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Percutaneous closure of the patent ductus arteriosus: Opportunities moving forward

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Abstract

The optimal treatment method for infants with a patent ductus arteriosus (PDA) necessitating closure remains a subject of controversy and debate. While the risks associated with surgical PDA ligation are well described, the available evidence base for alternative management strategies during infancy, including percutaneous closure or conservative (nonintervention) management, are not well explored. Among infants, the goals of this review are to: (a) use rigorous systematic review methodology to assess the quality and quantity of published reports on percutaneous closure vs surgical ligation; (b) compare outcomes of percutaneous closure vs conservative management; and (c) based on recommendations from the International PDA symposium, to elucidate needs and opportunities for future research and interdisciplinary collaboration. The available evidence base, as well as on broad consensus reached at the International PDA Symposium, suggests that a contemporary, pragmatic clinical trial comparing PDA treatment strategies is warranted. Additionally, quality assurance safeguards are necessary in the implementation of newer PDA closure devices. Finally, to determine best approaches to treatment for infants with PDA, tools for consistent data collection and reporting across centers and disciplines are needed to minimize heterogeneity and permit pooled analysis.

KEYWORDS

catheter-based PDA closure, patent ductus arteriosus (PDA), percutaneous ductal closure

1 | INTRODUCTION

The optimal treatment method for infants with a patent ductus arteriosus (PDA) necessitating definitive closure remains a subject of tremendous controversy and debate.[1-4] Surgical ligation has traditionally been used to provide definitive ductal closure, and while ligation for PDA closure has demonstrated decreased mortality, it has carried a risk of vocal cord paralysis, postoperative cardiovascular dysfunction,[5-7] and neurodevelopmental impairment.[8] In fact, recent data suggest that surgical ligation of the PDA may be an independent risk factor for moderate-to-severe functional disability, developmental delay, and motor impairment.[9] These observations have led health care providers to increased consideration of nonsurgical alternatives to close the PDA, including percutaneous (or catheter-based) techniques.[10]

Percutaneous closure of the PDA is among the safest of interventional cardiac procedures and is considered to be the procedure of choice for PDA closure beyond infancy (≥5 kg).[11] Robust evidence among older and more mature patients has led investigators to study the feasibility and safety profile of catheter-based interventions to close the PDA during infancy.[12] Over the past decade, our institution (Nationwide Children's Hospital, NCH) has undergone a marked shift

away from surgical PDA ligation, and currently emphasizes conservative management (described below) followed by percutaneous closure for infants needing definitive ductal closure (Figure 1).[13] Changes in the management of PDA closure away from surgical ligation are well described in the literature,[14] however the evidence driving those marked changes is limited. Thus, the primary objectives of this article are to: (a) use rigorous systematic review methodology to assess the quality and quantity of published reports on percutaneous closure vs surgical ligation during infancy; (b) compare outcomes of percutaneous closure vs conservative management; and (c) based on recommendations from the International PDA symposium, to elucidate needs and opportunities for future research and interdisciplinary collaboration.

2 | PERCUTANEOUS CLOSURE VS SURGICAL PDA LIGATION

Among older, more mature patients, percutaneous closure offers several potential benefits over surgical PDA ligation, including fewer complications, shorter recovery times, and lower health care expenditures.[15] However, procedures performed during infancy are more complex than are those performed during childhood or adulthood; thus, separate considerations of the potential risks and benefits in this at-risk subgroup are needed.[16]

To examine the available evidence base comparing percutaneous closure vs surgical ligation during infancy, we conducted a literature search using PubMed/Medline database. Combinations of the relevant medical subject heading terms, key words, and word variants are shown in Table 1. PubMed/Medline was searched electronically on February 15, 2018, and then updated on July 5, 2018; the search was limited to reports published prior to June 1, 2018. The reference lists of relevant articles and reviews were searched by hand for additional reports. Studies were included if they compared outcomes of percutaneous closure and surgical ligation for PDA in an infant population (mean or median age at time of closure <12 months). Two reviewers (C.M., C.B.) independently assessed the methodological quality of included studies. The three studies[17-19] that were identified were evaluated using the Newcastle-Ottawa Scale, which uses a star system to assess studies on the basis of: (a) selection of study groups; (b) comparability of groups; and (c) ascertainment of exposure/outcome.[20] No studies were excluded on the basis of quality.

Study characteristics among identified studies are summarized in Table 2. Our review of the available evidence suggests that the quantity of data addressing the superiority of percutaneous PDA closure over surgical ligation during infancy is insufficient. This is unfortunate, in view of the increasing numbers of percutaneous closures being performed during infancy.[13,15-18] Based on the paucity of available data, health care providers must be careful not to trade the known risks of surgical PDA ligation for the lesser known risks of percutaneous PDA closure without obtaining and examining the necessary evidence base.

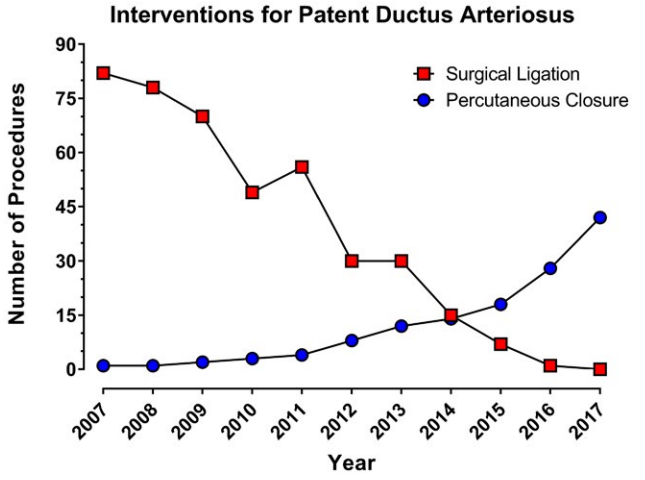

FIGURE 1 Plot showing the number of surgical PDA ligations compared to catheter-based PDA ligations among infants at Nationwide Children's Hospital from January 2007 to January 2017

3 | PERCUTANEOUS CLOSURE VS CONSERVATIVE MANAGEMENT

Since all forms of PDA closure are associated with adverse effects, health care providers are increasingly using conservative management.[14] Conservative treatment typically includes fluid restriction, diuretic therapy, and positive pressure ventilation to reduce symptoms from the PDA, thereby providing time for the ductus to close spontaneously and *potentially* avoid unnecessary interventions.[21] Despite no clear data on the effectiveness of fluid restriction, diuretic therapy, and positive pressure ventilation in improving important outcome that are commonly associated with PDA, or data on the risks associated with prolonged exposure to the ductus,[22,23] recent data suggest a marked change among health care providers toward the conservative treatment approach.[14] Using conservative treatment, Koch et al noted that 34% of extremely premature infants underwent spontaneous PDA closure by 8 postnatal days,[24] while Rolland et al reported that 73% of extremely premature infants closed their PDAs by 165 days.[25] Furthermore, Semberova et al reported that among 280 VLBW (<1500 g) infants receiving conservative treatment for PDA and followed with consecutive echocardiography, 85% underwent spontaneous ductal closure prior to hospital discharge.[26]

While conservative treatment may be a useful adjunct to ductal closure and potentially reduce unnecessary interventions in an

TABLE 1 Literature search strategy

PubMed/Medline search strategy included the terms "patent ductus arteriosus" AND "congenital," "patent ductus arteriosus" AND "infant," "patent ductus arteriosus" AND "newborn," "ductus arteriosus" AND "congenital," "ductus arteriosus" AND "infant," "ductus arteriosus" AND "newborn," "ductus" AND "surgery," "ductus" AND "percutaneous," "ductus" AND "catheter," "ductus" AND "transcatheter." The singular terms "patent ductus arteriosus" or "ductus arteriosus," and "ductus" were searched with limitations: humans-only and infants (0-1 year).

TABLE 2 Characteristics and quality of comparative studies (*N* = 3)

Source (last name of first author, year of publication)	Inclusion criteria/ patient characteristics	Exclusion criteria	Age at procedure mean ± SD or median (range)	Outcome variable(s)	Newcastle-Ottawa Scale		
					Selection (Out of 4 stars)	Comparability (Out of 2 stars)	Outcome (Out of 3 stars)
Abu Hazeem, 2013[17]	2-5 kg at procedure; PPV	Significant congenital heart disease	*Percutaneous closure* (*N* = 8): 3.7 mo (1.0-5.3) *Surgical ligation* (*N* = 8): 1.4 mo (0.2-4.2)	Time to return to baseline respiratory status	****	**	***
Pamukcu, 2018[19]	PDA-related symptoms; left-sided cardiac enlargement	>2 kg; sepsis; bleeding diathesis	*Percutaneous closure* (*N* = 26): 27.6 ± 17.9 days *Surgical ligation* (*N* = 31): 31.3 ± 13.0 days	Closure success, complication rates	****	**	***
Lin, 2009[18]	Term infants ≤3 mo, PDA >3.0 mm with symptoms	Infants <36 wk; other cardiac anomalies	*Percutaneous closure* (*N* = 20): 51.8 ± 21.1 days *Surgical ligation* (*N* = 18): 39.9 ± 20.7 days	Clinical course, complication, ECHO results	***	**	***

Abbreviations: ECHO, echocardiogram; PPV, positive pressure ventilation.

appreciable number of infants,[27,28] uncertainty remains as to what health care providers should do when PDAs fail to close following a period of conservative treatment. The only randomized clinical trial comparing definitive PDA closure (surgical ligation) vs conservative management of the ductus was performed over 35 year ago.[29] The investigators in that study reported that, among 25 preterm infants, those randomized to surgical ligation had less need for mechanical ventilation than did infants managed conservatively. As those findings may demonstrate limited applicability to modern clinical neonatal practice,[4] contemporary comparative trials are needed to inform the practice of evidence-based medicine in the present era.[1,8] However, a lack of clinical equipoise has precluded the conduct of such trials, and many providers remain unwilling to accept either the potential risks of surgery or potential risks of nonintervention.[4] Moreover, the practice of percutaneous PDA closure has not been compared prospectively to conservative management, leaving providers without evidence-based data to guide clinical decision making.

Given the lack of available evidence, we conducted a single-center (NCH), retrospective cohort study (January 1, 2015-December 31, 2017) of PDA treatment practices among preterm infants (<30 weeks of gestation). Consistent with PDA guidelines at our institution, all infants were managed conservatively during the first month of life. We compared outcomes among infants undergoing percutaneous closure vs those receiving continued conservative treatment.

Infants in the percutaneous closure group were matched with infants managed conservatively on the basis of the following four variables: (a) gestational age at birth (weeks); (b) gender; (c) intrauterine growth restriction (yes/no); and (d) composite outcome of PDA intensity, defined as the product of PDA duration (number of days exposed to the ductus), and ductal size (smallest ductal diameter, mm). Thus, infants in each matched pair had a similar PDA size and PDA exposure duration (prior to closure in the percutaneous group). We used a quantitative measure of pulmonary status (Pulmonary Score) as an outcome.[30]

The Pulmonary Score is a composite metric that uses an arithmetic sum of weighted clinical therapies, including: (a) type of respiratory support (mechanical ventilation, continuous positive airway pressure, nasal cannula, or room air); (b) amount of supplemental oxygen (FiO_2) required; and (c) pulmonary medications (systemic steroids, bronchodilators, diuretics) administered. The Pulmonary Score assigns more weight (numeric value) to respiratory support that reflects a greater degree of disease (eg, mechanical ventilation receives a 2.5, nasal cannula a 1.0). Over time, lower cumulative scores reflect improving respiratory status. FiO_2 was calculated as described by Benaron and Benitz for nasal cannula use.[31] Pulmonary Scores were calculated on a weekly basis for 28 weeks (or matched time point for those managed conservatively). Baseline scores were taken at one week prior to the procedure or matching time point as a reference, and the change in pulmonary score at each postprocedural time point was calculated relative to this value. The group means at each time point were compared using *t* tests. A Bonferroni correction was applied to account for multiple comparisons, such that $P < .005$ was considered statistically significant.

We observed decreases in pulmonary scores, reflecting improved respiratory status, in both groups over time (Figure 2). Interestingly, the trajectories for improvement were not similar across the two groups, with evidence of greater improvements in respiratory status beyond four weeks of age among infants who underwent percutaneous closure than among infants treated with continued conservative management.

Our observation of improved respiratory status over time for both treatment strategies (percutaneous closure, continued conservative management) is noteworthy. However, in the absence of therapy randomization, health care providers must weigh the risks of continued exposure to a PDA (while waiting and hoping for spontaneous closure) vs the risks of percutaneous PDA closure. To that end, identification of subgroups of infants most likely to benefit from PDA closure, or alternatively most likely to undergo spontaneous closure, would help minimize unnecessary and potentially harmful PDA overtreatment. Thus, the unanswered question is not whether to treat all PDA in preterm and VLBW neonates, but rather whom to treat and when.

4 | FUTURE RESEARCH AND INTERDISCIPLINARY COLLABORATION

4.1 | Randomized controlled trial (RCT)

The need for a RCT comparing percutaneous closure vs conservative management was a recommendation heard repeatedly throughout the symposium. Many symposium attendees suggested that this approach could provide the type of scientifically rigorous evaluation that would translate to evidence-based practice. To inform the design of a future RCT comparing percutaneous PDA closure vs conservative management, the following research should be prioritized: (a) characterize "high-risk" subgroups of infants with a PDA based on genetic, epigenetic, and clinical (echocardiographic measurements, biomarkers) profiles that are associated with adverse outcomes; (b) validate prediction models to permit early identification of infants with increased probabilities of persistent PDA and PDA-associated harm; and (c) define what constitutes clinical success following PDA treatment, including an emphasis on longer-term neurocognitive performance and quality of life.

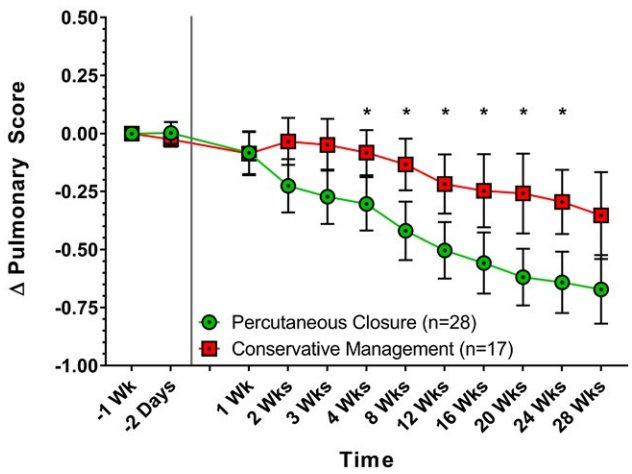

FIGURE 2 Plot showing the mean ± 95% confidence intervals (CI) for the change in pulmonary score over time, normalized relative to the one-week pre-closure time point. The asterisks in the figure denote statistically significant differences at $P < 0.005$

4.2 | Quality assurance safeguards

Broad consensus was expressed about the need for quality assurance processes in the use of percutaneous closure among lower weight infants. While the St. Jude Medical AMPLATZER Duct Occluder II AS (ADO II AS) device may be uniquely suited for catheter-based closure of preterm infants, those in attendance agreed that waiting for the published results of the recently completed multicenter (St. Jude Medical, Inc., St. Paul, Minnesota) trial prior to widespread adoption was sensible.[32] Moreover, practitioners were encouraged to report on strategies used to minimize the risks of catheter-based closures among lower weight infants.

4.3 | Research network

In the setting of the current ADO-II AS trial,[32] the broad consensus emphasized the need for more consistent data reporting, including the alignment of key measurements and outcomes based on multidisciplinary input and collaboration (interventionalists, pediatric cardiologists, and neonatologists).

CONFLICT OF INTEREST

The authors have no financial relationships or conflicts of interest related to this article to disclose.

AUTHOR CONTRIBUTIONS

Courtney C. Mitchell and Carl H. Backes were involved in the acquisition of data and analysis and interpretation of data conception and design of manuscript, drafting the article and revising it critically for important intellectual content; final approval of the version to be published, and provides agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Brian K. Rivera was involved in substantial contributions to conception and design of manuscript, analysis and interpretation of data; drafting the article and revising it critically for important intellectual content; final approval of the version to be published, and provides agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Jennifer N. Cooper was involved in the analysis and interpretation of data; drafting the article and revising it critically for important intellectual content; final approval of the version

to be published, and provides agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Charles V. Smith, Darren P. Berman, and Jonathan L. Slaughter were involved in drafting the article and revising it critically for important intellectual content; final approval of the version to be published, and provides agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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