PATENT DUCTUS ARTERIOSUS IN THE PRETERM INFANT
EVIDENCE FOR & AGAINST TREATMENT

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Introduction

- Exposure to chronic persistent patent ductus arteriosus is associated with several neonatal morbidities.

- Such outcomes:
  - persistent L to R shunt across PDA
  - consequence of prematurity

- Significant benefit to early PDA closure:
  - Animal studies
  - Not replicated in any human trial.

- Pharmacological and surgical closure for PDA have their own morbidities.
PDA in Preterm Infants:

- High incidence
- High rate of spontaneous closure.

• Treatment: - Not benign.
  - Did not prevent morbidities associated with prematurity.

• For this, much recent debate as when PDA is pathologic and when closure is indicated.

• We will focus on the debate, treatment options for PDA, and outcomes associated with PDA and its treatment.
Debate

• In recent years, growing debate about whether or not to treat persistent PDA during neonatal period.

• PDA associated with several important neonatal morbidities, its role in causing these morbidities is in question.

• Hard to tell whether association is result of L→R PDA shunt, or immaturity of infant who is likely to develop PDA.

• Only one RCT in 1978 designed specifically to examine role of persistent untreated PDA in neonatal morbidity.
• Trial size too small to examine PDA’s effect on other morbidities.

• Furthermore, it is unknown if prophylactic and/or symptomatic PDA therapy will cause substantive improvements in outcome.

• Despite nearly 3 decades of research, the question of whether the benefits of treatments to prevent ductal patency or promote closure outweigh the risks of these treatments remains unanswered.
Findings from the Literature

- ~ 65% of infants <28 weeks’ gestation have persistent PDA.

- Spontaneous permanent ductus closure occurs in ~ 34% of ELBW neonates 2-6 days postnatally, and in majority of VLBW neonates within first year of life.

- 60%-70% of preterms <28 weeks’ gestation receive medical or surgical therapy for PDA.

- Natural history of PDA in premature infants cared for in today’s NICUs remains unknown (Pediatrics 125; 5, May 2010).
Spontaneous Closure of PDA

- Direct relationship between gestational age and closure.

- Even with significant lung disease, DA in infants >30 weeks gestational age usually closes by 5 days.

- 60% spontaneous DA closure: Many infants unnecessarily exposed to drugs with potentially serious adverse effects.
New Concepts on Platelet-driven DA Sealing

- Platelets recruited to luminal aspect of murine DA immediately after birth.

- Dysfunction of platelet adhesion or transgenic defects → persistent DA.

- NSAI’s (indomethacin or ibuprofen) increase rather than decrease platelet-mediated thrombosis in both mice & humans, and indomethacin actually promotes platelet accumulation after endothelial injury.

- Platelets crucial for DA closure by promoting thrombotic sealing of the constricted DA and luminal remodeling.
Treatment to Prevent Patency of DA

Beneficial or Harmful?

- Despite strong association between presence of PDA & bronchopulmonary dysplasia, treatments that successfully close PDA have not resulted in reduction in the incidence of BPD.

- Despite ~ 50% reduction in incidence of PDA in Prophylactic Trials, the incidence of BPD among treated infants and those in placebo group was virtually identical.

- Relationship between PDA & development of BPD is not one of cause and effect.

(Cochrane Database Syst. Rev. 2004 (1): CD0003480)
Retinopathy of Prematurity

No causal role has been found for a PDA in ROP.
Morbidities Associated with Ligation

- Thoracotomy.
- Pneumothorax.
- Infection.
- Vocal cord paralysis.
- Impaired LV systolic performance in premature infants weighing <1000g.
- >50% of infants with BW ≤ 1000g will require inotropic support for profound hypotension during postoperative period.
- Increased incidence of neurodevelopmental abnormalities, in addition to CLD and ROP.
• Neonates treated surgically were particularly sick or whether PDA ligation itself contributed to adverse neurodevelopment.

• Strong evidence exists for causal relationship between ligation & CLD.

• Surgical ligation: longer durations of continuous positive airway pressure than those treated with indomethacin.
Conservative Treatment of PDA in the Preterm

- Adjustment of ventilation (lowering inspiratory time & increasing PEEP) and fluid restriction.
- Similar outcome to prophylactic medical treatment, but without harmful side effects of medication.
- Ductal closure rate of 94% after conservative treatment (infants ≤ 30 weeks’ gestation).
- None required ductal ligation or medical treatment.
- Larger trials needed.

Arch Dis Child Fetal Neonatal Ed 2007; 92: F244-F247.
Patency of the Ductus Arteriosus in the Premature Infant

Is It Pathologic? Should It Be Treated?

- Recent meta-analyses of RCT of indomethacine for prevention & treatment of PDA: No decrease in morbidities associated with PDA after treatment, despite success in PDA closure.

- PDA may represent a normal physiologic adaptation to allow shunting from either systemic-to-pulmonary circulation (e.g. in the first day of life) or from pulmonary-to-systemic circulation (e.g. in the presence of severe lung disease).
Treatments

- If the PDA is related to morbidity in a causal relationship, closure should result in a reduction in incidence of the morbidity.
Systematic review of RCT of indomethacin for treatment of PDA:

- Divided 22 trials into 3 groups: prophylactic therapy, presymptomatic therapy, and symptomatic therapy.

- The only significant result was the decreased incidence of PDA in the indomethacin groups.

- No difference in death, CLD, ROP, or NEC between the groups.
Dilemma

- What to do in the absence of evidence of benefit and a clear delineation of risk.
- Dilemma is limited to the care of extremely low gestational age newborns.
- Little or no justification for using COX inhibitors for preventing the persistence of ductal patency in more mature infants:
  - Risk of BPD is low
  - Spontaneous closure is common.
• Given the current lack of evidence of benefit from closure of PDA, even a symptomatic PDA, and in the consideration of potential for significant harm from therapies used to close PDA, these therapies should not be considered a standard of care.

• An acceptable alternative to routine closure of PDA would be to avoid fluid overload and observe for signs of left ventricular failure.
Neonatal medicine has a storied history of therapies, the use of which was supported by plausibility but which had unintended, and in some cases, drastic consequences.

Clinicians who believe that biological plausibility or beneficial short-term outcome (e.g. ductal closure) are sufficient justification for the use of COX inhibitors need only be reminded of other apparently beneficial therapies that proved to be harmful.

Retrolental fibroplasia (ROP) is a modern parable.
Many commonly acceptable therapies, whose use was supported by plausibility and an improvement in short-term surrogate outcomes, were ultimately proved to be ineffective, hazardous and occasionally catastrophic. (William Silverman; the father of modern neonatal intensive care)
STATE-OF-THE ART

Treatment of Persistent PDA in preterm infants: Time to accept the null hypothesis? (Journal of Perinatology 2010,30,241-252)

- Objective evidence to support these medical and surgical interventions to close PDA practices is lacking.
- Treatment may be detrimental.
Neither individual trials, pooled data from groups of randomized-controlled trials, nor critical examination of the immediate consequences of treatment provide evidence that medical or surgical closure of the ductus is beneficial in preterm infants. These conclusions are supported by sufficient evidence.
• Closing the ductus does not shorten duration of respiratory support required.
• Most infants with persistent PDA beyond 3rd day after birth - particularly with BW>1000g - do well without treatment to close PDA.
• 50 years after Burnard (1959), 49 controlled trials involving nearly 5000 infants to close PDA in preterms: No evidence that this widespread practice benefits its recipients.
Thank You