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EDITORIAL

Unwinding old habits: deimplementation of treatment regimens for patent ductus arteriosus in preterm infants☆,☆☆

Livrando-se de velhos hábitos: desimplantação de esquemas terapêuticos para persistência do canal arterial em prematuros

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The year 2018 marks the seventieth anniversary of Burnard's observation that patent ductus arteriosus (PDA) in infants could be recognized using phonocardiography.[1] Soon after, this method was used to demonstrate that ductal patency is often prolonged in preterm infants and is associated with greater severity of respiratory distress. Linkage of ductal patency to respiratory compromise and other adverse outcomes led to the thesis that intervention to achieve earlier ductal closure would improve results. Development of techniques for ligation of the ductus in small newborn infants in the early 1970s provided a means for doing so. With the advent of ultrasonography for diagnosing prolonged ductal patency and recognition that prostaglandin synthesis inhibitors promote ductal constriction, the stage was set for adopting strategies for early and widespread treatment to close PDA in preterm infants. The pathophysiological rationale for doing so – reduction in aortopulmonary shunting would reduce pulmonary edema, alleviate respiratory failure, and spare exposure to injurious oxygen and positive pressure ventilation – was so compelling that the landmark National Collaborative Study on Patent Ductus Arteriosus was designed to ensure that no infant still had a PDA by study completion.[2] Nonetheless, by the beginning of this century, it had become apparent that numerous randomized trials of ductal closure in preterm infants had failed to provide evidence that treatment produced the expected better outcomes, such as reduced rates of death, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and neurosensory impairment, despite achieving ductal closure. The sole benefit demonstrated in these trials – a lower rate of intraventricular hemorrhage (IVH) following indomethacin prophylaxis[3] – does not appear to be mediated by ductal closure.

More recent analyses have strengthened and placed boundaries around this inference. Most trials focused on very early treatment, in the first 24 h after birth. For that approach, it is not just true that there is a lack of evidence for efficacy; there *is* evidence for a *lack* of efficacy (beyond ductal closure *per se* and prevention of IVH).[4] This conclusion is robust, even after excluding trials in which many control subjects (>33% or >50%) received open treatment, or those which included few extremely low gestational age newborns or were conducted in the pre-surfactant era.[5]

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Because of the large numbers of subjects (2000 to nearly 6000, depending on inclusion criteria) and narrow confidence intervals on odds ratios for important outcomes, it is unlikely that these conclusions will be changed by additional early treatment trials.

The question of whether later, more selective treatment might be beneficial remains open. Of eleven trials that enrolled subjects between 1 and 6 days of age, only four (including 434 subjects) were published after the year 2000. Those trials provided no evidence of reduction in death, BPD, NEC, IVH, or retinopathy of prematurity (ROP), but the confidence intervals for those odds ratios are broad (typically from approximately 0.5–2), so evidence for lack of benefit is not compelling. Of the nine trials that enrolled subjects at 7–14 days of age, only the recently published PDA-TOLERATE trial is <35 years old. In that trial, 202 subjects <28 weeks gestation with moderate-to-large PDA were enrolled between 6 and 14 days of age and randomized to immediate treatment or to deferral of treatment unless prespecified respiratory and hemodynamic criteria were reached. There were no differences in the primary outcome of ductal ligation or patency at discharge, or in secondary outcomes including death, BPD, or the combined outcome of death or BPD. Among subjects born at ≥26 weeks, early treatment was associated with delayed achievement of full feedings, higher rates of late onset sepsis caused by organisms other than coagulase-negative *Staphylococcus*, and greater mortality.[6] These possible compromised outcomes for the early treatment group represent *post hoc* analyses of patient groups and outcome subcategories, and may not be reproducible. Although the study lacked power to exclude benefit from early treatment, due to sample size and potential effects of open treatment in 44% of control subjects (at 21 ± 8 days of age, *vs*. 8 ± 2 days in the treatment group), it did not provide evidence of benefit from ductal closure (other than ductal closure itself and less need for rescue treatment). Only a single small trial (published in 1980) enrolled subjects after the second postnatal week, so interventions in infants older than 14 days must be viewed as untested and therefore unproven. There is very little evidence to guide management of ''older'' preterm infants with persistent PDA, so there should be equipoise about their participation in randomized controlled trials and circumspection regarding expectations of benefit from treatment.

In the past decade, recognition of evidence that broad, early use of measures to close the PDA in preterm infants is not beneficial and lack of evidence that later or selective use of these measure is beneficial has led to reduced utilization of nonsteroidal anti-inflammatory drugs (NSAIDs) and surgical ligation in individual centers and across healthcare consortia, regions, and countries. Reports of impacts of those practice changes are now appearing. Administrative data from a consortium of Children's Hospitals in the United States from 2005 through 2014 revealed declining NSAID use and ligation, beginning in 2010, as well as an increase in BPD beginning a year earlier.[7] Stratified multivariate regression demonstrated no changes in outcomes among infants weighing 1000–1499 g, with the exception of more cases of renal failure. Among 400–999 g infants, mortality decreased and BPD, periventricular leukomalacia (PVL), acute renal failure, and ROP (but not treatment for ROP) increased. In both weight strata, diuretic use declined and systemic steroid treatment increased. Contemporaneous practice changes make the relationship between changes in PDA management and outcomes uncertain. These data suggest that increased adverse outcome rates may simply reflect – and be offset by – decreased mortality among the smallest infants in this cohort. Clinical data from a large consortium of NICUs across the United States for the years 2005–2016 showed similar reductions in indomethacin or ibuprofen use and in rates of ductal ligation.[8] These trends were associated with reduced mortality and no increase in any measured morbidity. Subgroup analysis found an increased BPD rate among infants born at 23–24 weeks gestation, who also experienced the largest increase in survival. National data from Canada from 2006 to 2012 showed reductions in medical and surgical closure of PDA in infants born between 23 and 32 weeks gestation, with the proportion of infants receiving conservative (noninterventional) management increasing from 14 to 38%.[9] The rate of survival without IVH ≥ grade 3, PVL, ROP ≥ stage 3, BPD, or NEC ≥ stage 2 increased from 35% to 45%. Subgroup analysis and adjustment for risk factors identifiable at birth suggested that this improvement accrued to infants managed conservatively in the latter half of the study period. Analysis of data from 119 nurseries in California from the years 2008 to 2015 showed that unit-specific reductions in PDA treatment rates were associated with decreased rates of BPD or BPD and death among infants with birth weights of 1000–1499 g, but with increased mortality among infants with birth weights between 400 and 749 g.[10] Although the latter suggests mortality reduction from PDA treatment in the smallest infants, the authors caution against the ecological fallacy of extrapolation from population effects to individual benefits. Overall, these population surveys have been reassuring, as there has been no apparent resurgence of adverse outcomes as treatment rates declined. Rates of treatment in these cohorts remained substantial, particularly among the smallest or least mature infants, so it may be that more selective strategies reduced unnecessary treatment but still identified and treated all or most infants who stood to benefit. Effect differences between different weight or gestational age strata also suggest that important effects may be concealed by heterogeneity among study subjects with offsetting impacts in different subgroups.

These uncertainties are addressed, to some extent, by experiences from single centers or small consortia, such as that provided by Borràs-Novell et al. in this issue of the *Jornal*.[11] These reports now describe >1000 conservatively managed very low birth weight (VLBW) infants.[12] Although most individual sample sizes are not large, complete or nearly complete elimination of treatment has not produced worse outcomes compared to historical data from the same hospitals or peer-institution benchmarks. Two centers reported substantial *reduction* in BPD rates after complete[13] or near-complete[14] elimination of PDA treatment. The largest series, combining data from Prague, Czech Republic, and Dublin, Ireland, documented high rates of spontaneous ductal closure without intervention and provided much-needed current data on the age at which closure occurs across several gestational age strata.[15] Outcomes compared favorably to VON benchmarks, even though only 6% of their cohort received PDA treatment. Weisz et al.

recently reported that spontaneous ductal closure can be expected even among VLBW infants who fail to respond to indomethacin treatment, with 85% closing the ductus by 11 weeks of age.[16] Compared to infants at the same institution who underwent surgical ligation after failure of medical management, this non-ligation group had no greater incidence of BPD, ROP, NDI or death, or NDI. However, mortality was significantly greater, due to much higher rates of death from sepsis or severe central nervous system injuries, suggesting confounding by contraindication. While reductions in treatment rates that greatly exceed those in population-based surveys apparently are not injurious, it is notable that about 5% of the infants in those reports received treatment to close the PDA. This suggests that it should be feasible to markedly reduce, but possibly not entirely eliminate, treatment of PDA without incurring adverse consequences. The challenge will lie in determining which babies fall among the 5% (or perhaps fewer) of all VLBW infants who need – and will benefit from – treatment, as the criteria for intervention in those experiences were not explicitly defined.

The present report adds to this body of post-implementation surveillance in several ways. These authors report on a practice transition in two NICUs in Spain, from routine treatment of all infants who met the Vermont Oxford Network criteria for PDA to a more selective strategy in which treatment was reserved for infants who had clinical signs of instability not related to another condition. Fewer infants (56 *vs*. 86%) were treated, at later postnatal ages (6 *vs*. 3 days). There was no apparent increase in adverse outcomes, but the statistical power was likely insufficient to detect even moderate-sized changes. Subjects $\leq$ 26 weeks gestation had reduced BPD and increased survival without morbidity, in contrast to prior results suggesting potential adverse impacts of reduced treatment in the most immature preterm infants.[10,17] This is important, as disparate results in this high-risk population should promote equipoise regarding enrollment in randomized trials to resolve the question of who to treat, using which criteria, and when. Consistent with other studies,[18] they reported a high rate of ductal closure among infants discharged with PDA, affirming that spontaneous closure after discharge can generally be expected. Finally, they reported that no infants with PDA at discharge developed pulmonary hypertension, for which they were carefully monitored. This places an upper 95% confidence limit of 12% on the prevalence of pulmonary hypertension, providing previously unavailable quantitative evidence that fears of pulmonary vascular disease in infants discharged with PDA likely have been overestimated.

Critical examinations of the effects of changes in practice, like that presented by Borràs-Novell et al., are important because they provide an essential safety net for identification of unanticipated consequences of practice changes. These studies provide opportunities to extend observations to interventions and outcomes that have not been adequately investigated, such as post-discharge pulmonary hypertension as described by these authors. The conclusion that a practice change is not consequential must be tempered by recognition that we cannot see things that we do not look for. These *post hoc* studies are essential tools for identifying unsuspected sequelae, which in this instance were not found. It is unlikely that sufficient randomized trials will be performed to illuminate everything we need to know about this matter. We are indebted to those who do this difficult work of post-implementation surveillance.

Conflicts of interest

Dr. Benitz is a Neonatal Medical Advisory Board member for Abbott, a manufacturer of devices for catheter-based ductal occlusion. He has also received honoraria for speaking on this topic at Continuing Medical Education and other conferences.

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