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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

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ABSTRACT

Objectives : To identify risk factors for patent ductus arteriosus (PDA) without spontaneous closure of the ductus arteriosus (DA) in very low birth weight infants (VLBWIs).

Method : All 169 VLBWIs admitted to our hospital from 2001 through 2006 were included in this study. After 11 infants were excluded, the 158 remaining subjects were divided into two groups : 54 who required treatment for closure of the DA (PDA(+) group) and 104 in whom the DA closed spontaneously (PDA(−) group). The risk factors for PDA were examined statistically.

Results : Gestational age and surfactant administration were identified with stepwise logistic analysis as risk factors for PDA. Birth weight, 1-minute Apgar score, mechanical ventilation, respiratory distress syndrome, and red blood cells were nominated as risk factors for PDA, with significant differences between the groups, but were rejected with logistic analysis adjusted by gestational age and surfactant adminstration. The prevalence of pulmonary hemorrhage and severe intraventricular hemorrhage was significantly higher in the PDA(+) group.

Conclusions : In the management of early-gestation VLBWIs who require treatment with surfactant, we must consider that the DA is not likely to close spontaneously and, therefore, will require treatment. We must also be aware that the risks of pulmonary hemorrhage and intraventricular hemorrhage increase when the DA does not close spontaneously.

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Key words : very low birth weight, patent ductus arteriosus, risk factors, gestational age, pulmonary surfactant

INTRODUCTION

Short- and long-term outcomes of very low birth weight infants (VLBWIs) (birth weight <1,500 g) are influenced by treatment received in neonatal intensive care units (NICU). The ductus arteriosus (DA) generally closes spontaneously after birth but might remain patent and produce symptoms in preterm infants. Patent DA (PDA), when hemodynamically significant, occasionally causes neonatal complications such as pulmonary hemorrhage, intraventricular hemorrhage (IVH), intestinal perforation, and chronic lung disease[1]. Therefore, it is necessary to treat PDA with intravenous administration of indomethacin.

Indomethacin causes decreased vascular flow in organs such as the brain, kidney, and intestines by

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vasoconstriction[2–4]. As a result, indomethacin can cause renal insufficiency, surgical necrotizing enterocolitis, and isolated intestinal perforation, bleeding tendency by disturbance of platelet aggregation, and hypoglycemia[5,6]. Therefore, indomethacin should be used with care. In addition, PDA can be treated surgically if it remains hemodynamically significant despite treatment with indomethacin. However, the DA closes spontaneously in some VLBWIs[7]. In such cases, there is no need for treatment with indomethacin, and tube feeding can be started. In other words, spontaneous closure of the DA is preferable in premature infants. We wondered whether there is a method for avoiding treatment with indomethacin for PDA and whether the failure of the DA to close spontaneously is problematic for VLBWIs after birth. To improve the management of this condition, in this retrospective study we attempted to identify perinatal risk factors for PDA without spontaneous closure in VLBWIs.

METHOD

Subjects

The subjects of this retrospective study were 169 VLBWIs admitted to the NICU of The Jikei University Hospital Women's and Children's Medical Center from November 2001 through March 2006. We excluded 5 infants who died in the first 24 hours after birth, 1 infant who died of congenital infection in the first week, 2 infants with complex congenital cardiac abnormalities other than atrial septal defect and ventricular septal defect, 1 infant with chromosomal abnormality, and 2 infants of uncertain gestational age born to mothers who did not undergo prenatal examinations. Therefore, a total of 158 infants were enrolled and divided into two groups for comparison : 54 who required treatment for closure of the DA (PDA(+) group) and 104 in whom the DA closed spontaneously (PDA(−) group).

Measurements and data analysis

Data were obtained retrospectively from the patients' records. We examined gender, gestational age, birth weight, 1- and 5-minute Apgar scores (Ap1 and Ap5) as variables after birth of all VLBWIs enrolled in this study ; body temperature, pH of blood gas, base excess of blood gas, ionized calcium, C-reactive protein, red blood cells (RBC), hemoglobin, initial hematocrit were measured in the NICU of The Jikei University Hospital ; and the use of mechanical ventilation, the onset of respiratory distress syndrome (RDS), and surfactant administration were recorded. Obstetrical factors examined included choice of cesarean section, maternal administration of prenatal corticosteroids, prenatal magnesium sulfate, prenatal ritodrine hydrochloride, maternal complications of premature labor, premature rupture of membranes, inflammation of the placenta, and pregnancy-induced hypertension. We also examined pulmonary hypertension, mild IVH, severe IVH, periventricular leukomalacia, chronic lung disease, intestinal perforation, retinopathy of prematurity, blindness, and mortality as short-term outcomes.

The variables were defined as continuous or as indicators. The continuous variables were gestational age, birth weight, Ap1, Ap5, body temperature, pH of blood gas, base excess of blood gas, ionized calcium, C-reactive protein, RBCs, hemoglobin, and hematocrit. The indicator variables were gender, mechanical ventilation enforcement, onset of RDS, surfactant administration, cesarean section, prenatal steroids, prenatal magnesium sulfate, prenatal ritodrine hydrochloride, premature labor, premature rupture of membrane, inflammation of placenta, pregnancy-induced hypertension, pulmonary hypertension, mild IVH, severe IVH, periventricular leukomalacia, chronic lung disease, intestinal perforation, retinopathy of prematurity, blindness, and mortality.

RDS was diagnosed on the basis of symptoms, X-ray findings, and a stable microbubble test. We used surfactant Tokyo-Akita as the surfactant. Corticosteroids were administered twice to mothers before birth by intramuscular injection (12 mg) at an interval of 24 hours. We reviewed the prenatal administration of magnesium sulfate and ritodrine hydrochloride to mothers, but did not consider the duration, quantity, or the method. The diagnosis of placental inflammation was based on the presence of inflamma-

tory cell invasion of the chorion, amnion, and umbilical cord on pathological examination. IVH was diagnosed with cranial ultrasonography. The severity of IVH was adapted from the Papile grading method[8]. Papile grades I and II were considered to be mild IVH, and grades III and IV were considered to be severe IVH. Periventricular leukomalacia was diagnosed with ultrasonography and magnetic resonance of the head, and chronic lung disease was diagnosed on the basis of respiratory disturbance that required oxygenation after 28 days of age, in addition to the presence of specific findings on X-ray films. We did not differentiate between different types of chronic lung disease. We assumed retinopathy of prematurity was present in patients who required laser treatment. Among the retinopathies of prematurity requiring laser operations, blindness was defined as the presence of a broad retina that included an exfoliated macular area and the presence of vitreous hemorrhage.

We statistically analyzed these variables by comparing the PDA(+) and PDA(−) groups and by performing multivariate analysis. Comparisons between groups for each variable were performed with Fisher's exact test, Student's t-test, and the Mann-Whitney U test, which did not show normal distribution. The analysis of short-term outcomes was performed with Fisher's exact test. We used logistic analysis and stepwise logistic analysis for multivariate analysis, assuming a significant difference with significance level of $p<0.05$. We used the Stata 8.0 software program (StataCorp LP, College Station, TX, USA) for statistical analysis.

Protocol

VLBWIs who received indomethacin at least once for PDA were placed in the PDA(+) group. On the other hand, VLBWIs in whom the DA closed spontaneously without indomethacin were placed in the PDA(−) group. Manifestations of PDA included tachycardia, cardiac murmur, bounding pulse, precordial pulsatation, oliguria, abdominal distension, tachypnea, and elevation of respirator settings[9]. X-ray films showed cardiac dilatation, vascular shadow augmentation, and development of pulmonary edema[9]. We took these findings into account, but considered the echocardiographic findings the most important for determining whether to treat PDA. Treatment for PDA was started when echocardiography showed that the diameter of the DA was greater than 1.5 mm[10], the velocity of the end-diastolic left pulmonary artery was 0.25 m/s[11], or the ratio of the diameters of the left atrium to that of the aorta was 1.4[12]. Pediatricians performed echocardiography at 12-hour intervals until the DA had completely closed. Echocardiography could also be performed at shorter intervals.

Indomethacin was administered to treat PDA. A course of treatment with indomethacin included 3 doses of 0.1 mg/kg, each administered over 1 hour, at intervals of 12 hours. Echocardiography was usually performed 12 hours after each dose to assess the patency of the DA or was performed 6 hours after the dose if the symptoms of PDA worsened. After the first dose, indomethacin could be administered in two ways. If complete closure of the DA was confirmed with echocardiography, no further doses of indomethacin were given. However, if the DA remained patent, all three doses of indomethacin were given. To minimize side effects, courses of indomethacin were administered at intervals of at least 24 hours. Considering the therapeutic effects and side effects, the dose was sometimes increased to 0.20 or 0.25 mg/kg.

Surgery to ligate the PDA was performed when left-to-right shunting through the DA increased even immediately after treatment with indomethacin or repeatedly increased after temporary decreases even after several courses of indomethacin.

Results

Of the 158 subjects, 54 (34%) were in the PDA(+) and 104 (66%) were in the PDA(−) group (Table 1). Variables nominated as risk factors for PDA ($p<0.01$) were gestational age, mechanical ventilation, RDS, and surfactant administration. Factors with a significance level of $p<0.05$ were birth weight, Ap1, and RBC count. There were no variables that showed a significant difference with regard to complications or drugs administered to mothers.

Table 1. Comparison of characteristic of the PDA(+) and PDA(−) groups

Variable	PDA(+)	PDA(−)	p
The number of VLBWIs	54	104	
Male/Female	26/28	51/53	1.000
Gestational age, weeks	28.3±2.4 (23.8–34.3)	29.8±2.7 (23.3–36.1)	0.001§
Birth weight, g	1,004±283 (397–1,457)	1,107±257 (518–1,499)	0.029*
Apgar score, 1 minute	4.8±2.4 (1–9)	5.6±2.4 (0–9)	0.040*
Apgar score, 5 minutes	7.1±1.8 (3–9)	7.6±1.6 (1–9)	0.070
Body temperature, ℃	36.9±0.8 (34.3–39.4)	36.8±0.6 (35.3–38.9)	0.856
pH of blood gas	7.38±0.09 (7.21–7.62)	7.37±0.09 (7.13–7.64)	0.213
Base excess of blood gas	−3.5±3.1 (−12.8–2.7)	−3.5±3.4 (−20.4–4.4)	0.921
Ionized calcium, mmol/l	1.21±0.09 (1.00–1.39)	1.23±0.08 (1.00–1.43)	0.338
C-reactive protein, mg/dl	0.11±0.15 (0.00–0.83)	0.19±0.51 (0.00–4.16)	0.619
RBCs, $\times 10^4/\mu$l	388.8±48.6 (269–524)	408.3±57.1 (200–571)	0.034*
Hemoglobin, g/dl	15.4±1.8 (11.0–20.0)	15.9±2.2 (8.3–21.8)	0.090
Hematocrit, %	45.3±5.0 (32.7–57.3)	46.7±5.8 (25.0–58.4)	0.081
Mechanical ventilation	53 (98%)	82 (79%)	0.001§
RDS	50 (93%)	71 (68%)	0.002§
Surfactant administration	51 (94%)	72 (69%)	0.000§
Caesarian section	51 (94%)	96 (92%)	0.750
Antenatal corticosteroids	26 (48%)	55 (53%)	0.617
Antenatal magnesium sulfate	19 (35%)	34 (33%)	0.859
Antenatal ritodrine hydrochloride	22 (41%)	45 (43%)	0.865
Premature labor	26 (48%)	50 (48%)	1.000
Premature rupture of membranes	16 (30%)	29 (28%)	0.854
Inflammation of placenta	12 (22%)	29 (28%)	0.566
Pregnancy-induced hypertension	18 (33%)	48 (46%)	0.130

Continuous variables are shown as means ± standard deviation (range).
Categorical variables are shown as number of subjects (percentage of group).
§=significant difference $p<0.01$ *=significant difference $p<0.05$

Stepwise logistic analysis identified gestational age ($p=0.034$) and surfactant administration ($p=0.017$) as risk factors for PDA.

Logistic analysis comparing the two groups nominated birth weight, Ap1, RBC count, mechanical ventilation, and RDS as risk factors for PDA at a significance level of $p<0.05$. However, when we adjusted for gestational age and surfactant administration, which stepwise logistic analysis showed to be profoundly related variables, logistic analysis rejected all variables as risk factors for PDA (Table 2).

Fisher's exact test for comparison of short-term outcomes between the two groups showed that the prevalence of pulmonary hypertension and that of severe IVH were significantly higher in the PDA(+) group ($p<0.05$, Table 3). In other words, PDA requiring treatment was a risk factor for pulmonary hypertension and severe IVH. We did not find any significant difference in the rate of mortality, mild IVH, periventricular leukomalacia, chronic lung disease, retinopathy of prematurity, or blindness. Because our series included no cases of intestinal perforation, either surgical necrotizing enterocolitis classified as Bell's stage III[13] or localized intestinal perforation distinguished pathologically from necrotizing enterocolitis, we were not able to detect a relationship between intestinal perforation and the course of DA.

In the PDA(+) group, the PDA closed after 1 dose of indomethacin in 14 patients, after 1 course of indomethacin in 28 patients, after 2 courses in 3 patients, and after 3 or more courses in 1 patient (Fig. 1). Surgery to ligate the PDA because of increased left-to-right shunting was performed in 1 patient who had received 1 course of indomethacin and in another

Table 2. Logistic analysis adjusted by gestational age and surfactant administration

Variable	PDA(+)	PDA(−)	*p*
Number of VLBWIs	54	104	
Birth weight, g	1,004±283 (397-1,457)	1,107±257 (518-1,499)	0.842
Apgar score, 1 minute	4.8±2.4 (1-9)	5.6±2.4 (0-9)	0.891
RBCs, $\times 10^4/\mu l$	388.8±48.6 (269-524)	408.3±57.1 (200-571)	0.692
Mechanical ventilation	53 (98%)	82 (79%)	0.368
RDS	50 (93%)	71 (68%)	0.188

Continuous variables are shown as means±standard deviation (range).

Table 3. Comparison of short-term outcomes of the PDA(+) and PDA(−) groups

Variable	PDA(+)	PDA(−)	*p*
Number of VLBWIs	54	104	
Death	1 (2%)	1 (1%)	1.000
Pulmonary hemorrhage	4 (7%)	0 (0%)	0.013
IVH (I-II)	3 (6%)	5 (5%)	1.000
IVH (III-IV)	6 (11%)	5 (5%)	0.047
Periventricular leukomalacia	4 (7%)	2 (2%)	0.182
Chronic lung disease	21 (39%)	32 (31%)	0.375
Intestinal perforation	0 (0%)	0 (0%)	−
Retinopathy of prematurity	15 (28%)	16 (15%)	0.090
Blindness	2 (4%)	0 (0%)	0.115

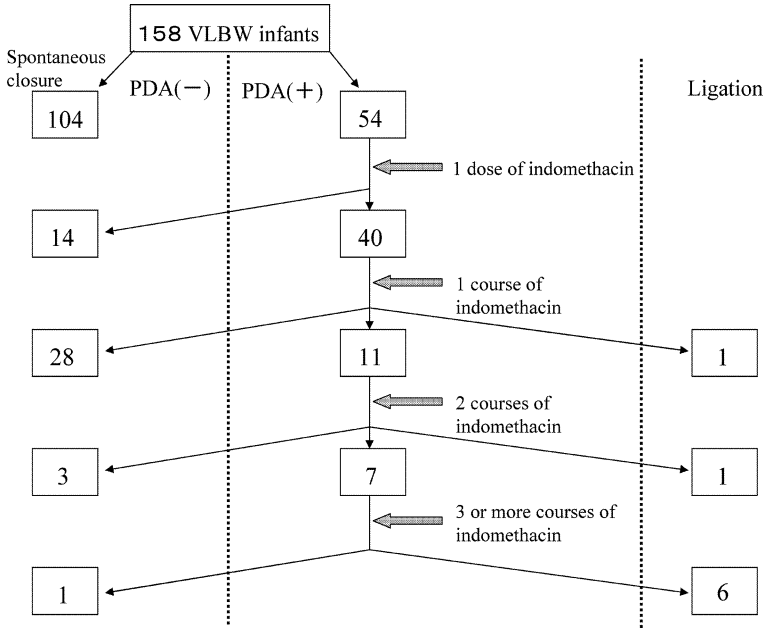

Fig. 1. Spontaneous closure occurred at a mean time of 40.8±43.5 (± SD) hours after birth (range, 12.0 to 408.0 hours). Ligation was performed a mean of 19.1±12.6 days after birth (range, 4.0 to 35.0 days)

patient who had received 2 courses. Surgery was also performed for 6 patients in whom the DA repeatedly deteriorated after temporal remission after 3 or more courses of indomethacin.

DISCUSSION

In this study, the DA closed spontaneously without treatment in 104 (66%) of 158 VLBWIs. A comparable study by Yoshimoto et al.[14] has found a higher rate of spontaneous DA closure (75%, 92 of 122 subjects), whereas Koch et al.[7] found a much lower rate (34%, 42 of 122 subjects) in a study of extremely low birth weight infants (ELBWIs, birth weight < 1,000 g). Our rate of spontaneous closure was intermediate between the rates of these previous studies. Although Yoshimoto et al. focused on less-mature ELBWIs rather than on VLBWIs, this percentage should be noted. We would like to find ways to increase the rate of spontaneous DA closure at our institution's NICU.

In this retrospective study, the variables identified with multivariate analysis as risk factors for nonclosure of the DA were gestational age[7] and surfactant administration[15]. Previous studies have also identified these variables as risk factors. If birth occurs at an early gestational age, spontaneous closure of the DA is believed to be difficult. Possible reasons are that the response of the spiral smooth muscle fibers of the DA to oxygen is poor[16] and that the blood concentration of prostaglandins is high[17,18].

Surfactant is indispensable as a treatment for RDS in VLBWIs[19]. However surfactant administration causes a sudden decrease in pulmonary vascular resistance in VLBWIs[20]. This decrease causes an increase in DA left-to-right shunting. Therefore, surfactant administration is believed to be a cause of PDA, which itself requires treatment[5,21].

In addition to gestational age and surfactant administration, variables found to differ significantly between the PDA(+) and PDA(−) groups were birth weight, Ap1, mechanical ventilation, RDS, and RBC count. However, logistic analysis adjusting for gestational age and surfactant administration, which have been accepted to have a profound relation to the course of DA, rejected these variables as risk factors for PDA at a significance level of $p<0.05$. Therefore, we do not consider the association between these variables to be statistically significant. Furthermore, when we consider each variable, Ap1 is a factor that cannot easily be improved with treatment, and birth weight, mechanical ventilation and RDS have already been reported as risk factors for PDA[7,22]. However, few reports have identified the RBC count as a risk factor for PDA[23]. In addition, the RBC count is the factor that should be paid the most attention because of the finding that the DA tends to close spontaneously if the RBC count is higher. This finding suggests late umbilical cord clamping might encourage spontaneous DA closure in premature infants.

In premature infants, the increasing total circulating RBC volume during the first day after birth has been reported to improve clinical features, such as the rate of IVH, blood pressure at 1 hour, the 5-minute Apgar score, the severity of RDS, transfusion needs, time to regain birth weight, and survival[24]. Late umbilical cord clamping at delivery raises RBC volume, hematocrit, and hemoglobin, and improves the circulation of premature infants[25]. In other words, the rate of spontaneous closure of the DA may increase with late umbilical cord clamping in VLBWIs. In addition, late umbilical cord clamping has been reported to decrease the frequency of IVH, necrotizing enterocolitis, retinopathy of prematurity, and late-onset sepsis, the severity of RDS, and the need for transfusion in preterm infants[25,26]. Our finding that RBC counts were higher in the PDA(−) group suggests that that late umbilical cord clamping should be performed to increase the RBC count at birth. Late umbilical cord clamping, i.e., after 30 to 45 seconds, provides a significant benefit without major side effects for neonates born at less than 33 weeks' gestation[25,26] However, late umbilical cord clamping for VLBWIs might delay resuscitation, which should be started as soon as possible. If the umbilical cord is clamped promptly after birth and resuscitation is started, milking of the umbilical cord is recommended[23].

Mammoto et al. have reported that the milking of the umbilical cord toward a neonate just after birth improves circulatory and respiratory conditions and reduces the incidence of IVH and of PDA[23].

The RBC transport oxygen to tissues. Increasing the RBC volume increases the oxygen transport capacity. We can consider the possibility that smooth-muscle contraction in the DA accelerates when oxygen levels increase in the blood[23]. In contrast, when the RBC volume is small, both the heart rate and cardiac output increase. This cardiac state is equivalent to that in which premature infants have received fluid administration, i.e., increased cardiac preload. The increase in fluid administration to premature infants causes an increase in the quantity of left-to-right shunting through the DA[27]. In other words, the decreased RBC volume and the increased cardiac output inhibit closure of the DA. Therefore, if the RBC volume is large, this vicious circle can be avoided. According to a recent report, the increase in erythropoietin in anemia induces the production of endogeneous nitric oxide[28]. Nitric oxide is believed to inhibit DA closure. Further studies are necessary of methods for achieving an optimal RBC volume at birth in VLBWIs.

The comparison of short-term outcomes showed higher rates of pulmonary hypertension and severe IVH in the PDA(+) group. This finding is consistent with those of previous studies in which PDA was identified as a risk factor for pulmonary hypertension and IVH[1,29]. The following are considered causes of pulmonary hemorrhage and sequential IVH.

As stated above, increased left-to-right shunting through the DA increases pulmonary blood flow[30]. The increase in pulmonary blood flow also raises the afterload of the right side of the heart. This state induces the stasis of venous return to the right atrium which finally causes IVH[29]. In addition, left-to-right shunting through the foramen ovale can further increase the already elevated pulmonary blood flow caused by an increase in left-to-right shunting through the PDA[31,32]. Therefore, we should consider left-to-right shunting through the foramen ovale in the future. Both venous congestion and fluctuating cerebral blood flow have been shown to be causes of IVH[29]. PDA also induces this fluctuation[33]. We administered indomethacin to all VLBWIs with PDA who needed treatment. Here, we must consider that indomethacin inhibits platelet aggregation[5]. Disorders of platelet aggregation are considered a possible cause of IVH[29]. Recently, indomethacin has been recommended to prevent IVH in premature infants[34]. On the other hand, considering that indomethacin can exacerbate IVH, it should be used with caution. The results of our analysis suggest that serial echocardiography should be improved to monitor PDA and to determine the optimal timing of indomethacin treatment.

A noteworthy finding of our study was that the PDA closed after a third course of indomethacin in only 1 of 7 VLBWIs (Fig. 1). In fact, indomethacin showed little ability to close the PDA after 2 courses of treatment had failed. In other words, surgical ligation should be performed if PDA remains after 2 courses of indomethacin therapy. This suggestion could be an indicator for the management of PDA in premature infants.

In this retrospective study attempting to identify risk factors for PDA in VLBWIs, the factors that were strongly associated with PDA were gestational age and surfactant administration. In other words, when caring for VLBWIs of early gestational age who require surfactant administration, we should consider that the DA will very likely not close spontaneously and will require treatment. We must also be aware that the risks of pulmonary hypertension and severe IVH increase when the DA does not close spontaneously and require treatment. Treatment aimed to induce DA closure should be started as soon as the lack of spontaneous closure has been confirmed[35]. The results of our study suggest that serial echocardiography allows PDA to be diagnosed, monitored, and appropriately treated[36]. Our findings also suggest that spontaneous, natural closure of the DA is preferable in VLBWIs. It is important that we identify risk factors for PDA so that appropriate treatment can be planned and started.

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