PDA - Pathological or innocent physiologic bystander?

PDA - Not yet!!

Which PDA are we talking about?

Table 1 Rates of Spontaneous Ductus Arteriosus Closure

<table>
<thead>
<tr>
<th>Gestation</th>
<th>Closed on Day 4</th>
<th>Closed on Day 7</th>
<th>Closed at Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full term</td>
<td>100</td>
<td>100</td>
<td>Closed</td>
</tr>
<tr>
<td>27-28 weeks</td>
<td>22</td>
<td>36</td>
<td>64%</td>
</tr>
<tr>
<td>25-26 weeks</td>
<td>20</td>
<td>32</td>
<td>68%</td>
</tr>
<tr>
<td>24 weeks</td>
<td>8</td>
<td>13</td>
<td>87%</td>
</tr>
<tr>
<td>Birth weight</td>
<td>1000-1500 g</td>
<td>36</td>
<td>67%</td>
</tr>
<tr>
<td>&lt;1000 g</td>
<td>21</td>
<td>34</td>
<td>NA</td>
</tr>
</tbody>
</table>

Clyman et al; Seminars in Perinatology, 2012

PDA Morbidity/Mortality associations

<table>
<thead>
<tr>
<th>Risk</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic hypotension</td>
<td>Sarkar 2007</td>
</tr>
<tr>
<td>IVH/Low blood flow</td>
<td>Kluckow &amp; Evans 2000</td>
</tr>
<tr>
<td>Pulmonary haemorrhage</td>
<td>Kluckow &amp; Evans 2000</td>
</tr>
<tr>
<td></td>
<td>Kluckow, Gill, Evans 2013</td>
</tr>
<tr>
<td>CLD</td>
<td>Marshall 1999</td>
</tr>
<tr>
<td>NEC</td>
<td>Dollberg 2005 (OR 1.8)</td>
</tr>
<tr>
<td>ROP?</td>
<td>Gonzalez Viejo 2011</td>
</tr>
<tr>
<td>Mortality</td>
<td>Noori 2009 (OR 1.8)</td>
</tr>
<tr>
<td></td>
<td>Brooks 2005 (OR 1.8)</td>
</tr>
<tr>
<td></td>
<td>Selmer 2013 (5 fold risk)</td>
</tr>
</tbody>
</table>

Is waiting for a PDA to close spontaneously a good idea?

- Some PDA’s will be very large and have an effect on the systemic or pulmonary circulation
- A proportion of PDA’s will not close spontaneously and may require treatment at a later stage – risk of other complications, treatment less efficacious, risk of surgery
- 25% of infants with PDA at hospital discharge required a coil occlusion
- Is it possible to identify a small non significant PDA that will close vs large significant PDA that will not?
Patent Ductus Arteriosus
Diagnosis and assessment of size

Accuracy of clinical signs
- Many clinicians still rely on clinical signs & symptoms - murmur, pulse pressure, bounding pulse, active precordium
- Specificity/Sensitivity
  - Day 1 – Sensitivity = 0
  - Sensitivity reasonable only by Day 5


Accuracy of clinical signs
100 infants<1750gm Day 3-7

<table>
<thead>
<tr>
<th>Sign</th>
<th>Average Sensitivity</th>
<th>Average Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased pulse volume</td>
<td>43 (33, 60)</td>
<td>74 (58, 83)</td>
</tr>
<tr>
<td>Active precordium</td>
<td>28 (5, 42)</td>
<td>85 (59, 91)</td>
</tr>
<tr>
<td>Cardiac murmur</td>
<td>42 (33, 50)</td>
<td>87 (72, 95)</td>
</tr>
<tr>
<td>Cardiophrenic ratio</td>
<td>14 (5, 25)</td>
<td>95 (88, 98)</td>
</tr>
<tr>
<td>Relative increase</td>
<td>8 (6, 133)</td>
<td>94 (89, 96)</td>
</tr>
<tr>
<td>Increased vascular markings</td>
<td>27 (17, 35)</td>
<td>88 (78, 95)</td>
</tr>
</tbody>
</table>

Davis 1995 Arch Pediatric Adolescent Medicine

PDA Assessment
- Diagnosis
  - Pulsed Doppler
  - Direct imaging
  - Diameter assessment/Rate of constriction
- Hemodynamic effects
  - Systemic blood flow
  - Pulmonary blood flow
- Clinical effects
  - Systemic
  - Pulmonary

Assessment of PDA
Clinician Performed US (CPU)
Allows real time, serial assessment of
- Ductal patency
- Degree of ductal constriction
- Direction of shunting
- Hemodynamic significance
- Any associated lesions which may be important (eg duct dependent CHD)
Clinician Performed Ultrasound (CPU)

- Focused
- Target treatment
- Real time
- Serial
- Function

Is the ductus arteriosus patent?
Pulmonary artery diastolic turbulence

Closed duct
Patent duct

Is the ductus arteriosus patent?
Colour Doppler imaging of the duct.

Closed duct
Patent duct

Measurement of ductal diameter

Diameter 2.5 mm
Diameter 0.8 mm

Duct diameter has best correlation with Qp:Qs

- 69 echo’s on 24 prems (<1500g) with minimal atrial shunt.
- Correlation with QpQs.

- PDA color diameter $r = 0.8$
- LA:AO ratio $r = 0.45$
- LVSV or LVO $r = 0.38$
- Descending Aortic diastolic flow – significant difference

Kluckow & Evans. J Paediatrics 1995
Evans et al. J Paediatrics 1994
Patent Ductus Arteriosus
Predicting PDA persistence?

Duct diameter on Day 1 predicts later symptomatic PDA

83% sensitive, 90% specific for infants <29 weeks in predicting subsequent PDA requiring treatment.

126 babies born before 30 weeks Kluckow & Evans. J.Pediatrics 1995

Methods
Flow pattern characterisation

Pulmonary HT (1) Growing (2)

Pulsatile (3) Closing (4)

Pulmonary HT (1)
Growing (2)

Type 3-4

Pulsatile (3)
Closing (4)

Echo Doppler flow patterns

Pulmonary Hypertension
Growing pattern

Pulsatile pattern
93.5% sensitive, 100% specific for predicting a clinically significant PDA

Su et al Arch Dis Child Fetal Neonatal 1999;84

Measurements
Assessment of ductal significance

- Possible criteria.
  - LA:AO ratio reflecting left atrial dilation. Silverman 1974
  - LV output or stroke volume. Wathir 1989
  - Absent or reversed descending aortic diastolic flow.
  - Increased diastolic velocity in the LPA. Suzumura Pediatr Int 2001
  - Ductal flow patterns Su et al 1999
  - SVC Flow/LVO ratio El Hajjar et al Arch Dis Child 2005
  - Ductal diameter on 2D measure or color flow >1.5mm, 2mm sahn Circulation 1978, Kluckow et al J.Pediatrics 1995

Table 1: Assessment of ductal significance

<table>
<thead>
<tr>
<th>Criteria (quantified)</th>
<th>Morphology/position of duct flow</th>
<th>No PDA</th>
<th>Small</th>
<th>Medium</th>
<th>Large</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic of the ductus arteriosus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ductal diameter (mm)</td>
<td>Normal/midline, duct cine view</td>
<td>0</td>
<td>1.5</td>
<td>3.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Ductal diameter (mm)</td>
<td>Normal/midline, right duct view</td>
<td>0</td>
<td>1.5</td>
<td>3.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Antegrade PDA, diastolic flow (sec)</td>
<td>PWD at left ductal entry</td>
<td>0</td>
<td>≥2</td>
<td>3.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial enlargement</td>
<td>ice-echo, long axis view</td>
<td>1.35</td>
<td>1.64</td>
<td>1.84</td>
<td>2.04</td>
</tr>
<tr>
<td>Left ventricular size</td>
<td>ice-echo, long axis view</td>
<td>1.06</td>
<td>1.24</td>
<td>1.42</td>
<td>1.60</td>
</tr>
<tr>
<td>E-wave mitral valve</td>
<td>Ew Brandes Doppler</td>
<td>&lt;1</td>
<td>1.5</td>
<td>3.0</td>
<td>4.0</td>
</tr>
<tr>
<td>PWD max</td>
<td>PWD between subclavian and main arteries</td>
<td>≤150</td>
<td>150-500</td>
<td>500-900</td>
<td>≥900</td>
</tr>
<tr>
<td>SVC Flow/LVO Ratio</td>
<td></td>
<td>≤0.30</td>
<td>0.30-30</td>
<td>30-90</td>
<td>≥90</td>
</tr>
<tr>
<td>Ductal flow (mm/sec)</td>
<td></td>
<td>≤1.5</td>
<td>1.5-4</td>
<td>4-6</td>
<td>≥6</td>
</tr>
<tr>
<td>Large</td>
<td></td>
<td>≤1.5</td>
<td>1.5-4</td>
<td>4-6</td>
<td>≥6</td>
</tr>
</tbody>
</table>


Summary
Assessment of PDA significance

PDA Disease staging?

Table 1: Proposed staging system (adapted from McLaren and Holloway, updated clinical staging system for decision of patient during pregnancy) for determination of the hemodynamically significant ductal arterioles (PDA), which is based on clinical and echocardiographic criteria.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No evidence of significant ductus arteriosus (DAM)</td>
</tr>
<tr>
<td>II</td>
<td>Significant ductus arteriosus (DAM) present</td>
</tr>
<tr>
<td>III</td>
<td>Clinical evidence of ductus arteriosus (DAM)</td>
</tr>
<tr>
<td>IV</td>
<td>Echocardiographic evidence of ductus arteriosus (DAM)</td>
</tr>
</tbody>
</table>

Summary

Assessment of PDA significance

- First week of life
  - Duct size on color Doppler, Flow pattern
  - Descending aortic flow pattern
  - LPA velocities (Mean >0.41 m/sec, End diastolic>0.25m/sec)
- Later (after 7 days) – longitudinal assessment important!
  - Clinical – cardiovascular (CCF), respiratory
  - Duct size on color Doppler (>1.5mm)
  - Diastolic descending aortic flow – absent/reversed
  - Dilation (LA:Ao >1:1.5, LVEDD>15mm/kg)
  - Left ventricular output very high (>450ml/kg/min)

Early targeted intervention for PDA

- Early – in the first 24 hours before the hemodynamic complications of a PDA manifest
- Targeted – select a group of patients who are most likely to benefit from PDA closure or whom are likely to be exposed to treatment in the future
- Intervention – Medical (COX inhibitors) – indomethacin vs ibuprofen

Non targeted prophylaxis

Early COX Inhibitor

Benefits
- Close PDA
- Reduce IVH

2yr follow up

Improved outcome

PDA – direction of shunt

126 infants, <30 weeks, First 5 hours of life

PDA vs Respiratory physiology

- Normal term baby physiology - DA closed by 24 hours
- Improving respiratory management – many of our smallest infants on minimal respiratory support early
- Slow rate of constriction of the DA - significant systemic/pulmonary pressure difference across a large PDA
- Systemic to pulmonary shunt develops
- Risks of morbidity can follow
Systemic to pulmonary shunt

Early effects
- Hypotension/Low SBF
- Cerebral-IVH/PVL
- Decreased gut blood flow
- NEC
- Renal impairment
- ?Mortality

Later effects
- Pulmonary oedema/haemorrhage
- Possible BPD
- Cardiac failure
- Need for ligation

Left pulmonary artery flow and PDA significance

Suzumurza H, Pediatrics International 2001

Left pulmonary artery (LPA) flow and PDA significance

- Total LPA flow
- Diastolic flow velocities
  - Peak diastolic
  - End Diastolic (>0.25 m/sec)
  - Mean diastolic (>0.41 m/sec)

Suzumurza H, Pediatrics International 2001
El-Harjar, Arch Dis Child 2005
Hiraishi, Circulation 1987

Left ventricular output increases

Iyer & Evans, Arch Dis Child 1994, Knight D Unpublished

LA:AO ratio

1.4 1.9

Volume of ductal shunt & dilation of cardiac chambers

- LA:Aortic ratio
  - Variable usefulness in studies, Not reliable Day 1
  - Role of PFO in decompressing LA
    - Closed PDA = 1.17
    - Restrictive PDA = 1.21
    - Wide Open PDA = 1.61
  - Cut off of 1:1.5 is 79% sensitive, 95% specific

- LV End Diastolic Diameter
  - >15 mm/kg = Large PDA

Iyer & Evans, Arch Dis Child 1994, Knight D Unpublished

El-Harjar, Arch Dis Child 2005
Hiraishi, Circulation 1987

Iyer & Evans, Arch Dis Child 1994, Knight D Unpublished

Hirsashi, Circulation 1987

Iyer & Evans, Arch Dis Child 1994, Knight D Unpublished

El-Harjar, Arch Dis Child 2005
Hirsashi, Circulation 1987

Iyer & Evans, Arch Dis Child 1994, Knight D Unpublished

Hirsashi, Circulation 1987

Iyer & Evans, Arch Dis Child 1994, Knight D Unpublished

Hirsashi, Circulation 1987
Haemodynamic importance
Descending Aortic diastolic flow

- Closed ductus
- Large ductus

Left ventricular output

- LVO in first 48 hrs
- Ductal diameter>median
- Reverse flow in DescAo vs no reverse flow
- Normal 200-300mls/kg/min
- LVO>450mls/kg/min suggests a large shunt with hemodynamic effect

Haemodynamic importance
Effect on SMA/Renal artery flow

- 19 infants<1000gms with HSPDA vs controls
- Before and after treatment with Mefenamic acid

Hemodynamic importance
Cerebral perfusion effects

- 8 infants with HS PDA (Echo)
- PDA size defined by carotid flow patterns
- 10 controls

Hemodynamic importance
ACA Pulsatility Index

- Perlman J Pediatrics 1981
Larger PDA
Reduced systemic blood flow/BP

<table>
<thead>
<tr>
<th>Low SVC Flow</th>
<th>Normal SVC Flow</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (hours)</td>
<td>$9$ hrs</td>
<td>$5$ hrs</td>
</tr>
<tr>
<td>Ductal diameter (mm)</td>
<td>$2.1 (0.9-3)$</td>
<td>$1.6 (0.3-3.5)$</td>
</tr>
<tr>
<td>Age (hours)</td>
<td>$12$ hrs</td>
<td>$12$ hrs</td>
</tr>
<tr>
<td>Ductal diameter (mm)</td>
<td>$1.35 (0-2.8)$</td>
<td>$1.1 (0-2.8)$</td>
</tr>
</tbody>
</table>

- Infants < 1000gms
- Day 1-7 of life
- Mean BP lower in infants with HS PDA
- HS PDA = LA:Ao ratio > 1.5 with PDA on ECHO

PDA - Effect on IVH?

Fowlie 2011 Prophylactic indomethacin for prevention of severe IVH (3/4)

Pulmonary Hemorrhage vs Ductal diameter
121 babies, <30wks, First 6 hours

<table>
<thead>
<tr>
<th>Pulmonary hemorrhage (n=12)</th>
<th>No pulmonary hemorrhage (n=109)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal diameter (mm)</td>
<td>$2.0 (0.7-3.4)$</td>
<td>$0.5 (0.3-3.5)$</td>
</tr>
<tr>
<td>Maximum left to right ductal</td>
<td>$1.2 (0.7-2.7)$</td>
<td>$1.6 (0.3-3.1)$</td>
</tr>
<tr>
<td>Abnormal velocity (m/s)</td>
<td>$2.8 (1.75-3.63)$</td>
<td>$2.13 (0.7-3.75)$</td>
</tr>
<tr>
<td>Artial shunt diameter (mm)</td>
<td>$0.63 (0.3-1.3)$</td>
<td>$0.45 (0.1-1.2)$</td>
</tr>
<tr>
<td>Right ventricular output</td>
<td>$257 (158-407)$</td>
<td>$223 (91-465)$</td>
</tr>
<tr>
<td>Estimated ductal area</td>
<td>$85 (9.216)$</td>
<td>$50 (29.3)$</td>
</tr>
<tr>
<td>Estimated blood flow (mll/hr/min)</td>
<td>$228 (123-598)$</td>
<td>$236 (101-569)$</td>
</tr>
</tbody>
</table>

Evans & Kluckow J Pediatrics 2000

PDA & need for ligation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events</th>
<th>Total Events</th>
<th>Total Weight</th>
<th>M1 Ratio, %DF (95% CI)</th>
<th>Risk Ratio, %DF (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>$58$</td>
<td>$105$</td>
<td>$105$</td>
<td>$0.94 (0.1-1.8)$</td>
<td>$0.94 (0.1-1.8)$</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>$43$</td>
<td>$93$</td>
<td>$93$</td>
<td>$1.00 (0.2-4.1)$</td>
<td>$1.00 (0.2-4.1)$</td>
</tr>
<tr>
<td>Placebo</td>
<td>$56$</td>
<td>$105$</td>
<td>$105$</td>
<td>$1.00 (0.1-1.8)$</td>
<td>$1.00 (0.1-1.8)$</td>
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</tr>
</tbody>
</table>


PDA & need for ligation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>Events</th>
<th>Total Events</th>
<th>Total Weight</th>
<th>M1 Ratio, %DF (95% CI)</th>
<th>Risk Ratio, %DF (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>$58$</td>
<td>$105$</td>
<td>$105$</td>
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<td>$1.00 (0.2-4.1)$</td>
</tr>
</tbody>
</table>

Fowlie & Davis Cochrane review 2010

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Assessment of PDA significance

- First week of life
  - Duct size on color Doppler, Flow pattern
  - Descending aortic flow pattern
  - LPA velocities (Mean >0.41 m/sec, End diastolic>0.25m/sec)
- Later (after 7 days) – longitudinal assessment important!
  - Clinical – cardiovascular (CCF), respiratory
  - Duct size on color Doppler (>1.5mm)
  - Diastolic descending aortic flow – absent/reversed
  - Dilation (LA:Ao >1:1.5, LVEDD>15mm/kg)
  - Left ventricular output very high (>450ml/kg/min)

When should we treat a PDA?

<table>
<thead>
<tr>
<th>Prophylaxis (first 0-12 hours)</th>
<th>Targeted Prophylaxis (6-24 hours)</th>
<th>Pre-symptomatic (echo-based)</th>
<th>Early symptomatic (hemodynamic symptoms)</th>
<th>Late symptomatic (early signs of organ failure)</th>
<th>Very late (heart failure)</th>
<th>No treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>?</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Pre-symptomatic</td>
<td>Early symptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>(echo-based)</td>
<td>(echo-based)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Early symptomatic</td>
<td>Late symptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>(hemodynamic symptoms)</td>
<td>(early signs of organ failure)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>No treatment</td>
<td>No treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

PDA Management

Does earlier usage mean less side effects?
- Prophylactic trials – no increase in GIT perforation, NEC or bleeding

<table>
<thead>
<tr>
<th>TIPP Trial</th>
<th>Indomethacin</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIT Perforation</td>
<td>36/601</td>
<td>32/601</td>
<td>0.56</td>
</tr>
<tr>
<td>NEC</td>
<td>64/961</td>
<td>58/961</td>
<td>0.53</td>
</tr>
<tr>
<td>DETECT Trial</td>
<td>GIT Perforation/Bleed</td>
<td>0/44</td>
<td>0/48</td>
</tr>
<tr>
<td>NEC</td>
<td>3/44</td>
<td>6/48</td>
<td>NS</td>
</tr>
</tbody>
</table>

HC Prophylaxis Trial

<table>
<thead>
<tr>
<th>GIT perforation</th>
<th>GIT perforation no HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>with HC 16/184 (8.7%)</td>
<td>2/91 (2.2%)</td>
</tr>
</tbody>
</table>

SIP: prophylaxis vs treatment

SIP vs No SIP

More SIP

Does earlier usage enhance efficacy?
139 ELBW infants, Echo Dx PDA

85% 11%

Fig. 5. Timing of the first dose of indomethacin and its effect on PDA closure rate (P=0.012)
Targeted early treatment of infants at high risk of persistent PDA

- Clinical risk factors
  - GA (<25 weeks only 15-20% chance of duct closure*)
  - Lack of antenatal steroid cover
  - Need for mechanical ventilation*

- Ultrasound factors
  - Size/diameter of PDA – Color Doppler diameter >1.5mm#
  - Flow pattern&
  - Multiple parameter assessment – (P McNamara/A Sehgal)

- Clinical effects of shunt
  - Systemic under perfusion/Steal effect
  - Pulmonary flooding

- Others
  - Biomarkers@


How to target?

Clinical risk factors

- GA (<25 weeks only 15-20% chance of duct closure*)
- Lack of antenatal steroid cover
- Need for mechanical ventilation*

Ultrasound factors

- Size/diameter of PDA – Color Doppler diameter >1.5mm#
- Flow pattern&
- Multiple parameter assessment – (P McNamara/A Sehgal)

Clinical effects of shunt

- Systemic under perfusion/Steal effect
- Pulmonary flooding

Others

Biomarkers@


DETECT TRIAL
Ductal Echocardiographic Targeting and Early Closure Trial

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2University of Sydney, Australia
3King Edward Memorial Hospital, Perth, Australia
4Royal Prince Alfred Mothers and Babies Hospital, Sydney, Australia

#Funded by North Shore Heart Research Foundation

Aim

1. Perform an early(3-12 hr) screen of <29 wk GA infants using ultrasound to classify PDA size as Large (>50th percentile) or Small (<50th percentile)
2. Randomise infants with Large PDA to receive indomethacin(0.2, 0.1, 0.1 mg/kg) or placebo before 12 hours of age
3. Open label treatment controlled but allowed
   - Early (1st 72hrs) – Pulmonary haemorrhage, prolonged refractory hypotension(>4hrs)
   - Late (after 72hrs) – HD significant on Echo(>1.5mm, No or reverse flow in DAo) with clinical effect

Outcome measure

Primary*

- Combined death and/or abnormal cranial US at hospital discharge
  - Abnormal cranial US = Grade 2-4 IVH/PVL/Cysts

*Underpowered due to trial stopping early (lack of indomethacin in Australia)

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>Combined outcome</td>
<td>8</td>
<td>9</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>
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</table>

*Some infants had more than one outcome

Kluckow, Jeffery, Gill & Evans, Arch Dis Child 2013
### Results

#### Secondary Outcomes - Large PDA

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<td>All Pulmonary haemorrhage</td>
<td>4 (9%)</td>
<td>11 (23%)</td>
<td>0.06</td>
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<tr>
<td>Pulmonary haemorrhage, First 72 hrs</td>
<td>1</td>
<td>10</td>
<td>0.008</td>
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<tr>
<td>GIT Perforation, GIT Bleeding*</td>
<td>0</td>
<td>0</td>
<td>NS</td>
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<tr>
<td>NEC*</td>
<td>3 (7%)</td>
<td>6 (13%)</td>
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<td>Creatinine &gt;220umol/L</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
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<tr>
<td>Postnatal steroids</td>
<td>10 (23%)</td>
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<td>14 (32%)</td>
<td>18 (38%)</td>
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<tr>
<td>Laser ablation treatment for ROP</td>
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<td>NS</td>
</tr>
<tr>
<td>Open label treatment PDA</td>
<td>9 (20%)</td>
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<tr>
<td>Surgical ligation PDA</td>
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<td>2 (4%)</td>
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* Kruckow, Jeffery, Gill & Evans. Arch Dis Child 2013

### No side effects if treated early

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### Early treatment benefits

- Infants at high risk of PDA
  - Shunt related benefits
    - In the right time frame to reduce IVH, hypotension, low systemic blood flow, pulmonary haemorrhage
  - PDA closed early – less morbidity/mortality
  - Less ligation which is clearly associated with risk
  - Better timing – less likely to be significantly fed, less later treatment and risk due to long standing ductal steal and borderline gut/kidney perfusion
  - More efficacious

* Kruckow, Jeffery, Gill & Evans. Arch Dis Child 2013

### Practicalities

#### Early targeted treatment PDA

- High risk group
  - GA <27 weeks
- Significant respiratory support @ 27/28 weeks
- Early cardiac ultrasound first 24 hours
- PDA >2.0mm first 6 hrs, >1.5mm 6-24 hrs with either
  - Reverse flow in descending aorta and/or
  - Increased LPA end diastolic velocity and/or
  - Clinical signs – hypotension, increased ventilation, pulmonary haemorrhage
When should we treat a PDA?

Hoellering A J Paed and Child Health 2009

The final word in ductal treatment?
- 49 Randomised controlled trials
- 5000 babies
- Primary outcome of ductal closure achieved
- No medium/long term benefits using these analysis methods (Except IVH prevention)
- Persisting uncertainty
- Are we doing something wrong here?

Variable enrolment criteria

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The establishment of the diagnosis of a PDA and the criteria used for the definition of an HS/DA in 67 randomised trials evaluating ductal treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>How was the PDA diagnosis established</td>
<td>Studies (%)</td>
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<tr>
<td>Not mentioned</td>
<td>17 (25)</td>
</tr>
<tr>
<td>Clinical only</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Clinical</td>
<td>41 (62)</td>
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<tr>
<td>Ultrasound only</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

HS/DA = haemodynamically significant duct; PDA = patent ductus arteriosus.

Variable definitions of HSPDA

<table>
<thead>
<tr>
<th>Table 2</th>
<th>The clinical and ultrasound parameters used in the definition of an HS/DA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical criteria used for the definition of an HS/DA</td>
<td>Studies</td>
</tr>
<tr>
<td>Respiratory signs</td>
<td>22</td>
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<tr>
<td>Physical signs</td>
<td>36</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>7</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>26</td>
</tr>
</tbody>
</table>

HS/DA = haemodynamically significant duct.

The final word in ductal treatment?
- Poor patient selection (GA/PNA)
- No/minimal documentation of underlying physiology
- Definition variations – PDA/HSPDA
- No assessment of physiological subgroups
- Lack of understanding of mechanisms
- Homogenize a heterogeneous group
- True benefits masked by movement in both directions

Meta-analysis of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis?

R. Beck

Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA, USA
Early (Day 1) treatment?

- Reduce effects of systemic hypoperfusion
- Refractory hypotension
- Cerebral injury
- Gastrointestinal compromise
- Protective effect from IVH if indomethacin used
- Avoid complications of pulmonary flooding
  - Pulmonary haemorrhage
  - Higher ventilation requirements
- But – need to be able to select infants who have a high risk of PDA needing treatment as both COX inhibitors may have adverse pulmonary effects (?via fluid retention)

Targeted early (prophylactic) therapy for PDA

- Using clinical criteria
  - Gestational age (<25 weeks*)
  - Lack of antenatal steroid cover
  - Need for mechanical ventilation (25-28 weeks with RDS*)
- Using early echocardiography criteria
  - Color Doppler diameter >1.5 mm in 24 hours*
  - Kluckow et al J Pediatrics 1996 - 17% chance of spontaneous ductal closure
  - Other criteria – DD/kg, LPA velocities, LA:Ao ratio, Ductal flow patterns
- DETECT (Ductal Echocardiographic Targeting and Early Closure Trial)

Conclusions

- Too simplistic to say treat all or don’t treat any
- Need to understand the physiological effect of a PDA
- Categorization of effects will allow identification of a significant PDA
- Targeting of treatment may allow benefits of treatment without increasing harm

Conclusions

- Focus on developing guidelines to identify infants at high risk of adverse effect from PDA
- This will require more physiological approach using CPU and clinical effects
- More study and understanding of pharmacokinetics and pharmacodynamics of PG inhibitors

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