PDA in Preterm Infants: To Treat or not to Treat?

Nick Evans
Newborn Care,
Royal Prince Alfred Hospital,
University of Sydney,
Australia.
The Ductus Arteriosus does just one thing in its life:

It constricts, closes and involutes to form a ligament.

Otherwise it is just a passive conduit between the pulmonary artery and aorta.
Variable early ductus constriction.
Babies born before 30 weeks: Range of ductal constriction at 5 hrs.


n=124.
Failed constriction and early large shunts
At 5hrs, most blood through the duct is going back to the lungs.

Arch Dis Child 2000;82: F188-194

n=124 <30 weeks
Early Impact on the Systemic Circulation.
SVC Flow and the Duct.

Arch Dis Child 2000;82: F188-194

At 5 hours:
Significantly lower SVC flow
p=0.001

At 48 hours:
SVC flow not different
p=0.2
Early Impact on the Pulmonary Circulation.

- 12 of 126 babies born before 30w had pulmonary haemorrhage at a mean of 38hrs.
Haemodynamic effect of a ductal shunt:

• **On the systemic circulation.**
  – May be most important in the early hours after birth.

• **On the pulmonary circulation.**
  – Later but usually within first 48 hrs.
Maybe........

• We’ve not worried enough about early ductal shunting and....
• We’ve worried too much about later ductal shunting.
Treatment of the Ductus Arteriosus

Disclosure

I don’t know how to treat PDA.
WHAT TO TREAT WITH?
Indomethacin vs Ibuprofen?

- Similar closure rates (about 75%) but………..
- Ibuprofen less side effects.
- Oral better than intravenous Ibuprofen?

Review: Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants

Outcome: Failure to close a PDA (after single or three doses)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Oral Ibuprofen n/N</th>
<th>Intravenous Ibuprofen n/N</th>
<th>Risk Ratio N-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio N-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiraf 2008</td>
<td>5/32</td>
<td>12/32</td>
<td>26.8%</td>
<td>0.42</td>
<td>0.17, 1.05</td>
</tr>
<tr>
<td>Eldev 2012</td>
<td>6/36</td>
<td>13/34</td>
<td>29.5%</td>
<td>0.44</td>
<td>0.13, 1.02</td>
</tr>
<tr>
<td>Golcan 2011</td>
<td>6/52</td>
<td>19/50</td>
<td>43.3%</td>
<td>0.30</td>
<td>0.13, 0.76</td>
</tr>
</tbody>
</table>

Total (95% CI) 120 116 100.0% 0.37 [0.23, 0.61]

Total events: 17 (Oral Ibuprofen), 44 (Intravenous Ibuprofen)
Heterogeneity: TMR = 0.42, df = 2 (P = 0.311); P = 0.66
Test for overall effect: z = 3.06 (P = 0.0011)
Test for subgroup differences: Not applicable
Paracetamol?

- Is as good as Ibuprofen at closing PDA?

  - Less gastrointestinal and renal complications.
  - Neurodevelopmental and autism associations.
    - No difference in one study (Oncel 2014)
WHEN TO TREAT?
Treatment Regimens

• **Symptomatic:**
  - Few trials: no evidence of benefit.

• **Targeted:**
  - Heterogenous trials: More treated, less later PDA.

• **Prophylactic: best evidence**
  - **Indomethacin (n=2872)**
    • Less later PDA, major IVH and pulmonary haemorrhage
    • No difference in neurodevelopmental outcomes
  - **Ibuprofen (n=869)**
    • Less later PDA
    • No neurodevelopmental follow up
Argument 1:
PDA causes significant morbidity.
Argument 2:
PDA is an innocent bystander.

Patency of the ductus arteriosus in the premature infant: is it pathologic? Should it be treated?
Matthew M. Laughon, Michael A. Simmons and Carl L. Bose

STATE-OF-THE-ART
Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis?

WE Benitz
Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA, USA
PDA: Is it an innocent bystander?

“In preterm infants, patency of the ductus arteriosus may represent a normal physiologic adaptation…..”

Laughon et al, 2004

“…neither continued routine use of these treatments (to close PDA) nor additional clinical trials using similar designs seem justified…..”

Benitz WE, 2010
HAVE WE REALLY TESTED NEVER (OR RARELY) TREATING PDA?

Lack of evidence of effect is not the same as evidence of lack of effect.
Has not treating PDA been tested?

Treatment of pre-symptomatic PDA:

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Placebo</th>
<th>Control Arm Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahony*</td>
<td>1982</td>
<td>47</td>
<td>Yes</td>
<td>54% Medical or Surgical</td>
</tr>
<tr>
<td>Hammerman*</td>
<td>1987</td>
<td>28</td>
<td>Yes</td>
<td>79% Medical or Surgical</td>
</tr>
<tr>
<td>Weesner*</td>
<td>1987</td>
<td>26</td>
<td>Yes</td>
<td>31% Medical or Surgical</td>
</tr>
<tr>
<td>Aranda</td>
<td>2008</td>
<td>136</td>
<td>Yes</td>
<td>49% Medical or Surgical</td>
</tr>
<tr>
<td>Overmeire</td>
<td>2001</td>
<td>127</td>
<td>Yes</td>
<td>40% Medical</td>
</tr>
</tbody>
</table>
What we’ve tested in clinical trials is:

- Treating more PDAs earlier vs less PDAs later.
Reported clinical experience of not treating PDA?
• 30 babies born before 30 weeks.
• 10 developed PDA.
• All eventually closed. Not stated when they closed.
• No control group
  – Complications similar to literature and Vermont Oxford Network.
• 178 babies born before 27 weeks:
• No differences in morbidity and mortality.
• BPD rates 58% before vs 35% after (p<0.05)
• But…..
  – PDA ligation 82% before vs 0% after.
• This study compares aggressive (mainly surgical) PDA ligation vs no treatment,
• 103 babies born before 28 weeks; PDA not treated medically.
• Excluded 12 babies who died before 72 hours (3 pulm haem, one gde 4 PIVH).
• Spontaneous closure in 59/91 (64%).
• But….  
  – 20 babies PDA closure unknown  
  – One ligated.
358 babies treated for PDA
68 (18%) discharge with DA still patent
52 (81%) of these closed
12 (19%) remained patent of whom 5 (8%) had interventional closure.
Evidence Based Medicine at its best.

- **Basic Research**: Well researched disease pathophysiology with well researched treatment effect.

- **Clinical Trials**: Large with design based on good understanding of the disease.

- **Systematic Review**: Amalgamating only good quality clinical trials.
Physiological premise about PDA of most clinical trial designs.

- That early shunting is not important.
  - Assumed that any shunt not important because of pulmonary hypertension.
  - Shunt importance develops after first few days as PA pressures fall.
Evidence Base for Treatment of PDA. Have we asked the right questions?

- Physiological observations suggest haemodynamic impact of duct is early.

- **Prophylactic?** Is there a subgroup that benefit from early indomethacin and a subgroup who are harmed? Overall null effect.

- Can the subgroup that benefit be identified from early ultrasound findings?
ECHOCARDIOGRAPHIC PREDICTION OF SPONTANEOUS CLOSURE.
Predicting persistent PDA: Ductal constriction at 5 hrs and PDA.

*J Pediatrics* 2000;137:68-72
Ductus diameter at 5 hours and late grade 2-4 IVH.

Treat these early? Leave these?
A randomised placebo-controlled trial of early treatment of the patent ductus arteriosus

Martin Kluckow, Michele Jeffery, Andy Gill, Nick Evans

ABSTRACT
Objective Failure of closure of the patent ductus arteriosus (PDA) may be associated with harm. Early cardiac ultrasound-targeted treatment of a large PDA may result in a reduction in adverse outcomes and need for later PDA closure with no increase in adverse effects.

Study design Multicentre, double-blind, placebo-controlled randomised trial.

Setting Three neonatal intensive care units in Australia.

Patients and interventions Eligible infants born...
Ductal Echocardiographic Targeting and Early Closure Trial (DETECT)

Babies < 29 weeks

Cardiac US before 12 hours

n=164

Big Duct: n=94

Small Duct: No Rx n=70

Randomise

Indo n=44

Placebo n=48

Trial stopped early due to withdrawal of IV Indomethacin
# Results

## Primary Outcome – Large PDA

<table>
<thead>
<tr>
<th></th>
<th>Indomethacin</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>44</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>#Combined outcome</td>
<td>8 (18%)</td>
<td>9 (19%)</td>
<td>NS</td>
</tr>
<tr>
<td>Died</td>
<td>4</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>IVH Grade 2-4</td>
<td>2</td>
<td>6*</td>
<td>0.16</td>
</tr>
<tr>
<td>PVL/Cysts/Dilation</td>
<td>4</td>
<td>4</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Some infants had more than one outcome*
# Results

## Secondary Outcomes - Large PDA

<table>
<thead>
<tr>
<th></th>
<th>Indomethacin</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>44</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Pulmonary haemorrhage</td>
<td>4 (9%)</td>
<td>11 (23%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Pulmonary haemorrhage &lt;72 hrs</td>
<td>1 (4%)</td>
<td>10 (21%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Spontaneous intestinal perforation*</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>GIT Bleeding*</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>NEC*</td>
<td>3 (7%)</td>
<td>6 (13%)</td>
<td>NS</td>
</tr>
<tr>
<td>Postnatal steroids</td>
<td>7 (16%)</td>
<td>4 (8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Inotropes</td>
<td>10 (23%)</td>
<td>10 (21%)</td>
<td>NS</td>
</tr>
<tr>
<td>Sepsis</td>
<td>14 (32%)</td>
<td>18 (38%)</td>
<td>NS</td>
</tr>
<tr>
<td>Laser ablative treatment for ROP</td>
<td>0</td>
<td>3 (6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Oxygen/Resp support @36 wks PMA</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Open label treatment PDA</td>
<td>9 (20%)</td>
<td>19 (40%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Surgical ligation PDA</td>
<td>0</td>
<td>2 (4%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Note no increased risk*
DETECT Trial Conclusions

Targeted early treatment of large PDA resulted in:

- No difference (but underpowered) in
  - Intraventricular haemorrhage
  - Abnormal cranial ultrasound
  - Mortality
- Less open label treatment
- Clinically important trend toward less pulmonary haemorrhage
- No increased risk of SIP/NEC or GIT bleeding
How I treat PDA in 2018

How I treat PDA in 2018:
Babies born before 28 weeks

• Early Targeted Treatment.
• Cardiac ultrasound between 3 and 9 hrs
  – If PDA diameter >2.0mm
  – And Rt to Lt component of shunt < 30%
• Treat with indomethacin 0.2 mg/kg
• Repeat cardiac ultrasound 24 hrs later.
  – If PDA diameter <1.6mm, no more doses
  – If >2.0 mm, two more doses of 0.1 mg/kg
How I treat PDA in 2018: Babies born after 27 weeks

- **Symptomatic treatment. Treat if**
  - Clinically apparent PDA
  - Cardiac ultrasound criteria of significance
    - Diam > 2.0mm
    - Retrograde desc Ao diastolic flow
  - Respiratory problems likely related to ductal shunting.
- **Treat with Indomethacin or Ibuprofen**
- **Consider oral ibuprofen if tolerating some milk.**
How I treat PDA in 2018: Ducts that fail to close

- Conservative if no apparent clinical impact.
- Consider second course of COX inhibitor
  - Usually doesn’t work
- Consider course of paracetamol
  - Sometimes works
- Surgery
  - Only if ventilator dependent.
  - Since Jan 2011, of 248 babies born before 30 weeks, only 1 (0.4%) ductal ligation.
PDA ligation in NSW network <30 weeks

1/248 = 0.4%
The SMART trial: The PDA trial that needs to be done.

Babies < 29 weeks

Echo before 72 hours

Duct >1.5mm

Small Duct: No Rx

Randomise

Indo

Placebo

No subsequent PDA treatment.
Overall Conclusions: Diagnosis and physiology

- In babies with significant ducts:
  - Haemodynamic impact is often very early.

- But there is a wide individual diversity in:
  - Early ductal constriction.
  - Significance of early shunting.
  - Subsequent postnatal constriction
  - Response to treatment.
Conclusions:

In light of this diversity:

One universal truth in PDA treatment may prove elusive.

Maybe the answer lies in individualised (precision based) treatment?

That is difficult to test.
Thank for your attention.