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Patent Ductus Arteriosus: Evidence For and Against Treatment

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Numerous studies have shown that a prolonged, persistent left-to-right shunt through a patent ductus arteriosus (PDA) shortens the life span of animals and humans(1–4). In preterm infants, a persistent PDA is due in large part to alterations in prostaglandin metabolism. Inhibition of prostaglandin production with indomethacin has been the mainstay of preterm PDA treatment since the mid 1970's (5). In recent years there has been a growing debate about whether or not to treat a persistent PDA during the neonatal period(6). Preterm infants have a high rate of spontaneous PDA closure during the first 2 years. Therefore, early treatment runs the risk of exposing infants to drugs or procedures they might not need. In this issue of *The Journal*, the report by Kabra et al(7) fans the flames of this controversy. In the following review, we will examine the evidence for and against PDA treatment during the neonatal period.

Although a persistent PDA is *associated* with several important neonatal morbidities, its role in *causing* these morbidities is currently in question (6). Based on existing clinical trials, it is hard to tell whether the reported association between a persistent PDA and other neonatal morbidities is due to the left-to-right PDA shunt itself, the therapies used to treat it, or the immaturity of the infant that is likely to develop a PDA. Only one randomized, controlled trial, performed more than 25 years ago, was designed specifically to examine the role of a persistent untreated PDA in neonatal morbidity(8). The investigators found that a persistent PDA increased pulmonary morbidity and prolonged the need for respiratory support. The trial size was too small to examine the PDA's effect on other neonatal morbidities.

Unfortunately, the vast majority of PDA treatment trials were never designed to examine the role of a persistent PDA in neonatal morbidity; they were designed to assess the relationship between "timing," or initiation, of treatment and efficiency of PDA closure. All of the trials utilized "back up treatments" to close the PDA if it persisted beyond several days. These "timing" trials can give us information about the role of a PDA in producing morbidity, only if the morbidity's appearance and/or underlying cause occur during the period of PDA exposure (between the initial and back up treatments) (Figure). On the other hand, these trials tell us nothing about the role of the PDA in morbidities that occur after infants have received their back up treatment, or in morbidities that occur before the trial begins (Figure).

What information can be gleaned from these "timing" trials? There are basically two types of "timing" trials: Prophylactic (where treatment starts within 24 hours of birth) and Symptomatic (where treatment starts when symptoms appear: start times are usually between 2 and 7 days after birth).

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Prophylactic Trials

Morbidities affected by the PDA (or its treatment) that could be detected in prophylactic trials are those that occur between birth and the time of back up treatment (2–3 days after birth) (Figure). Both, the individual prophylactic trials and a meta-analysis of their results (reviewed in (9,10)) consistently show that prophylactic use of indomethacin increases the effectiveness of pharmacologic closure and decreases the need for surgical ligation, decreases the incidence of early, serious pulmonary hemorrhages, and decreases the incidence of serious (grades 3/4) ICH. Indomethacin's ability to reduce grade 3/4 ICH appears to be independent of its effect on PDA closure. This action only occurs when indomethacin is administered in a prophylactic mode, and has not been observed with other cyclooxygenase inhibitors, such as ibuprofen (11).

Symptomatic Treatment Trials

Like the prophylactic trials, the symptomatic treatment trials can only detect PDA-related morbidities that occur between the time of initial treatment (>2 days after birth) and the time of back up closure (Figure). In these trials, infants were exposed to a symptomatic PDA for varying time spans before back up closure was invoked (mean (range)= 5 (1–14) days). For the purposes of discussion, we analyzed only those trials that waited at least 6 days (mean = 9 $\pm$ 3 days) before resorting to back up closure (8,12–18). By doing this, we hoped to maximize our ability to detect any detrimental effects of a PDA on a particular morbidity.

Pulmonary Morbidity

Five of the 7 trials that reported pulmonary morbidity (8,12–17) (and a meta-analysis of the 7 trials) showed that exposure to a symptomatic PDA, for at least 6 days, prolonged the need for supplemental oxygen and/or mechanical ventilation. Information about longer exposures to a PDA can be found in studies of preterm baboons. These studies provide evidence for more long lasting pulmonary morbidity following exposure to a persistent PDA. Premature newborn baboons, exposed to a moderate-size PDA shunt for 14 days, have altered pulmonary mechanics and arrested alveolar development(19). Arrested alveolarization is the histologic hallmark of the “New BPD”(20). Pharmacologic closure of the PDA significantly increases alveolarization (alveolar surface area and branching) and prevents the deterioration in pulmonary function(19).

Necrotizing Enterocolitis

There is little evidence to support or refute the role of a PDA in necrotizing enterocolitis. A meta-analysis of the trials (8,13,15,16,18) that delayed back up treatment for at least 6 days showed that early treatment of a PDA may decrease the incidence of NEC, but only among infants less than 1000 gm birthweight. This analysis has some uncertainty since it is heavily weighted by a single study(18); no significant association between a PDA and NEC was found when this study was removed from the analysis.

Retinopathy of Prematurity (ROP)

No causal role has been found for a PDA in ROP.

Any discussion of PDA treatment must consider the possibility of treatment-related morbidities. Although none of the treatment trials were specifically designed to examine the incidence of morbidities caused by indomethacin or surgery, the prophylactic treatment trials do provide some information about those associated with indomethacin. In these trials, less than 50% of Control group infants were exposed to indomethacin (compared with 100% in the Prophylactic group) (see (9)). Therefore, one might expect that if indomethacin produced

significant problems, some noticeable differences would be apparent between the groups. Transient alterations in renal function and urine excretion are common problems with the initial doses of indomethacin (this appears to be less of a problem with ibuprofen). These renal abnormalities return to normal after the initial doses of indomethacin or with drug discontinuation(21). Indomethacin, by itself, does not appear to increase the incidence of other neonatal morbidities (e.g., necrotizing enterocolitis, gastrointestinal perforation, ROP, chronic lung disease (CLD), or cerebral white matter injury) (9)). However, an increased incidence of gastrointestinal perforations has been observed when indomethacin and postnatal steroids are administered simultaneously (22,23). Although indomethacin's cerebral vasoconstrictive effects are frequently cited as a concern for neonatologists (24,25), a recent Cochrane systematic review found that indomethacin prophylaxis is more likely to decrease rather than increase the incidence of periventricular leukomalacia (9). Studies of neurodevelopmental outcome (26–28), also, are reassuring. There is no evidence that prophylactic indomethacin has any adverse effect at 18 months (29); in fact, there is evidence that it may have long term benefits at 4.5 and 8 years (27,28).

What happens when pharmacologic treatment fails to close the PDA? Surgical ligation of a PDA is associated with its own set of morbidities: thoracotomy, pneumothorax, chylothorax, infection, and vocal cord paralysis. More than 50% of infants with birthweights ≤ 1000 gm will require inotropic support for profound hypotension during the postoperative period(30). In addition, neonatal transport to another facility may be required if surgical expertise is not readily available. The paper by Kabra et al(7) in the current issue of the Journal raises even more concerns about the use of surgical ligation in the neonatal period. They found an increased incidence of neurodevelopmental abnormalities, in addition to CLD and ROP, among infants treated with ligation. This is consistent with prior reports that link sensorineural abnormalities with surgical procedures in the neonatal period(31,32). These findings are still quite preliminary. The observational design of Kabra's study makes it impossible to determine if surgical ligation plays a causative role or is simply a surrogate marker for infants who are more critically ill or who have a developmental profile that leads to increased morbidity. In addition, other observational studies have failed to find a similar connection between surgical ligation and neurodevelopmental abnormalities or ROP (33). Although the link between neurodevelopmental abnormalities, ROP and ligation may be somewhat tenuous, stronger evidence exists for a causal relationship between ligation and CLD (33). One trial in humans has compared surgical ligation with pharmacologic closure(34); infants who were surgically ligated required longer durations of CPAP than those treated with indomethacin ($p=0.06$). Recent findings in premature baboons support the concept that surgical ligation may have a detrimental effect on lung function and growth. Although pharmacologic closure prevents the arrest in alveolar development caused by a PDA(19), no benefit on alveolar growth has been observed following surgical ligation (35,36).

Based on this review we offer the following conclusions: a moderate left-to-right PDA shunt alters pulmonary mechanics, increases the risk of pulmonary hemorrhage, and alters alveolar surface area (at least in preterm baboons). If left untreated, prolonged exposure to the left-to-right shunt can lead to congestive failure, pulmonary hypertension, and death. We suggest that pharmacologic treatment of a PDA in the newborn period offers measurable benefits without an increase in clinically significant adverse effects. If pharmacologic treatment is to be used, early treatment is more likely to result in successful ductus closure. In certain settings (where ICH, pulmonary hemorrhage, and PDA ligations are frequent occurrences), indomethacin prophylaxis may even be a preferred alternative. On the other hand, ductus ligation, although eliminating one potential cause for neonatal morbidity, may introduce its own set of problems. Further investigations will be needed to determine which infants are most likely to benefit from surgical ligation and which infants might best be left untreated when pharmacologic approaches are no longer an option.

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Figure.

Relationship between treatment times in randomized PDA trials and the occurrence of common neonatal morbidities. Each trial type (Prophylactic or Symptomatic) entered infants into an *Initial* Early treatment or Control (no treatment) group. Several days later a *Back up* treatment was used to close any remaining clinically significant PDA shunts. These trials can detect morbidities affected by the PDA that present or develop during the interval between *Initial* and *Back up* treatments (i.e., during the interval that the ductus is closed in the Early group and open in the Control group). For example, Prophylactic trials have the potential to examine the role of PDA on the incidence of ICH or pulmonary hemorrhage, whereas the symptomatic trials would not be able to examine this relationship. Conversely, the Symptomatic trials might

be able to examine the relationship between PDA and NEC, whereas the Prophylactic trials would be unlikely to do so. Shaded bar represents the postnatal age when a morbidity either develops or is apparent. Shaded bars with ??? represent morbidities that may or may not have their origins during this period.