Management of Patent Ductus Arteriosus: Are We Looking at the Right Outcomes?

The management of the patent ductus arteriosus (PDA) and its impact on neonatal outcomes continues to be one of the most controversial topics in neonatal medicine. Despite the possible association between lung damage and a PDA documented in animal models and in retrospective clinical studies, multiple trials evaluating different management strategies to close the PDA have failed to show clear long-term benefits from early PDA closure in infants born preterm.[1] Prophylactic indomethacin therapy is one of the strategies that has been shown to be effective in closing the PDA with some short-term advantages, including less need for PDA ligation and decreased incidence of severe intraventricular hemorrhage (IVH). No significant effects on long-term respiratory or neurologic outcomes, however, have been demonstrated.[2]

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A possible negative consequence of a large PDA is arterial hypotension due to the steal of systemic blood flow into the pulmonary circulation. Because of this, closure of the PDA may improve systemic blood flow and arterial blood pressure.[3,4] In this volume of *The Journal*, Liebowitz et al[5] report the effect of 2 different PDA management strategies on the incidence of vasopressor-dependent hypotension. During the first epoch, all infants born extremely preterm received prophylactic indomethacin to close their PDA, whereas in the second period, PDA treatment was withheld during the first week after birth. The prophylactic indomethacin epoch was associated with a significantly lower incidence of moderate-to-large PDA at 1 week of age, less vasopressor-dependent hypotension (need for vasopressors for at least 24 hours during postnatal days 4-7), and less need for respiratory support compared with the conservative treatment epoch.

When compared with previous trials of prophylactic indomethacin, this study achieved a greater rate of PDA closure during the prophylactic epoch. This result was due most likely to the close monitoring and use of up to 6 doses of the drug compared with 3 doses in most of the previous trials.[1] During the conservative management epoch, no infant received treatment for the PDA during the first week after birth. This resulted in 2 distinct epochs with no other confounding factors related to PDA management.

The investigators compared the need for vasopressors, used as a surrogate of hypotension, during the 2 different treatment periods. Although it is a fact that prophylaxis with indomethacin results in a greater ductal closure than in nontreated infants, there are many infants born premature who do not experience closure of their ductus after treatment with indomethacin whereas others who are not treated experience closure of their ductus spontaneously. At the end, what should drive the hemodynamic consequences is not whether or not the infants are treated with indomethacin but whether the ductus constricts or remains wide open. This was confirmed in this study with the multivariate model, which showed that the presence of a moderate-to-large ductus had the strongest association with the use of vasopressors for low arterial blood pressure.

The significance of vasopressor-dependent hypotension as an outcome measure is open to debate. Although there is some evidence of an association between arterial hypotension and poor neurologic outcome, the cause-and-effect relationship between the two has not been established clearly. Interestingly, in the current study the prophylactic indomethacin epoch was associated with significantly less incidence of hypotension, but the rate of severe IVH did not differ between the 2 epochs. This finding is in contrast to previous trials, which consistently have shown a reduction in severe IVH with the use of prophylactic indomethacin.[6] This absence of protective effect in the present study could be due to the relatively low baseline incidence of severe IVH in both epochs.

An interesting result of this study was the need for lower mean airway pressure and lower respiratory severity score during the prophylactic indomethacin epoch. This finding is in contrast to most previous studies that have not shown a clear effect of different PDA management strategies on respiratory outcomes. It would be important to learn more details about the respiratory outcomes, including bronchopulmonary dysplasia, during the 2 epochs of the present study.

Because of the lack of conclusive evidence that early PDA closure improves short- or long-term outcomes, there has been a shift in recent years from an aggressive PDA closure approach to a more expectant attitude, allowing for spontaneous closure in many infants, thus avoiding the need for therapeutic interventions.[7] Whether the data presented by Liebowitz et al are sufficient evidence to change this approach and go back to a more proactive closure of the PDA to prevent arterial hypotension is doubtful. Although prophylactic indomethacin is an effective strategy to close the PDA and reduce the incidence of vasopressor-dependent hypotension, the uncertain long-term consequences of transient hypotension in infants born premature limits the clinical implications of these results. The possible effects of prophylactic or early indomethacin for PDA closure on respiratory or neurologic outcomes still awaits to be established definitely in large, well-designed prospective randomized trials. ■

IVH	Intraventricular hemorrhage
PDA	Patent ductus arteriosus

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Eduardo Bancalari, MD
Deepak Jain, MD
Department of Pediatrics
Division of Neonatology
University of Miami Miller School of Medicine
Miami, Florida

Reprint requests: Eduardo Bancalari, MD, Department of Pediatrics, Division of Neonatology, University of Miami Miller School of Medicine, P.O. Box 016960 (R-131), Miami, FL 33101. E-mail: Ebancalari@med.miami.edu

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Altered Cerebellar Development in Preterm Newborns: Chicken or Egg?

Of all the structures in the brain, the cerebellum undergoes the greatest proportional degree of growth and development during the third trimester.[1] A recent increased research focus on the cerebellum in premature newborns has demonstrated that this structure is especially vulnerable to injury and impaired growth,[2-7] and that these abnormalities are associated with adverse motor and cognitive outcomes.[7-10] The impact of prematurity on microstructural cerebellar development has remained largely unexplored to date. In this volume of *The Journal*, Brossard-Racine et al[11] make the important observation that microstructural organization of the cerebellum is altered in preterm newborns compared with healthy term newborns.

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The authors performed a case-control study of regional cerebellar microstructure measured by diffusion tensor imaging (DTI) in 73 preterm newborns (≤32 weeks gestation and ≤1500 g at birth) imaged at term-equivalent age, along with 73 healthy term-born controls. Infants with a congenital malformation or dysmorphic features, chromosomal abnormality, confirmed metabolic disorder, or central nervous system infection were excluded. Also excluded were infants with evidence of cerebellar parenchymal injury, to mitigate the confounding effects of this common form of brain injury in premature infants.[3,4] Cases and controls were scanned with high-resolution advanced magnetic resonance imaging (MRI), and metrics of microstructural organization, including fractional anisotropy (FA) and mean diffusivity, were obtained in 7 predefined regions of interest in the cerebellum by the manual placement of voxels. To enhance the validity of their findings, the authors showed excellent intrarater and interrater reliability, and placed additional regions of interest in well-characterized supratentorial regions in the genu and splenium of the corpus callosum. Compared with the healthy term controls, the preterm infants had higher FA in the dentate nucleus and middle cerebellar peduncle and lower mean diffusivity in the vermis at term-equivalent age. Using an exploratory analytic approach, the authors identified clinical risk factors that were independently associated with altered DTI scalars, such as low 5-minute Apgar score, supratentorial brain injury, and markers of greater illness severity (ie, cardiorespiratory compromise and surgery for necrotizing enterocolitis or patent ductus arteriosus). Taken together, these data suggest that complications of preterm birth are associated with altered cerebellar microstructure compared with that of healthy term infants.

DTI has the powerful potential to delineate brain microstructure in vivo, using the properties of water molecules as a window into regional axonal density and white matter integrity. Although DTI has been used in a number of studies to evaluate supratentorial white matter microstructure in premature newborns, published data on cerebellar microstructure in premature infants are limited. One study found no differences in the diffusion characteristics of the middle cerebellar peduncles between 75 preterm infants at term age and 15 term infants[12]; however, the small number of controls may have resulted in limited power. Other studies have shown that diffuse white matter injury[13] and severe intraventricular hemorrhage[14] are associated with altered connectivity of the superior and middle cerebellar peduncles. Although this finding

DTI	Diffusion tensor imaging
FA	Fractional anisotropy
MRI	Magnetic resonance imaging

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