PDA Management–A Reflection on the Evidence: Does it Help with Management?

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The speaker has signed a disclosure form and indicated he has no significant financial interest or relationship with companies or the manufacturer(s) of any commercial product/service that will be discussed as part of this presentation.

Session Summary

This session will provide a brief review of the pathophysiology of PDA followed by a comprehensive review of the evidence regarding management strategies for PDA, to include prevention, medical management, and surgical management.

Session Objectives

Upon completion of this presentation, the participant will be able to:

- describe the anatomy and function of the ductus arteriosus;
- discuss the physiologic mechanism involved in closure of the ductus arteriosus;
- recognize physiologic differences in preterm neonates promoting increased incidence of patent ductus arteriosus (PDA);
- identify complications related to untreated PDA;
- discuss evidence-based approach to treating and managing PDA in preterm neonates.

References


Session Outline

See handout on the following pages.
PDA Management
A Reflection on the Evidence

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Disclosures
I have no potential conflicts of interest

Objectives
• Describe the anatomy and function of the ductus arteriosus
• Discuss the physiologic mechanism involved in closure of the ductus arteriosus.
• Recognize physiologic differences in preterm neonates promoting increased incidence of patent ductus arteriosus (PDA)
• Identify complications related to untreated PDA
• Discuss evidence based approach to treating and managing PDA in preterm neonates

PDA
• Normal fetal structure connecting upper descending aorta to main PA
• 2 – 8mm in length and 4 – 12mm in diameter
• Especially sensitive to prostaglandin-mediated relaxation and pO2-induced constriction
  • Fetal blood levels of PGE1 are high
  • PGE1 also supplied by placenta
• In fetus, 60-90% of right ventricular output is diverted across PDA from PA to Ao
• Increased pO2 after birth inhibits prostaglandin synthetase, decreasing prostaglandin levels

PDA
• Ductal closure in term infants occurs in three stages:
  • Initial smooth muscle constriction narrowing ductal lumen
  • Loss of ductal responsiveness to prostaglandin vasodilation
  • Irreversible anatomic remodeling resulting in permanent occlusion
• Functional closure usually occurs within a few hours in term neonates (90% by 48 hrs)
• Permanent closure usually occurs within 1 - 6 weeks

Reversible and incomplete DA constriction is the initial step that triggers DA closure. The luminal aspect of the DA wall adopts a prothrombotic phenotype with endothelial activation, deposition of von Willebrand factor and fibrinogen, and eventually endothelial cell (EC) detachment from the internal elastic lamina, which lead to collagen exposure. Triggers the accumulation of platelets circulating in the residual DA lumen. The platelet plug that forms across the residual lumen of the contracted DA and facilitates subsequent intraluminal remodeling.
PDA

- Accounts for up to 10% of all congenital heart defects
- Occurs in 1:1600 term live births
- Twice as common among females
- Maternal rubella virus in first trimester increases risk
- More common in infants born at high altitude

- Incidence in preterm infants approaches 30%
  - Increased incidence with lower GA and BWt
    - 34 – 36 wks: 21%
    - 28 – 30 wks: 77%
  - 55% of ELBW infants ultimately receive some form of treatment for PDA

- Why the higher incidence in preterm infants?
  - Immature ductal tissue less sensitive to pO2 mediated constriction
  - More sensitive to prostaglandin mediated vasodilation

PDA

- Clinical Presentation
  - Related to size of PDA and therefore size of shunt
  - Murmur, usually systolic in neonates
  - Oxygen requirement and difficulty weaning support
  - Widened pulse pressures
  - Bounding pulses
  - Oliguria
  - Metabolic acidosis

- Diagnosis
  - Echocardiography (Gold Standard)
  - EKG and CXR are not diagnostic

- Management Strategies
  - Prophylaxis
    - Indomethacin
  - Conservative management
    - Fluid Restriction
    - Diuretics
    - Vent management
    - Typically in term neonates or if small asymptomatic PDA

- Why treat it?
  - Contributes to morbidity from NEC, RDS, BPD
  - Implicated in development of pulmonary edema and hemorrhage, abnormal cerebral blood flow, feeding intolerance, poor weight gain
  - Retrograde flow in descending Ao in diastole leads to decreased systemic flow and predisposes to end organ ischemia
  - Large unrestricted left to right shunting across a PDA leads to LA dilation, LV overload, and progressive CHF
  - Over time may eventually lead to irreversible pulmonary hypertension
  - Increased risk of infective endocarditis

- Management Strategies
  - Medical / Pharmacological
    - Cyclooxygenase (COX) inhibitors
      - COX is key enzyme in synthesis of PGE2
      - PGE2 is vasodilator that promotes patency of DA
      - Indomethacin
        - Effective up to 14 – 28 days of age
        - Contraindicated in renal failure, active bleeding, significant thrombocytopenia, NEC or suspected NEC
      - Ibuprofen
        - Equally effective + Fewer renal and GI side effects
        - Case reports of fatal PHTN with ibuprofen
        - Similar contraindications
        - Interferes with bilirubin protein binding thereby increasing risk of kernicterus
        - Not readily available

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PDA

- Management Strategies
  - Surgical
    - Conventional vs VATS
    - Appropriate for infants with Mod to Large PDA
    - Indicated in infants who fail medical management or where medical management is contraindicated
    - Many centers perform ligation at bedside

Which approach does the evidence support?

Evidence?
No RCTs comparing outcomes of three management strategies

PDA // Prophylaxis

- Fowlie et al published a Cochrane Review in 2010 “Prophylactic IV indomethacin for preventing mortality and morbidity in preterm infants”
  - RCTs comparing prophylactic indomethacin vs placebo or no drug
  - 2872 infants in 19 trials
  - Most infants ELBW to VLBW
  - Incidence of symptomatic PDA, and surgical ligation significantly lower in treated group (especially if first dose given < 24 hrs of age)
  - Significant reduction in incidence of severe IVH
  - Treated group had significantly lower urine output
  - No effect on mortality or severe neurodevelopmental disability at 18 to 36 months

PDA // Prophylaxis

- Fanos V et al published an excellent review in Clinics Dec 2011 titled “Should we definitely abandon prophylaxis for PDA in preterm newborns?”
  - Reiterated findings published in Cochrane Review regarding indomethacin prophylaxis
  - Also addressed ibuprofen prophylaxis and prophylactic ligation
    - Ibuprofen prophylaxis associated with harmful side effects (oliguria) and no proven benefit in short term outcomes, therefore not recommended.
    - Current evidence does not support prophylactic ligation, given high rate of spontaneous closure, availability of safe and effective medical therapies and potential complications of ligation.

PDA // Prophylaxis

- Conclusion
  - Prophylaxis with indomethacin has clear short term benefits but no clear evidence of effect on mortality or neurodevelopment.
  - There are still concerns about drug safety and potential side effects
  - Its routine use should be discouraged, but strongly consider if high risk of IVH, BW <1000g and surgical ligation not available on site
PDA // Conservative Management

- **Conservative Approach**
  - Fluid Restriction
    - Avoid over 170 ml/kg
  - Diuretics
    - Furosemide stimulates renal synthesis of PGE2 which maintains ductal patency
  - PEEP
    - Reduce shunting
    - Target low O2 sats and permissive hypercapnia
    - To reduce lung injury and incidence of BPD
  - Target Hct 35 – 40

- **Diuretics**
  - Recommend thiazide diuretics

- **PEEP**
  - Reduces shunting
  - Target low O2 sats and permissive hypercapnia
  - To reduce lung injury and incidence of BPD

- **Target Hct 35 – 40**

PDA // Medical Treatment

- **When is it the right time to treat?**
  - When PDA is “Symptomatic” or “Hemodynamically Significant”
  - Clinical criteria
    - Increased vent support
    - Pulmonary hemorrhage
    - Hypotension
  - Echo criteria
    - Left atrial enlargement
    - Diameter of PDA
    - LV enlargement
  - Cerebral Doppler
    - Increased resistance index indicates cerebral steal
  - B-type Natriuretic Peptide Elevation
    - Plasma BNP correlates with size of ductal shunt
    - In infants <28 wks, BNP > 550 pg/ml on DOL #2 predicted PDA intervention
    - Changes in BNP following initiation of medication can be followed as marker of PDA closure

- **Ibuprofen vs. Indomethacin**
  - Several recent articles comparing these two COX inhibitors
  - Indomethacin has more COX 1 inhibition
  - Associated with GI, renal, cerebral side effects
  - Decreases cerebral flow and oxygen consumption, mechanism for prevention of IVH when used for prophylaxis
  - Ibuprofen has less COX 1 inhibition
  - Less vasoconstrictive side effects

- **Timing Age Parameter**
  - Prophylactic <24 h Yes if <1000 g and ligation is difficult on site
  - Early prehypertensive 2–3 days Yes if echocardiographic signs present
  - Therapeutic 3–7 days Yes if echocardiographic signs present
  - Late therapeutic >7 days Yes if clinically evident

- **In 2008, Sekar et al published evidence based recommendations for initiation of pharmacologic therapy for PDA**

- **Simultaneous efficacy with duct closure (60 – 80%)**
- **Decreased efficacy in extremely preterm infants (<26 wks)**
- **In addition only about 40% success rate with second course**
- **No evidence that more than 2 courses would result in benefit**
- **No significant difference in adverse events**
- **Trend towards more NEC with indomethacin and more BPD with ibuprofen, but not significant**
PDA // Medical Treatment

- Ibuprofen vs. Indomethacin
  - LJ Jones et al published "Network Meta-Analysis of indomethacin vs ibuprofen vs placebo for PDA in preterm infants" in 2011
  - Indomethacin twice as likely as placebo to close PDA
  - No diff in NEC, IVH, CLD and death
  - Ibuprofen twice as likely as placebo to close PDA
  - Trend toward increased in CLD
  - Indomethacin and ibuprofen equally effective in closing PDA
  - No diff in NEC, IVH, death
  - Incr risk of CLD with ibuprofen

PDA // Surgical Closure

- Indications
  - Pharm therapy or contraindicated or therapy has failed following 2 rx courses
  - Beyond 4 weeks of age medication is less likely to work

- Complications
  - Include infection, injury to recurrent laryngeal nerve, chylothorax, pneumothorax
  - Increased incidence of BPD, ROP
  - Associated with neurosensory impairment and cerebral injury

- No recent RCT comparing surgery to medical treatment

Putting it all together

- An evidence-based approach
- Supportive Care for all
  - NTE, fluid restriction, PEEP, Hct, vent management, thiazide diuretics if indicated
  - COX Inhibitors
  - No clear evidence to support prophylaxis
  - Use for symptomatic or significant PDA
  - Use up to 2 full courses of medication if tolerated
  - Ligation
  - Large PDA with high vent support
  - Failed or contraindicated med therapy