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Potential Unintended Consequences of a Conservative Management Strategy for Patent Ductus Arteriosus

Justin J. Elhoff, MD^{*}, Myla Ebeling, MS[†], Thomas C. Hulsey, MSPH, ScD[†], and Andrew M. Atz, MD^{*}

^{*}Division of Cardiology, Department of Pediatrics, Medical University of South Carolina, Charleston, SC, USA

[†]Division of Epidemiology, Department of Pediatrics, Medical University of South Carolina, Charleston, SC, USA

Abstract

Background—A recent review supports a strategy of deferring treatment of patent ductus arteriosus (PDA) in the preterm neonate until at least the second week after birth. In light of previous suggestion that later initiation of treatment may be less efficacious for closing PDAs it is reasonable to question if delayed treatment may be less effective.

Design—We conducted a single center retrospective review of a neonatal intensive care unit database of infants 37 weeks gestation with the diagnosis of PDA and treated with indomethacin from 1999 to 2007. We determined gestational age (GA), timing of indomethacin initiation, and status of the PDA at hospital discharge. Treatment failure was defined as neonates requiring further intervention to close their PDA or those who died without echo-proven PDA closure.

Results—Of the 341 infants meeting the study criteria, 77 (23%) had defined treatment failure. The failure group had a younger median GA of 25 weeks (interquartile range [IQR], 24–26) vs. 28 weeks (IQR, 26–30) for the successful group ($P < .0001$). The failure group had a median treatment initiation on day of life (DOL) 4 (IQR, 1–8) compared with DOL 3 (IQR, 1–6) for those in the successful group ($P = .15$). Taken as a whole, infants treated after DOL 5 were significantly more likely to have treatment failure (30.1% vs. 19.3% for those treated DOL 1–5, $P = .03$).

Conclusions—Our study confirms that younger GA at birth is correlated with increased likelihood of failed PDA closure. We also show a trend indicating that later initiation of treatment may decrease the chances of successfully closing a PDA. Future examination of PDA management should consider the potential unintended consequences that may accompany a delayed treatment strategy.

Corresponding Author: Justin Elhoff, MD, The Children's Heart Program of South Carolina, 165 Ashley Avenue, Charleston, SC 29425, USA. Tel: (843) 792-3300; Fax: (843) 792-3284; elhoff@musc.edu.

Author Contributions

Justin Elhoff did concept/design, data analysis/interpretation, drafting of the article, approval of article, and data collection. Myla Ebeling did the data analysis/interpretation, statistics, and approval of article. Thomas Hulsey did the data analysis/interpretation, statistics and approval of the article. Andrew Atz did concept/design, data analysis/interpretation, critical revision of the article, and approval of article.

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Keywords

Patent Ductus Arteriosus; Indomethacin; Neonatal Cardiology; Preterm Infants; Ligation

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Introduction

Since the publication of the first studies on the use of indomethacin to close the patent ductus arteriosus (PDA) in 1976, use of cyclooxygenase (COX) inhibitors for treatment of PDAs has been a mainstay in the neonatal intensive care unit (NICU).^{1,2} This long-standing practice is rooted in the known association between PDA and neonatal morbidity and mortality, as well as physiologic plausibility and anecdotal evidence of clinical improvement following treatment. Initially, research on PDAs primarily addressed the question of “how” to best close a PDA, virtually ignoring the question of “if” it is actually beneficial to do so. Recently, the standard of care practice of closing PDAs has come under scrutiny. At best, there is conflicting evidence as to whether closing a PDA has beneficial effect on neonatal outcomes including death, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, length of hospitalization, retinopathy of prematurity, duration of ventilation, and neurodevelopmental outcomes.^{3,4}

Considering the lack of evidence that closing PDAs in preterm infants provides benefit as well as the potential side effects that accompany treatment with COX inhibitors, management of this condition is in a state of evolution. While some practitioners continue to aggressively treat PDAs, others advocate abstaining from pharmacologic intervention. Many practitioners attempt to assess significance of the open ductus to determine which patients may benefit from treatment, although consistently defining hemodynamic significance of a PDA remains elusive.^{5–12} Within this milieu where no general consensus exists, a recent systematic review supported a strategy proposed by Nemerofsky, et al., which calls for clinicians to refrain from treatment altogether in infants with birth weights >1000 g and defer treatment until at least the second week after birth in smaller infants.^{3,13}

An issue with this strategy is that numerous studies have suggested that earlier initiation of treatment correlates with higher rates of PDA closure.^{14–19} In light of the suggestion that later initiation of medical treatment may be less efficacious for closing PDAs, it is reasonable to question whether delaying medical treatment in premature infants may result in decreased efficacy of this therapy. The current study retrospectively examines the relationship among gestational age (GA), timing of medical treatment, and PDA closure in order to investigate if a policy of delayed treatment may result in an increase in treatment failure in cases where medical therapy is deemed warranted.

Methods

We used a single-center institution’s NICU database to identify all patients admitted between January 1, 1996 and July 15, 2009 with the diagnosis code for PDA and documented to have been treated with indomethacin. Exclusion criteria included GA greater than 37 weeks, diagnosis of congenital heart disease, and receiving less than two doses of indomethacin (a standard course of therapy at our institution has consisted of three doses of

indomethacin). We recorded the GA at birth for these infants, day of life (DOL) on which treatment with indomethacin was initiated, and need for more invasive treatment for PDA (surgical ligation or transcatheter device closure). The date of discharge and status at discharge (alive or deceased) was compiled for each patient. Echocardiogram reports for each patient were analyzed to determine the status of the ductus at discharge. Post-NICU discharge records were reviewed to determine if further intervention was required for those infants without echo-proven closure of their PDA during admission. This study was approved by the Institutional Review Board at the Medical University of South Carolina.

We defined two groups: those deemed to have treatment success and those with presumed failed treatment. The successfully closed group consisted of those neonates discharged home either with echo-proven closure of their PDA or with no need for further evaluation/intervention and thereby deemed clinically insignificant and presumed closed. The failure group consisted of those neonates requiring further invasive intervention to close their PDA or those who died without echo-proven closure.

As the continuous data were not normally distributed we utilized nonparametric (Wilcoxon) statistics and reported the results as medians with interquartile ranges (IQRs) for group differences in GA and timing of indomethacin. Grouped data were analyzed using the chi-square test. The optimal cut-point in the GA distribution that best predicted PDA closure was determined by use of the receiver operator characteristic (ROC).

Results

During the period of review, 341 infants met study criteria: 264 infants (77%) were defined as treatment successes, while 77 infants (23%) either required invasive intervention for PDA closure or died prior to echo-proven closure, and were therefore defined as treatment failures. Those with treatment failure had a median GA of 25 weeks vs. 28 weeks for patients in the successful treatment group ($P < .0001$). When examining timing of treatment, those defined as having treatment failure had a median treatment initiation of DOL 4 compared with DOL 3 for those in the successful group ($P = .15$) (Table 1).

The patients in our study were further divided into equal-sized quartiles based on DOL of treatment initiation. The fourth quartile consisted of those treated on DOL 6 or later. As this group corresponds closely to the recommendation to delay treatment until after the first week of life, this quartile was compared with the other three quartiles with earlier treatment. We found a statistically significant difference in closure success rate, with 46 of 238 (19.3%) treated on DOLs 1–5 defined as failing treatment compared with failure in 31 of 103 (30.1%) of those treated on or after DOL 6 ($P = .03$).

An ROC curve of GA by PDA closure revealed GA area under the curve was 0.76 (95% confidence interval: 0.69–0.82, $P < .001$) (Figure 1). The sensitivity of GA as a predictor of successful closure is above 75% for neonates born at 26 weeks or less, while the specificity remains greater than 78% for those born at 27 weeks gestation or greater before dropping precipitously.

Table 2 further details mortality, status of PDA at discharge, initiation of medical treatment, average number of echocardiograms, and number of PDA ligations needed for our population by GA.

Of the 341 infants examined, 280 (82%) were discharged from the NICU alive. As our institution did not have a standardized follow-up imaging protocol during the study period, we utilized ductal status at the time of discharge as the primary study outcome. Of those discharged from the NICU alive, only 43 (15.3%) were classified as treatment failures. This contrasts with 61 neonates who died prior to discharge from the NICU, of whom 34 (55.7%) were classified as having failed closure ($P < .0001$). Not surprisingly, those who survived to hospital discharge had a median GA of 27 weeks (IQR 25–30) compared with 25 weeks (IQR 24–26) for those who died prior to discharge ($P < .0001$). As the more premature neonates tended to be treated earlier in life, those discharged alive had median indomethacin initiation on DOL 3 (IQR 1–6) compared with DOL 2 (IQR 1–7) for those who died prior to discharge ($P = .2$).

While this study cannot speak to the role, if any, that presence of a PDA had in relationship to patient death, those who were treated earlier in life were of younger GA, and therefore more likely to die prior to follow-up imaging. Given the potential confounding of both mortality and lack of a standardized follow-up imaging protocol the results were reanalyzed after removing the 25 patients who died prior to follow-up imaging. These 25 patients had a median GA of 24 weeks and median initiation of indomethacin on DOL 1. This analysis did not change the relationship between GA and treatment success, but did reveal a stronger trend toward significance for later initiation of treatment and treatment failure (Table 3).

Our analysis includes subjects receiving two or more doses of indomethacin, while a typical course of indomethacin at our institution is three doses. Patients who received only two doses tended to have an earlier initiation of treatment and were more likely to be classified as treatment failures. Removal of the 28 patients who received two doses does not change the association between GA and treatment success, but also reveals a stronger trend toward significance for later initiation of treatment and treatment failure (Table 4).

Discussion

As controversy regarding management of persistent PDA in the premature infant continues, the broad clinical question has evolved from how to best manage the PDA to which patients, if any, will benefit from treatment. Within this large question remains the problem of which patients are likely to actually respond to medical treatment. Two important factors that bear consideration regarding this problem are GA of the patient and timing of treatment initiation.

This study supports previous research by showing that younger GA at birth is strongly correlated with increased likelihood of treatment failure with indomethacin. In our study, the median GA of those neonates with treatment failure was 25 weeks, compared with 28 weeks for those who did have documented closure. The ROC curve showed GA to be a fair predictor of successful ductal closure, with an area under the curve of 0.76.

The fact that the youngest neonates seem to be more likely to fail treatment for PDA is a difficult conundrum. These patients are often the most ill and most sensitive to the effects of a large left-to-right shunt and may benefit most from elimination, or at least reduction, of this shunt. Additionally these more premature infants may be most susceptible to cardiorespiratory instability following PDA ligation.^{20–22} This tenuous patient population may receive the greatest benefit from early recognition of hemodynamic significance of a PDA as well as predictive algorithms to help estimate likelihood of successful ductal closure.

Our study indicates a reasonable probability that timing of initiation of therapy influences likelihood of PDA closure. Those deemed to have unsuccessful closure began treatment on DOL 4, as opposed to DOL 3 for those with treatment success, a finding that trends toward statistical significance. When taken as a whole, those treated within the first 5 DOL were found to be significantly more likely to have documented closure of their PDA than those treated on or after DOL 6.

Certain aspects of this study result in bias against showing significance for later treatment initiation as a factor in treatment failure. First, patients of a younger GA tended to be treated earlier in life, and we have demonstrated younger GA to correlate with higher incidence of treatment failure. Likewise, these more premature patients inevitably have increased mortality for multiple reasons, and this study's definition of treatment success and failure predisposes those who died prior to discharge as being classified as treatment failures. As discussed earlier, inclusion of patients who died prior to follow-up imaging as well as those patients who received only two doses of indomethacin both seem to promote bias against the correlation between later initiation of treatment and treatment failure.

Further interesting data that emerge from this study is resource utilization devoted to the PDA. Patients had an average of 3.2 echocardiograms performed. Unfortunately, the fact that these were not necessarily done at standard intervals, and that many patients never had follow-up studies, limits our ability for retrospective evaluation. This lack of standardization makes it nearly impossible to assess the effectiveness of our management strategies from a clinical standpoint, and may highlight an important lesson in cost-effectiveness and resource utilization.

This retrospective study has several limitations. During the time period of this study, our institution did not have a consistently standardized approach to the assessment and treatment of the PDA. Management decisions, including prophylactic vs. symptomatic treatment and the utilization of echocardiography to assess the PDA, have traditionally been practitioner dependent. Additionally, the lack of a standardized imaging protocol following PDA treatment makes it impossible to definitively assess the efficacy of treatment. As the natural history of most PDAs is to close over time, we are unable to assess a causative vs. incidental relationship between indomethacin treatment and ductal closure. As discussed earlier, mortality was also a confounding factor in this study, with the patients who died being more immature and generally treated for PDA earlier, but more likely have no documentation of ductal closure. In many cases this is due to death occurring prior to reassessment of ductal

patency. Additionally, this study was not designed to assess the benefit of treatment of PDAs nor does it attempt to define hemodynamic significance.

With the suggestion that delayed initiation of therapy is associated with decreased efficacy, especially in the most premature neonates, the impetus for further research becomes not only defining the hemodynamically significant PDA that will benefit from treatment, but defining it very early in life. One revelation from our retrospective review is that without a standardized approach to examining this population, comparing these patients becomes extremely difficult. Our data show that these patients are undergoing a great number of echocardiograms, but as these have not been conducted in a standardized fashion at our institution it is difficult to draw meaningful conclusions from the data they may otherwise provide. By implementing an observational protocol for echocardiographic assessment of premature neonates, we may be able to glean more useful information allowing us to discern more accurately which PDAs are likely to close with treatment. This should be possible without increasing resource utilization or cost. Additionally, prospective observational imaging protocols, in conjunction with careful data collection documenting clinical status, will be a necessary tool in developing criteria to offer early prediction about the hemodynamic significance of a PDA.

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Figure 1.
Patent ductus arteriosus closure by gestational age.

Table 1

Correlation of Gestational Age and Treatment Initiation with Failed Treatment

	Treatment Success	Treatment Failure	P Value
Total patients (n)	264 (77%)	77 (23%)	
GA at birth (weeks)	28 (IQR 26–30)	25 (IQR 24–26)	<.0001
Indomethacin initiation (DOL)	3 (IQR 1–6)	4 (IQR 1–8)	.15
Hospital mortality (n)	27 (10.2%)	34 (44.2%)	<.0001

DOL, day of life; IQR, interquartile range.

Table 2

Patient Characteristics by Gestational Age

Gestational Age	Patients (n)	Discharged Alive (n)	Treatment Success (n)	Median DOL Indocin (IQR)	Mean Echocardiograms (n)	Ligations (n)
21	1	1 (100%)	1 (100%)	6	3	0
23	16	7 (44%)	5 (31%)	2 (1–7.5)	3.9	5 (31%)
24	45	24 (53%)	21 (47%)	1 (1–5)	3.2	12 (27%)
25	48	41 (85%)	37 (77%)	2 (1–8)	3.6	9 (19%)
26	43	34 (79%)	29 (67%)	2 (1–5)	3.3	10 (23%)
27	39	34 (87%)	31 (79%)	2 (1–5)	3.1	6 (15%)
28	39	35 (90%)	38 (97%)	2 (1–5)	3.1	0
29	25	24 (96%)	24 (96%)	5 (3–7)	2.6	1 (4%)
30	29	26 (90%)	26 (90%)	4 (3–8)	2.6	3 (10%)
31	24	22 (92%)	23 (96%)	4 (2–9.5)	2.9	1 (4%)
32	9	9 (100%)	8 (89%)	4 (3–6)	3.2	1 (11%)
33	6	6 (100%)	5 (83%)	2.5 (2–5)	3.8	1 (17%)
34	4	4 (100%)	4 (100%)	3.5 (2.5–6)	3	0
35	7	7 (100%)	7 (100%)	3 (2–4)	3	0
36	2	2 (100%)	2 (100%)	9.5 (4–15)	4	0
37	4	4 (100%)	3 (75%)	5 (3–8.5)	3.5	1 (25%)
Total	341	280 (82%)	264 (77%)	3 (1–6)	3.2	50 (15%)

DOL, day of life; IQR, interquartile range.

Table 3

Correlation of GA and Treatment Initiation with Failed Treatment—Analysis after Removal of Patients Who Died Prior to Follow-up Imaging

	Treatment Success	Treatment Failure	<i>P</i> Value
Total patients (n)	264 (84%)	52 (16%)	
GA at birth (weeks)	28 (IQR 26–30)	25 (IQR 24–27)	<.0001
Indomethacin initiation (DOL)	3 (IQR 1–6)	4.5 (IQR 1–8)	.07

DOL, day of life; GA, gestational age; IQR, interquartile range.

Table 4

Correlation of GA and Treatment Initiation with Failed Treatment—Patients Receiving Three or More Doses Only

	Treatment Success	Treatment Failure	P Value
Total patients (n)	246 (79%)	67 (21%)	
GA at birth (weeks)	28 (IQR 26–30)	25 (IQR 24–26)	<.0001
Indomethacin initiation (DOL)	3 (IQR 1–6)	4 (IQR 1–8)	.07

DOL, day of life; GA, gestational age; IQR, interquartile range.