cases). The data of the remaining 71 cases were analyzed in this study. In the comparison of the clinical characteristics between the enrolled and excluded groups, CWMI (enrolled group vs. excluded group, 1.4% vs. 26%), IVH (2.8% vs. 26%), and cerebral palsy (11% vs. 50%) were significantly more common in the excluded group than in the enrolled group ($p < 0.01$). There were no significant differences in any of the other investigated items between the two groups.

Clinical parameters associated with the mode of closure of the ductus arteriosus

Of the 71 subjects, 11, 37, and 23 were classified according to the mode of closure of the ductus arteriosus, into the spontaneous closure, COX inhibitor, and surgical ligation groups, respectively. The perinatal clinical parameters and hsPDA severity indices were compared among the three groups (Table 1). The RI of the renal artery was significantly higher in the COX inhibitor [1.00 (0.18)] and surgical ligation [1.00 (0.12)] groups than in the spontaneous closure group [0.75 (0.14)] ($p < 0.01$). Exposure time to hsPDA was significantly longer in the surgical ligation group [125 (89.5) h] than in the COX inhibitor group [19.0 (24.0) h] ($p < 0.01$). There were no significant differences in any of the other investigated items between the two groups.

Table 1. Comparison of perinatal parameters and indices of severity of the hsPDA among the three groups.

	Spontaneous closure (n = 11)	COX inhibitor closure (n = 37)	Surgical ligation (n = 23)
Perinatal parameters			
Gestational weeks	25.4 (4.00)	25.6 (2.70)	24.7 (1.30)
Birth weight (g)	689 (188)	652 (276)	696 (121)
Male	5 (45)	17 (46)	9 (39)
Multiple pregnancy	1 (9.1)	9 (24)	6 (26)
Antenatal betamethasone	3 (27)	7 (19)	5 (22)
Apgar score < 5 at 1 min after birth	5 (45)	18 (49)	7 (30)
Apgar score < 5 at 5 min after birth	0 (0.0)	3 (8.1)	1 (4.3)
pH < 7.25 in umbilical artery blood at birth	4 (36)	14 (38)	6 (26)
Respiratory distress syndrome	7 (64)	33 (89)	21 (91)
Cerebral white matter injury	0 (0.0)	1 (2.7)	1 (4.3)
Intraventricular hemorrhage	1 (9.1)	1 (2.7)	1 (4.3)
Cerebral palsy	3 (27)	3 (8.1)	1 (4.3)
Pulmonary haemorrhage	0 (0.0)	1 (2.7)	1 (4.3)
Intestinal perforation	0 (0.0)	2 (5.4)	1 (4.3)
Laser photocoagulation for ROP	6 (55)	16 (43)	13 (57)
Low vision	0 (0.0)	1 (2.7)	0 (0.0)
Home oxygen use	5 (45)	14 (38)	14 (60)
Indices of severity of the hsPDA			
Ventilatory index	0.05 (0.03)	0.04 (0.04)	0.05 (0.03)
Ventilatory efficiency index	0.18 (0.20)	0.21 (0.12)	0.18 (0.07)
Urine output (ml/kg/h)	2.40 (4.15)	3.10 (2.30)	3.00 (2.07)
Mean blood pressure (mmHg)	40.0 (9.70)	32.0 (10.0)	35.0 (11.7)
Blood lactate level (mg/dl)	17.2 (3.20)	17.1 (9.90)	18.0 (12.9)
Ratio of the left atrial to aortic diameter	1.06 (0.24)	1.30 (0.35)	1.30 (0.34)
RI of the renal artery	0.75 (0.14)	1.00 (0.18)*	1.00 (0.12)*
RI of the anterior cerebral artery	0.65 (0.13)	0.70 (0.15)	0.85 (0.15)
Time to PDA closure from the first use of indomethacin (h)	Not available	19.0 (24.0)	125 (89.5)**

Continuous variables are expressed as the median (the interquartile range) and were statistically analysed among the three groups using the Scheffe's test. Categorical variables are shown as the number of positive cases, with the percentages indicated in parentheses, and were statistically analysed using the chi-square test. *$p < 0.01$, compared to the spontaneous closure group. **$p < 0.01$, compared between the COX inhibitor and the surgical ligation group. There were no significant differences in any of the other investigated items between the two groups.

COX, cyclooxygenase; PDA, patent ductus arteriosus; hsPDA, hemodynamically significant PDA; ROP, retinopathy of prematurity; RI, resistive index.

Relationship between the mode of closure of the ductus arteriosus and the developmental prognosis

The DQ scores at 36 months of age were compared among the spontaneous closure, COX inhibitor, and surgical ligation groups (Table 2). There were no significant differences in the total DQ score or in the scores for posture-movement, cognition-adaptability, or language-sociability among the three groups. Patients with DQ < 70 accounted for 27.3%, 18.9%, and 21.7% of the patients in the spontaneous closure, COX inhibitor, and surgical ligation groups, respectively, with no significant differences among the three groups.

Clinical parameters associated with the DQ at 36 months of age

Of the 71 subjects, 56 and 15 were classified into the DQ ≥ 70 and DQ < 70 groups, respectively. The perinatal clinical parameters, hsPDA severity indices and the mode of closure of the ductus arteriosus were compared between the two groups (Table 3). The duration of gestation was lesser [DQ < 70 group vs. DQ ≥ 70 group; 23.9 (1.70) vs. 25.4 (2.50) weeks; $p < 0.05$], the birth weight was lower [595 (183) vs. 714 (192) g, $p < 0.05$], the proportion of patients with a 1 min Apgar score of < 5 was higher (67% vs. 36%, $p < 0.05$), and the proportion of patients who had undergone laser photocoagulation for ROP was higher in

Table 2. Comparison of DQ scores at 36 months corrected age among the three groups.

	Spontaneous closure (n = 11)	COX inhibitor closure (n = 37)	Surgical ligation (n = 23)
DQ total	92.0 (31.0)	89.0 (22.0)	92.0 (24.5)
Posture-movement	74.0 (10.5)	78.0 (33.0)	78.0 (47.0)
Cognition-adaptability	84.0 (27.0)	86.0 (20.0)	86.0 (26.0)
Language-sociality	95.0 (31.5)	94.0 (25.0)	94.0 (21.5)

Continuous variables are expressed as the median (the interquartile range). There were no significant differences in the scores on any of the items among the three groups.
COX, cyclooxygenase; DQ, developmental quotient.

Table 3. Comparison of perinatal parameters and indices of severity of the hsPDA and method of PDA treatment between the DQ ≥ 70 and DQ < 70 groups.

	DQ ≥ 70 (n = 56)	DQ < 70 (n = 15)
Perinatal parameters		
Gestational weeks	25.4 (2.50)	23.9 (1.70)*
Birth weight (g)	714 (192)	595 (183)*
Male	23 (41)	8 (53)
Multiple pregnancy	15 (27)	1 (6.7)
Antenatal betamethasone	10 (18)	5 (33)
Apgar score < 5 at 1 min after birth	20 (36)	10 (67)*
Apgar score < 5 at 5 min after birth	4 (7.1)	0 (0.0)
pH < 7.25 in umbilical artery blood at birth	17 (30)	7 (47)
Respiratory distress syndrome	48 (86)	14 (93)
Cerebral white matter injury	0 (0.0)	1 (6.7)
Intraventricular hemorrhage	3 (5.4)	0 (0.0)
Cerebral palsy	6 (11)	2 (13)
Pulmonary hemorrhage	1 (1.8)	1 (6.7)
Intestinal perforation	2 (3.6)	1 (6.7)
Laser photocoagulation for ROP	24 (43)	11 (73)*
Low vision	2 (3.6)	0 (0.0)
Home oxygen use	23 (41)	10 (67)
Indexes of severity of hsPDA		
Ventilatory index	0.04 (0.03)	0.05 (0.04)
Ventilatory efficiency index	0.21 (0.11)	0.17 (0.04)
Urine output (ml/kg/h)	3.10 (2.40)	2.45 (2.25)
Mean blood pressure (mmHg)	32.0 (10.0)	35.0 (15.5)
Blood lactate level (mg/dl)	17.4 (9.90)	17.7 (10.7)
Ratio of the left atrial to aortic diameter	1.29 (0.29)	1.30 (0.40)
RI of the renal artery	0.95 (0.19)	0.90 (0.18)
RI of the anterior cerebral artery	0.73 (0.16)	0.71 (0.18)
Time to PDA closure from the first use of indomethacin (h)	46.0 (105)	19.0 (52.0)
Outcome of PDA closure		
Spontaneous closure	8 (14)	3 (20)
COX inhibitor closure	30 (54)	7 (47)
Surgical ligation	18 (32)	5 (33)

Continuous variables are expressed as the median (the interquartile range) and were statistically analyzed using the Mann-Whitney U test. Categorical variables are shown as the number of positive cases, with the percentages shown in parentheses, and were statistically analyzed using the chi-square test. The values of time to PDA closure from the first use of indomethacin was compared based on those in the COX inhibitor and surgical ligation groups (DQ ≥ 70, n = 48; DQ < 70, n = 12). *$p < 0.05$.
DQ, developmental quotient; PDA, patent ductus arteriosus; hsPDA, hemodynamically significant PDA; ROP, Retinopathy of prematurity; RI, resistive index; COX, cyclooxygenase.

the DQ < 70 group than in the DQ ≥ 70 group (73% vs. 43%, $p < 0.05$). There were no significant differences in any of the other investigated items between the two groups.

Discussion

First, under our management policy in which surgical ligation is immediately performed when hsPDA is found to be refractory to COX inhibitor therapy in ELBWIs, there were no significant differences in the incidence of central nervous, respiratory, or ophthalmic complications (Table 1), or in the DQ scores at the corrected age of 36 months (Table 2), among the spontaneous closure, COX inhibitor, and surgical ligation groups. Next, comparison between the DQ ≥ 70 and DQ < 70 groups, in which the DQ was assessed at 36 months of age, also revealed no significant differences in the outcomes of hsPDA closure between the two groups, although there were significant differences between the groups in the items reflecting immaturity, such as the birth weight, gestational weeks, Apgar score at 1 minute after birth, and laser photocoagulation for ROP (Table 3). Therefore, our results suggested that surgical ligation might not be a risk factor for the development of complications or for a worse developmental prognosis in ELBWI under our circulatory management policy. In order to verify the conclusion, however, it is necessary to compare the long-term prognosis among the ELBWI performed surgical ligation to hsPDA with different time courses in further prospective clinical studies.

On the other hand, Weisz et al. (2014) carried out a meta-analysis which showed that surgical ligation reduces the mortality in premature infants, but increases the incidence of central nervous, respiratory, and ophthalmic complications in the surviving infants. However, in this aforementioned study, as described by the authors, since the severity of the hsPDA before the therapeutic intervention was not reflected in the analysis, it was probably difficult to distinguish between cerebrovascular disease due to the hsPDA itself and the influence of the surgical ligation on the central nervous system.

Is it more important to clarify the best timing of surgical ligation of hsPDA than to avoid the invasiveness of the surgical ligation itself if the surgical procedure could be performed as safely as possible? It was reported that lengthy exposure to hsPDA in premature infants decreased the oxygen saturation in cerebral tissue and resulted in a volume reduction of whole brain regions at term age (Lemmers et al. 2016). In addition, the repeated administration of a COX inhibitor may inhibit intimal thickening in the ductus arteriosus and thereby delay its closure (Yokoyama et al. 2010), likely resulting in an increase in the exposure time to hsPDA (Kabra et al. 2007; Adrouche-Amrani et al. 2012; Youn et al. 2013). In this context, the incidence of clinical complications and neurodevelopmental impairments in ELBWIs might be improved with clarification of the optimal timing for surgical ligation and the consequent shortening of the exposure time to hsPDA. We attempted to determine the optimum timing for surgical ligation based on the diagnosis of refractory hsPDA to indomethacin in the current study. As a result, the average exposure time to hsPDA in the surgical ligation group (133 h) was 103 h longer than those in the COX inhibitor group (29.6 h) (Table 1). The additional 103 h exposure time to hsPDA in the surgical ligation group might be within the safe neurodevelopmental outcome limits because the DQ values at 36 months of age did not deteriorate. Further prospective clinical studies are needed to evaluate the validity and safety of this time lag.

Lastly, the results of the study might include some biases because of a retrospective analysis of all patients born at a single institution. However, no apparent difference in the ratio of the closure mode of the ductus arteriosus was detected between the current study (15.5%, 52.1%, and 32.4% of subjects in the spontaneous closure, COX inhibitor, and surgical ligation groups, respectively) and other clinical studies with ELBWIs, showing 14 to 28%, 42 to 63%, and 23 to 32%, respectively (Madan et al. 2009; Adrouche-Amrani et al. 2012; Youn et al. 2013; Ochiai et al. 2014). In addition, in the present study, the mortality of the subjects and the incidence of neurodevelopmental impairment were 9.9% (11/111 subjects) and 21.1% (15/71 subjects), respectively, both lower than those (13% and 44%, respectively) reported in a previous study (Madan et al. 2009). Therefore, it is unlikely that the analysis results in the present study were significantly influenced by any bias based on the ratio of the closure mode or the mortality of patients.

Based on the above discussion, we conclude that surgical ligation for hsPDA in ELBWIs should be immediately carried out in order to minimize their exposure time to hsPDA without fearing future neurodevelopmental deterioration if the COX inhibitor failed to close hsPDA. Multivariate analyses involving a large number of patients and multicenter prospective clinical studies need to be conducted to further examine the reduction of the time of exposure of ELBWIs to hsPDA.

Conflict of Interest

The authors declare no conflict of interest.

References

Adrouche-Amrani, L., Green, R.S., Gluck, K.M. & Lin, J. (2012) Failure of a repeat course of cyclooxygenase inhibitor to close a PDA is a risk factor for developing chronic lung disease in ELBW infants. *BMC Pediatr.*, **12**, 10.

Alpan, G., Scheerer, R., Bland, R. & Clyman, R. (1991) Patent ductus arteriosus increases lung fluid filtration in preterm lambs. *Pediatr. Res.*, **30**, 616-621.

American Academy of Pediatrics (1984) An international classification of retinopathy of prematurity. *Pediatrics*, **74**, 127-133.

Baker, L.L., Stevenson, D.K. & Enzmann, D.R. (1988) End-stage periventricular leukomalacia: MR evaluation. *Radiology*, **168**, 809-815.

Chida, S. & Fujiwara, T. (1993) Stable microbubble test for predicting the risk of respiratory distress syndrome: I. compar-

isons with other predictors of fetal lung maturity in amniotic fluid. *Eur. J. Pediatr.*, **152**, 148-151.

Chida, S., Fujiwara, T., Konishi, M., Takahashi, H. & Sasaki, M. (1993) Stable microbubble test for predicting the risk of respiratory distress syndrome: II. prospective evaluation of the test on amniotic fluid and gastric aspirate. *Eur. J. Pediatr.*, **152**, 152-156.

Clyman, R. & Noori, S. (2012) The very low birth weight neonate with hemodynamically significant ductus arteriosus during the first postnatal week. In *Hemodynamics and Cardiology*, 2nd ed., edited by Kleinman, Charles. S. & Seri, Istvan. Elsevier, Philadelphia, PA, pp. 269-291.

Clyman, R.I. (2006) Mechanisms regulating the ductus arteriosus. *Biol. Neonate*, **89**, 330-335.

Clyman, R.I., Couto, J. & Murphy, G.M. (2012) Patent ductus arteriosus: are current neonatal treatment options better or worse than no treatment at all? *Semin. Perinatol.*, **36**, 123-129.

Clyman, R.I., Mauray, F., Heymann, M.A. & Roman, C. (1987) Cardiovascular effects of patent ductus arteriosus in preterm lambs with respiratory distress. *J. Pediatr.*, **111**, 579-587.

Friedman, W.F. (1972) The intrinsic physiologic properties of the developing heart. *Prog. Cardiovasc. Dis.*, **15**, 87-111.

Irmesi, R., Marcialis, M.A., Anker, J.V. & Fanos, V. (2014) Non-steroidal anti-inflammatory drugs (NSAIDs) in the management of patent ductus arteriosus (PDA) in preterm infants and variations in attitude in clinical practice: a flight around the world. *Curr. Med. Chem.*, **21**, 3132-3152.

Janz-Robinson, E.M., Badawi, N., Walker, K., Bajuk, B. & Abdel-Latif, M.E. (2015) Neurodevelopmental outcomes of premature infants treated for patent ductus arteriosus: a population-based cohort study. *J. Pediatr.*, **167**, 1025-1032.

Kabra, N.S., Schmidt, B., Roberts, R.S., Doyle, L.W., Papile, L. & Fanaroff, A. (2007) Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants: results from the Trial of Indomethacin Prophylaxis in Preterms. *J. Pediatr.*, **150**, 229-234.e1.

Kono, Y., Yonemoto, N., Kusuda, S., Hirano, S., Iwata, O., Tanaka, K. & Nakazawa, J. (2016) Developmental assessment of VLBW infants at 18 months of age: a comparison study between KSPD and Bayley III. *Brain Dev.*, **38**, 377-385.

Koyama, T., Osada, H., Tsujii, H. & Kurita, H. (2009) Utility of the Kyoto Scale of Psychological Development in cognitive assessment of children with pervasive developmental disorders. *Psychiatry Clin. Neurosci.*, **63**, 241-243.

Lemmers, P.M., Benders, M.J., D'Ascenzo, R., Zethof, J., Alderliesten, T., Kersbergen, K.J., Isgum, I., de Vries, L.S., Groenendaal, F. & van Bel, F. (2016) Patent ductus arteriosus and brain volume. *Pediatrics*, **137**.

Maalouf, E.F., Duggan, P.J., Rutherford, M.A., Counsell, S.J., Fletcher, A.M., Battin, M., Cowan, F. & Edwards, A.D. (1999) Magnetic resonance imaging of the brain in a cohort of extremely preterm infants. *J. Pediatr.*, **135**, 351-357.

Madan, J.C., Kendrick, D., Hagadorn, J.I. & Frantz, I.D. 3rd. (2009) Patent ductus arteriosus therapy: impact on neonatal and 18-month outcome. *Pediatrics*, **123**, 674-681.

Noori, S. & Seri, I. (2015) Hemodynamic antecedents of peri/intraventricular hemorrhage in very preterm neonates. *Semin. Fetal Neonatal Med.*, **20**, 232-237.

Ochiai, M., Kinjo, T., Takahata, Y., Iwayama, M., Abe, T., Ihara, K., Ohga, S., Fukushima, K., Kato, K., Taguchi, T. & Hara, T. (2014) Survival and neurodevelopmental outcome of preterm infants born at 22-24 weeks of gestational age. *Neonatology*, **105**, 79-84.

Oncel, M.Y. & Erdeve, O. (2015) Safety of therapeutics used in management of patent ductus arteriosus in preterm infants. *Curr. Drug Saf.*, **10**, 106-112.

Papile, L.A., Burstein, J., Burstein, R. & Koffler, H. (1978) Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J. Pediatr.*, **92**, 529-534.

Reller, M.D., Rice, M.J. & McDonald, R.W. (1993) Review of studies evaluating ductal patency in the premature infant. *J. Pediatr.*, **122**, S59-62.

Rheinlaender, C., Helfenstein, D., Pees, C., Walch, E., Czernik, C., Obladen, M. & Koehne, P. (2010) Neurodevelopmental outcome after COX inhibitor treatment for patent ductus arteriosus. *Early Hum. Dev.*, **86**, 87-92.

Sahn, D.J., DeMaria, A., Kisslo, J. & Weyman, A. (1978) Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation*, **58**, 1072-1083.

Smith, G.C. (1998) The pharmacology of the ductus arteriosus. *Pharmacol. Rev.*, **50**, 35-58.

Su, B.H., Watanabe, T., Shimizu, M. & Yanagisawa, M. (1997) Echocardiographic assessment of patent ductus arteriosus shunt flow pattern in premature infants. *Arch. Dis. Child. Fetal Neonatal Ed.*, **77**, F36-40.

Surveillance of Cerebral Palsy in Europe (2000) Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE). *Dev. Med. Child Neurol.*, **42**, 816-824.

Tauzin, L., Joubert, C., Noel, A.C., Bouissou, A. & Moulies, M.E. (2012) Effect of persistent patent ductus arteriosus on mortality and morbidity in very low-birthweight infants. *Acta Paediatr.*, **101**, 419-423.

Van Overmeire, B., Allegaert, K., Casaer, A., Debauche, C., Decaluwe, W., Jespers, A., Weyler, J., Harrewijn, I. & Langhendries, J.P. (2004) Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*, **364**, 1945-1949.

Weisz, D.E., More, K., McNamara, P.J. & Shah, P.S. (2014) PDA ligation and health outcomes: a meta-analysis. *Pediatrics*, **133**, e1024-1046.

Wickremasinghe, A.C., Rogers, E.E., Piecuch, R.E., Johnson, B.C., Golden, S., Moon-Grady, A.J. & Clyman, R.I. (2012) Neurodevelopmental outcomes following two different treatment approaches (early ligation and selective ligation) for patent ductus arteriosus. *J. Pediatr.*, **161**, 1065-1072.

Yokoyama, U., Minamisawa, S. & Ishikawa, Y. (2010) Regulation of vascular tone and remodeling of the ductus arteriosus. *J. Smooth Muscle Res.*, **46**, 77-87.

Youn, Y., Lee, J.Y., Lee, J.H., Kim, S.Y., Sung, I.K. & Lee, J.Y. (2013) Impact of patient selection on outcomes of PDA in very low birth weight infants. *Early Hum. Dev.*, **89**, 175-179.