Recent Advances in the Treatment of Preterm Newborn Infants with Patent Ductus Arteriosus

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KEYWORDS

• Patent ductus arteriosus • Preterm infant • Very low birth weight • Ibuprofen • Indomethacin • Paracetamol

KEY POINTS

- One third of all very low birth weight infants are diagnosed with a patent ductus arteriosus (PDA) during their neonatal intensive care unit stay.
- A PDA has been associated with several adverse clinical conditions; however, data on the potential benefits of PDA treatment on short-term neonatal and long-term neurodevelopmental outcomes are sparse.
- Several established treatment strategies, including medical treatment with indomethacin and ibuprofen, and surgical/interventional options are available.
- Recent approaches, such as oral ibuprofen, high-dose regimens, and the use of oral and intravenous paracetamol, provide new alternatives to established strategies.
- Further research is warranted in order to determine which patients require treatment and how treatment protocols should be designed and adapted to allow optimal, individualized (tailored) therapy.

INTRODUCTION

The ductus arteriosus (DA) is a fetal shunt vessel that, during prenatal life, diverts blood away from the pulmonary circulation into the systemic circulation toward the placenta. During normal postnatal adaptation, because of decreasing pulmonary

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vascular resistance and pulmonary artery (PA) pressure, and increasing systemic vascular resistance, the main ductal shunt direction changes to left to right (aorta to PA).[1] In healthy term and preterm newborn infants, the DA constricts within the first postnatal days, which is triggered by several mechanisms such as hypoxia and decreasing prostaglandin levels. The initial constriction is followed by definitive DA closure leading to vascular remodeling of the DA (discussed in detail elsewhere[2,3]). Inducible growth factors such as vascular endothelial growth factor and transforming growth factor beta, but also cellular mediators such as platelets and their paracrine effects, are most likely involved in definitive DA closure.[4–6]

When the DA fails to close within approximately the first 3 days of postnatal life it usually facilitates a left-to-right shunt that can cause pulmonary vascular and left ventricular volume overload (ie, persistently patent DA [PDA]). A large ductal left-to-right shunt (Qp/Qs >>1.5) has been associated with several adverse clinical conditions, such as pulmonary edema, decreased lung compliance, pulmonary hemorrhage, and ultimately prolonged ventilator dependence and chronic lung disease (CLD) in severe cases.[7–9] Moreover, other nonpulmonary conditions, including necrotizing enterocolitis (NEC), myocardial dysfunction, and systemic hypotension, as well as altered intracerebral blood flow (ductal steal) and hemorrhage (intracerebral hemorrhage [ICH]/intraventricular hemorrhage [IVH]), have also been associated with failed ductal constriction.[2,8,9] These observations provide the rationale for treating PDA in preterm newborn infants. However, to date, validated data regarding the benefit of PDA treatment on short-term and on long-term neurodevelopmental outcomes are sparse, and the optimal treatment strategies for neonates with PDA remain subject to several ongoing debates.[10] This article reviews current strategies for PDA treatment in neonates with a special focus on recent developments such as oral ibuprofen, high-dose regimens, and the use of oral or intravenous paracetamol.

SYMPTOMS AND HEMODYNAMIC SIGNIFICANCE OF PATENT DUCTUS ARTERIOSUS

Clinical symptoms of a hemodynamically significant PDA (hsPDA) such as a murmur, active precordium, pulsus celer et altus, poor growth, and increased work of breathing are nonspecific and might develop late in the clinical course.[11,12] The gold standard for diagnosing a PDA is transthoracic echocardiography. It allows direct visualization of the ductus, determination of its size at the pulmonary and aortic end, shunt direction and velocity, and a concomitant evaluation of ventricular volumes, mass, and function (**Fig. 1**). Several markers of hemodynamic significance have been used in order to assess a PDA. A left atrium to aortic root ratio greater than or equal to 1.4, left ventricular enlargement, increased mean and diastolic PA flow values, and reversed mitral E/A ratio are established indicators for pulmonary overcirculation (high Qp/Qs). Moreover, retrograde diastolic flow in the descending aorta and low-antegrade or retrograde diastolic flow in systemic arteries (eg, anterior cerebral artery, celiac artery, superior mesenteric artery) by pulsed wave Doppler indicate systemic hypoperfusion and ductal steal. A ductal diameter greater than or equal to 1.5 mm during the first 7 to 31 hours of life can be used to predict the development of a symptomatic DA in infants less than 29 weeks' gestational age (GA)[13,14] and is weakly associated with later PDA ligation and/or death.[15,16] However, diagnosis of hsPDA should be based on a combination of these variables. To date, there are no standardized protocols based on large trials that rigorously define echocardiographic criteria for hsPDA. Measurements of cerebral saturation by near-infrared spectroscopy and the use of urine and plasma biomarkers (eg, natriuretic peptides) might help identify patients with compromised hemodynamic status, but are beyond the scope of this article.[2,17,18]