Natural History of Patent Ductus Arteriosus in Very Low Birth Weight Infants after Discharge

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Data on the natural history of infants discharged with patent ductus arteriosus is sparse. We report on the 36-months follow-up after hospitalization in 68 infants discharged with an open ductus arteriosus. Notwithstanding a high spontaneous closure rate, catheter intervention in 5 infants illustrates a critical need for cardiologic follow-up. (J Pediatr 2015;167:1149-51).

A patent ductus arteriosus (PDA) in very low birth weight (VLBW) infants can be associated with several complications such as left ventricular volume overload, pulmonary edema, pulmonary hypertensive vascular disease resulting in Eisenmenger syndrome, or chronic parenchymal lung disease. Available options for pharmacological treatment of a hemodynamically significant PDA (hsPDA) include indomethacin, ibuprofen, and paracetamol. In VLBW infants not responding to cyclooxygenase (COX) inhibitors, surgical closure of the PDA is often considered. There is an ongoing debate about the thresholds and strategies for PDA treatment. Adverse effects of conservative and surgical therapies must be weighed against the increased mortality rates noted in infants whose PDA failed to close in the neonatal period. Some children are, nevertheless, discharged with an open ductus arteriosus (DA). These infants usually have small to moderately sized PDAs without hemodynamic relevance.

Although a high spontaneous DA closure rate during neonatal intensive care unit (NICU) stay has frequently been reported, little is known about the natural course of persistently PDA after discharge. Moreover, data on the natural history and outcome of VLBW infants with an open DA after discharge is sparse. Herman et al reported on 21 infants who were discharged with a PDA (out of a total of 391 VLBW infants admitted in the respective study period) from a US tertiary NICU; spontaneous closure was observed in 18 infants whereas 2 infants required catheter intervention (coil occlusion). One infant had a detectable PDA at the age of 14 months.

In order to establish safe criteria for definitely closing a PDA after discharge from the NICU, further information on spontaneous PDA closure rates after discharge is desirable. We retrospectively investigated a large cohort of 68 infants with a persistently PDA detectable at the time of discharge (out of 1433 VLBW infants admitted during the study period) from a German tertiary NICU. We report on ductal closure and catheter intervention rates for a 36-months follow-up.

Methods

This retrospective cohort study was conducted in the Department of Neonatology, Campus Virchow-Klinikum (1998-2008), Charité University Medical Center, Berlin, Germany. Of 1433 admitted VLBW infants, 68 were discharged with a detectable PDA (that was considered small to moderate in size). The initial algorithms for PDA diagnosis and treatment at our center are described in detail elsewhere. In brief, on day of life 4-5 and when clinically indicated, an echocardiogram was performed. COX inhibitor treatment was initiated for all infants with an hsPDA. A PDA with left-to-right shunt was considered hemodynamically significant if: (1) a respiratory set back with a supplemental oxygen requirement >30% and/or mechanical ventilation; (2) a left atrium to aortic root ratio ≥1.4 in the echocardiogram; (3) ductal diameter ≥2.5 mm; and/or (4) a decreased end diastolic flow in the anterior cerebral artery with a resistance index ≥0.85 in the cerebral ultrasound were present (at least 2 criteria had to be met before treatment was initiated). Infants received intravenous indomethacin or ibuprofen (Pedea, Orphan Europe, Recordati Group, Milano, Italy) as previously described. Pharmacotherapy may have included several courses of nonsteroidal anti-inflammatory drugs, and some infants even...
received both drugs. Data on the cardiologic follow-up were obtained by chart review in the cardiology outpatient follow-up program at the Charité University Medical Center, Berlin, Germany. Cardiologic follow-up was a mandatory part of VLBW infant follow-up if a cardiovascular abnormality was present at discharge. This follow-up was organized by a multidisciplinary outpatient sociopediatric center that encompasses neurologic, cardiologic, pulmonary, and psychosocial services.

**Results**

Out of 1433 VLBW infants, 358 were treated with COX inhibitors for hsPDA in the respective period. Treatment success (ie, DA closure, by either medical or secondary surgical treatment) was achieved in 253 infants. One hundred twenty-seven had DA ligation, which was considered an option in ventilated infants after failed pharmaceutical treatment or in the rare situation of existing contraindications against pharmaceutical treatment (eg, severe thrombocytopenia). Sixty-eight infants were discharged with a persistently PDA. The infants who were discharged with persistently PDA had a higher gestational age (GA) and birth weight compared with those whose DA were closed in the neonatal period (mean 950 g, range 442-1390 g, vs 851 g, range 465-1490 g, and mean 27 weeks 0/7 days, range 24 weeks 0/7 days-34 weeks 5/7 days, vs mean 26 weeks 2/7 days, range 23 weeks 0/7 days-33 weeks 3/7 days, respectively; all \( P < .05 \)), but did not receive different numbers of COX inhibitor cycles (1.3 vs 1.4; not significant). Two of the 68 infants discharged with a persistently PDA were lost to follow-up and 2 died during follow-up. One infant who died at a corrected age of 2 months and 21 days (born 30 weeks 5/7 days of GA to consanguineous parents) had an unknown syndrome with normal karyotype. The other infant (born 30 weeks 0/7 days of GA) died at a corrected age of 3 months and 5 days because of severe pulmonary hypertension unresponsive to therapy. Fifty-two of the 64 infants included in the final analysis had spontaneous closure, 5 required catheter intervention, and 7 infants had a detectable PDA at the age of 36 months without any signs of hemodynamic

**Table.** Demographic characteristics of VLBW infants with catheter intervention for PDA after discharge from the NICU

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at the time of intervention (mo)</th>
<th>Sex</th>
<th>GA (wk, d)</th>
<th>BW (g)</th>
<th>Type of intervention (coil/ADO)</th>
<th>Reason for intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.2</td>
<td>M</td>
<td>26 3/7</td>
<td>915</td>
<td>ADO</td>
<td>Large PDA (3.5 mm) with L/R-shunt (LA/Ao 1.47), MI I-II</td>
</tr>
<tr>
<td>2</td>
<td>10.1</td>
<td>F</td>
<td>25 2/7</td>
<td>885</td>
<td>ADO</td>
<td>Large PDA (4.5 mm) with DA infundibulum and enlarged LV and LA (LA/Ao 1.37)</td>
</tr>
<tr>
<td>3</td>
<td>24.0</td>
<td>F</td>
<td>27 1/7</td>
<td>826</td>
<td>Coil</td>
<td>Short PDA (2-3 mm), enlarged trunk of pulmonary arteries, reduction of endocarditis risk</td>
</tr>
<tr>
<td>4</td>
<td>26.7</td>
<td>M</td>
<td>26 2/7</td>
<td>1080</td>
<td>Coil</td>
<td>PDA 2 mm, L/R-shunt (LA/Ao 1.37), reduction of endocarditis risk</td>
</tr>
<tr>
<td>5</td>
<td>36.7</td>
<td>F</td>
<td>31 1/7</td>
<td>1020</td>
<td>Coil</td>
<td>Opitz trigonocephaly syndrome, small PDA, closure together with 2 MAPCAs in 1 session, reduction of endocarditis risk</td>
</tr>
</tbody>
</table>

ADO, Amplatzer duct occluder; Ao, aorta; BW, birth weight; F, female; L/R, left to right; LA, left atrium; LV, left ventricle; M, male; MAPCA, major aortopulmonary collateral artery; MI, mitral insufficiency.

Figure. **A,** Flow chart: Follow-up of 68 VLBW infants discharged with a persistently PDA out of 1433 initially admitted VLBW infants. **B,** Kaplan-Meier curve: Time of closure of the DA. Time is given in months after birth. Included are all children with spontaneous DA closure (n = 52) and with persistent DA (n = 7). ADO, Amplatzer duct occluder.
significance (Figure, A). The majority of the PDAs closed within the first 24 months during the follow-up period (Figure, B). Detailed characteristics of the 5 infants who required catheter intervention are given in the Table. Of note, the 7 infants whose DAs failed to close had a trend toward a higher GA and birth weight.

Discussion

The indications for PDA therapy are currently controversial,1,3-5 and 3 main factors have led to higher treatment thresholds and less aggressive approaches: (1) A high spontaneous DA closure rate during the neonatal period; (2) low reported comorbidities in patients with only small ductal shunt or mild symptoms; and (3) adverse effects of medical and surgical therapies.1,12 Therefore, it can be expected that a growing number of infants will be discharged with a detectable PDA. However, data on the natural course of PDAs in VLBW infants after discharge is sparse. Herrman et al9 reported the course of 21 infants discharged from the NICU with an open DA. There was a high spontaneous closure rate (18/21), a finding that is confirmed by our results in a different clinical setting. Herrman et al9 observed the median post-menstrual age of 48 weeks at which closure appeared. In line with this observation, we found a mean closure date of 9 months after birth (approximately 49 weeks postmenstrual age).

A close cardiologic follow-up is mandatory, as illustrated by the 5 infants that had catheter interventions for hsPDA. None of the infants discharged home with an open PDA received diuretics at discharge. Furthermore, these infants did not have an increased need for oxygen supplementation after discharge. Among the infants discharged with an open DA, there were no echocardiographic or clinical criteria that could be used to predict who needed later catheter-based closure. This limitation may, at least partly, be due to the fact that indications for intervention were based on individual assessment and not on strict standardized criteria. Furthermore, with improvement of closure techniques and more experience with device closure, indications changed during the study period (eg, today, device closure is considered a safe treatment option even in infants below <2000 g).

Besides cardiologic information, data on the general and neurologic follow-up of infants discharged with a persistently PDA is needed as well as prospective studies on criteria that define which DAs require aggressive treatment and which can safely be handled expectantly.

References