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Nutrition with a patent ductus arteriosus: feast, feed, or famine?

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The incidence of patent ductus arteriosus (PDA) is more than 50% in preterm infants ≤28 weeks gestation and is inversely related to gestational age. Several morbidities are associated with PDA and include intraventricular hemorrhage (IVH), pulmonary hemorrhage, necrotizing enterocolitis (NEC), spontaneous intestinal perforation (SIP), prolonged ventilation, bronchopulmonary dysplasia (BPD), and death. Despite being a common morbidity in extremely preterm infants and associated with adverse outcomes, which may have life-long implications, basic questions about the diagnosis and management of PDA remain unanswered.[1] What is a hemodynamically significant (hs) PDA? What echocardiographic and clinical criteria are most predictive of a hsPDA? Should a hsPDA be treated? If so, when and with which drug? Another important question that neonatologists face frequently in the neonatal intensive care unit (NICU) is should an infant on treatment for hsPDA with non-steroidal anti-inflammatory drugs be enterally fed. In this issue of Pediatric Research, the Section on Nutrition, Gastroenterology and Metabolism and the Circulation Section of the European Society for Pediatric Research have summarized the evidence in a narrative review to answer this question.[2] This is a welcome and timely addition to the literature on the subject.

This is not a trivial question. With-holding feeds or continuing feeds during treatment of hsPDA can both potentially lead to adverse outcomes. Stopping feeds for as little as 72 h in an extremely preterm infant can result in negative gastrointestinal outcomes such as villous atrophy, abnormal intestinal permeability, alterations of the microbiome, delayed intestinal maturation and function and feeding intolerance when feeds are started.[3] Longer time to full enteral feeds leads to longer duration of parenteral nutrition and central lines, risk factors for cholestasis and sepsis. Feeding preterm infants with a hsPDA also poses risks. A hsPDA with a significant left to right shunt is associated with the "steal phenomenon" where there is decreased blood flow to body organs including the intestines. Furthermore, drugs used to treat hsPDA have vasoconstrictor properties with indomethacin having the maximum effect. These two factors may blunt the normal and physiological post prandial increase in blood flow in the superior mesenteric artery leading to gut ischemia, a risk factor for feeding intolerance, NEC, and SIP. These concerns have led to a wide variation in practice about enteral feeding with a hsPDA among neonatologists in Europe and North America and the issue has gained more importance as the trend now is to treat PDAs later at which time infants may be on relatively larger volume of feeds.[4] Although data is limited, studies on enteral feeding during treatment of hsPDA do not support these fears of NEC or SIP. The two randomized controlled trials (RCTs) on treatment for hsPDA do not show any difference in outcomes of NEC, SIP and feeding intolerance between the fed and fasting groups. Both trials enrolled infants ≤30 weeks gestation with a combined study population of 303 infants. In one trial both indomethacin and ibuprofen were used and in the other only ibuprofen. Of note, the volume of feeds during treatment in the fed group was 15–20 mls/kg (trophic feeds) and majority of infants were on breast milk.[5,6] Observational studies also do not demonstrate any increased risk of gastrointestinal complications related to enteral feeding during treatment for hsPDA. A large retrospective cohort study from Canada found no association of feed volumes up to 162 mls/kg/day with adverse gastrointestinal outcomes in preterm infants being treated with indomethacin for hsPDA.[7] Doppler ultrasound studies on mesenteric blood flow also suggest that treatment with indomethacin does not significantly affect post prandial mesenteric blood flow in preterm infants on trophic feeds. In one of the studies, the post prandial increase in mesenteric flow after completion of treatment with indomethacin was earlier in infants who were enterally fed during treatment.[8,9] Although a recent study demonstrated no change in post prandial splanchnic oxygenation with enteral feeds in presence or absence of a hsPDA, data from near-infrared spectroscopy studies is limited to make any meaningful inferences. Two reviews have commented on enteral feeding during pharmacological treatment of a hsPDA. The authors of one, which specifically focused on the subject, state that there is not enough evidence to suggest either feeding or withholding feeds during pharmacological treatment of a hsPDA.[10] The other review states that early feeding with indomethacin treatment may help in reaching full feeds earlier, may not affect the post prandial increase in intestinal blood flow and is not associated with NEC or SIP.[1] Importantly, although a hsPDA is associated with NEC, studies on pharmacological treatment of hsPDA, whether prophylactic or therapeutic, have not demonstrated an increased rate of NEC.[1] Similarly, trials comparing expectant, conservative non-pharmacological management with ibuprofen or acetaminophen have not demonstrated any significant differences in clinical outcomes.[1,11] Although what constitutes conservative management of a hsPDA is ill-defined, it may include fluid restriction and diuretics, the former thought to reduce left to right shunt and the latter improving pulmonary edema. Both are controversial and may in fact be harmful, further reducing regional blood flow and reducing caloric intake leading to sub-optimal growth.[1,12] In the last few years, transcatheter device closure (TCC) of hsPDA has shown promise with less complications as compared to surgical ligation with the potential to starting feeds earlier after the procedure. However, several

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questions remain unanswered about the use of transcatheter devices and at present no definite recommendations can be made.[1,12]

Lembo and colleagues have addressed a significant and practical clinical question that healthcare workers face every day in the NICU.[2] Based on the available evidence, summarized in the review, they recommend initiation or maintenance of enteral feeds during treatment of hsPDA. In their conclusion, they also highlight the importance of nutrition as withholding feeds for even a short period can adversely affect neonatal outcomes.

This review will help in mitigating the fears and concerns that healthcare workers working in NICUs may have around feeding preterm infants with a hsPDA. The authors also recommend that, based on the rates of their morbidities such as NEC and SIP, NICUs develop clear protocols and guidelines for feeding of infants with a PDA. Such standardized protocols with volume and type of feeds may further help in alleviating apprehensions around enteral feedings. The importance of regular nutritional and growth assessment in these infants, before and after treatment of PDAs cannot be over emphasized.

What next? Several questions about enterally feeding neonates with a PDA remain unanswered. Outcomes with different types of feeding, breast milk or formula, human milk fortifiers, rate of increase of feeds, relationship with the different types of treatment including surgical and different drugs to treat PDAs are currently unknown. In addition, the population is heterogeneous and the role of clinical factors such as gestation, sex, growth restriction, hemodynamic instability, anemia, and antenatal factors like preeclampsia are also currently unknown. To answer these questions well-designed appropriately powered RCTs are urgently needed. However, RCTs on any aspect of PDA have been challenging. To date, several thousand infants have been enrolled in different trials related to PDAs and still the optimum management and diagnosis of hsPDA remains controversial.[13] This has resulted in infants whose PDA would have closed spontaneously being enrolled to the intervention arm and vice versa, and open label treatment of infants. RCTs on PDA treatment and diagnosis have heterogenous designs and endpoints, some long term like neurodevelopmental outcomes and some short term like IVH and NEC. Study populations are also heterogeneous with gestational ages ranging from 23 weeks to more than 30 weeks. Heterogeneity in RCTs could be lessened by the use of newer methodological and analytical approaches derived from machine learning models.[14] However, we believe the major factor contributing to the inconclusive data on PDA management and treatment, is lack of a definition of a hsPDA, with most studies using a ductal diameter cut-off to designate a hsPDA.[13] Establishing what constitutes a hsPDA is the need of the hour.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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