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Catheter-Based Closure of the Patent Ductus Arteriosus in Preterm Infants: Considerations in the Design of a Randomized Trial

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Patent ductus arteriosus (PDA) is the most common cardiovascular abnormality during infancy, increases mortality risk 8-fold, and is linked to chronic lung disease, pulmonary hypertension, and congestive heart failure.[1] Early pharmacological treatment is a commonly employed to close PDA in the first weeks of life, but 35-50% infants fail or have contraindications to drug therapy (failed early treatment). Considerable uncertainty exists regarding best treatment for the cohort of infants following failed early treatment who continue to have clinical and hemodynamic perturbations potentially attributable to the ductus.[2] Traditionally, surgery was used following failed early treatment, with some evidence, albeit limited, suggestive of lower mortality and improved outcomes following surgical closure.[3] Over the past decade, associations between surgical PDA ligation and adverse outcomes within large cohort studies led to a secular trend away from definitive ductal closure.[4]

Currently, most health care providers have adopted an observational (non-intervention) approach to the PDA following failed early treatment. This approach avoids (or at least delays) procedure-related complications, but prolongs the duration of PDA exposure while the clinician watchfully waits for a spontaneous ductal closure. However, consensus on how long observation can be tried is lacking, with some evidence of greater risks following prolonged exposure.[5] The American Academy of Pediatrics notes the urgent need for clinical trials to identify the optimal treatment strategy for this subgroup of infants, but lack of equipoise between the surgical and watchful waiting approaches' precluded the conduct of such trials.[2] In the absence of clear evidence, the fundamental question of whether closure versus non-closure of the ductus following failed early treatment improves important longer-term patient outcomes

remains unanswered. But what if there were an alternative, minimally-invasive approach to achieve definitive ductal closure? Might it lead to improved outcomes in infants deemed to be at high-risk for PDA-attributable complications?

On January, 11th, 2019, the US Food and Drug Administration approved the Amplatzer Piccolo™ Occluder (or Amplatzer duct occlude II additional sizes, or ADO-II AS).[6] The device is designed for ductal closure among infants weighing >700 grams with a postnatal age ≥3 days. While the device has been available in Europe for over 5 years, U.S. health care providers now have this non-surgical alternative to achieve definitive PDA closure. Design and technique modifications are attractive, including less bulky retention disks, low profile delivery system via 4 French catheters, and device delivery by venous-only cannulation. Promising data on technical feasibility, short-term safety, and of potential short and longer-term improvements in respiratory status (days on mechanical ventilation, need for diuretic therapy) from single-center, observational studies, has led to growing interest in percutaneous closure among lower weight infants. In fact, catheter-based closure has surgery as the primary technique for definitive PDA closure among preterm infants at some U.S centers.[7]

While catheter-based PDA closure provides the neonatal community with an opportunity to advance our understanding of optimal treatment practices, lack of comparisons with alternative treatments (e.g. conservative therapy) obscures risk/benefit profiles, reinforcing the need for well-designed, multicenter, randomized controlled trials (RCTs). Prior to the design and execution of such trials, a number of barriers to study conduct and execution must be overcome. At present, deeply entrenched beliefs and biases regarding optimal PDA care exist. Many health care

providers lack sufficient equipoise to support the conduct of robust, clinical trials. Liebowitz *et. al.* described that, in the PDA TOLERATE Trial, 152 potentially eligible infants were not recruited and received treatment of their PDA outside the trial due to lack of physician equipoise.[8] In the absence of consensus on optimal treatment practices, health care providers are encouraged to support patient enrollment into clinical studies.[2] Even if health care providers are willing to participate, parents/caregivers may be reluctant to provide consent. Differences between enrolled versus eligible but not enrolled infants, limit the external validity of study findings. Innovative qualitative research from adult studies has shown that clear and transparent discussions of the risks and benefits of treatment options, appropriately oriented to participants, can markedly increase consent rates in RCTs comparing intervention versus non-intervention arms.[9] Lack of formal training in the processes necessary to obtain parental consent, particularly for studies involving complex interventions among high-risk patient populations, also contribute to low rates of study consent. Strategies to support health care providers to effectively present high quality information and communicate successfully with adult patients have been developed,[10] but would need adapting for pediatric trials. Novel trial designs, such as comprehensive-cohorts, that incorporate parallel follow-up for caregivers who refuse randomization, can provide valuable observational data on outcomes to increase generalizability. Finally, evidence is growing on the importance of incorporating family-centered outcomes into proposed trials, with the goal of better understanding the impact these interventions have on caregivers.

A number of considerations in the design of contemporary, pragmatic trials on PDA management are warranted. Infants who fail early treatment and continue to have clinical and hemodynamic sequelae potentially attributable to the ductus are at the crux of the medical debate. These infants, beyond the window when drug therapy is typically used and spontaneous closure has yet to occur, represent an ongoing therapeutic dilemma for health care providers. In trials incorporating catheter-based closure, prioritization of this high-risk subgroup is paramount. Second, previous PDA trials are limited because of high rates of open label treatments in control (non-intervention) groups. To adequately explore if differences in the duration of PDA exposure contribute to adverse outcomes, rescue criteria in the control arm of RCTs should be carefully designed so they are infrequently used and consistently applied.

The practice of catheter-based PDA closure among premature infants has not been adequately compared to alternative treatment strategies, leaving health care providers without evidence-based data to guide clinical decision making. This reinforces the need for a well-designed, RCT. New strategies to increase the quality and efficiency of clinical studies on PDA management must be considered. Without high-quality randomized studies, the debate of how best to care for infants following failed early treatment will continue and prevent progress in the field.

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