Ductus treatment – best practise today and future prospects

Evidence-based Neonatology Stockholm 2-5 June 2011

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Hôpital Erasme – ULB Brussels – Belgium
President Belgian Society of Neonatology

1. Pharmacological treatment
   - Prophylactic or late?
   - Indomethacin or ibuprofen?
   - Higher-, prolonged-, or additional courses?
   - Oral administration?

2. Surgical treatment
   - Pro’s & con’s?
   - When to go for ligation?
Patent ductus arteriosus (PDA) is not disappearing

Rate of PDA in preterm infants in NICHD neonatal research network (2003-2007)

<table>
<thead>
<tr>
<th>Week</th>
<th>Symptomatic PDA in survivors &gt;12 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 wk (n = 1223)</td>
<td>60 (31-80)</td>
</tr>
<tr>
<td>25 wk (n = 1426)</td>
<td>55 (25-92)</td>
</tr>
<tr>
<td>26 wk (n = 1530)</td>
<td>48 (21-88)</td>
</tr>
<tr>
<td>27 wk (n = 1811)</td>
<td>42 (14-80)</td>
</tr>
<tr>
<td>28 wk (n = 1967)</td>
<td>32 (13-60)</td>
</tr>
</tbody>
</table>

Data expressed as % (center range)

Overall 46 % PDA in VLBW

Patent ductus arteriosus (PDA) is not disappearing

Rate of symptomatic PDA versus closed PDA in Belgium 2008
n = 1468  <1500g or <32w

(Ref: Nic College website)

- closed PDA : 74 %
- clinical PDA : 26 %
Patent ductus arteriosus decreases with postnatal age

1. Pharmacological treatment

- Prophylactic or late treatment?
- Indomethacin or ibuprofen?
- Higher-, prolonged-, or additional courses?
- Oral administration?
The best treatment approach for PDA

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservative</td>
<td>High spontaneous closure rates</td>
<td>Delaying treatment decreases response rate to COX inhibition</td>
</tr>
<tr>
<td></td>
<td>Minimizes exposure to drugs</td>
<td>PDA shunt may cause morbidity</td>
</tr>
<tr>
<td>Pharmacological</td>
<td>High success rates (30-80%)</td>
<td>Adverse effects of COX inhibitors</td>
</tr>
<tr>
<td>Surgical ligation</td>
<td>+/- 100% success rate when pharmacologic treatment is contraindicated or failed</td>
<td>Complications of surgery (hypotension, vocal cord paralysis, neurosensory impairment, BPD, …)</td>
</tr>
</tbody>
</table>

Indomethacin prophylaxis for preventing PDA

<table>
<thead>
<tr>
<th>Metaanalysis</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Symptomatic PDA</td>
<td>0.44</td>
<td>0.38 - 0.50</td>
</tr>
<tr>
<td>- PDA surgical ligation</td>
<td>0.51</td>
<td>0.37 - 0.71</td>
</tr>
<tr>
<td>- Severe IVH</td>
<td>0.66</td>
<td>0.53 - 0.82</td>
</tr>
<tr>
<td>- Mortality</td>
<td>0.96</td>
<td>0.81 - 1.12</td>
</tr>
<tr>
<td>- Death or severe neurodevelopmental disability at 18 to 36 m</td>
<td>1.02</td>
<td>0.90 - 1.15</td>
</tr>
</tbody>
</table>

Fowlie P. Cochrane Database Syst Rev 2010
Metaanalysis of prophylaxis for PDA

<table>
<thead>
<tr>
<th></th>
<th>Indomethacin</th>
<th>Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>n</td>
<td>2872</td>
<td>672</td>
</tr>
<tr>
<td>PDA</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Ductal ligation</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>IVH</td>
<td>↓</td>
<td>=</td>
</tr>
</tbody>
</table>


Indomethacin prophylaxis revisited

Alfaleh K:
Conclusive evidence is still lacking

DeMauro SB, Schmidt B:
Why would a sane clinician not prescribe prophylactic indomethacin?
### Pooled results of prophylaxis for PDA

#### Indomethacin IV Prophylaxis

<table>
<thead>
<tr>
<th>Ductal Patency</th>
<th>Odds Ratio (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2/0 (95% CI)</td>
<td>2/0 (95% CI)</td>
<td>2/0 (95% CI)</td>
</tr>
<tr>
<td>BPD</td>
<td>11/2 (95% CI)</td>
<td>12/2 (95% CI)</td>
<td>17/3 (95% CI)</td>
</tr>
<tr>
<td>Death or BPD</td>
<td>7/5 (95% CI)</td>
<td>8/5 (95% CI)</td>
<td>10/4 (95% CI)</td>
</tr>
<tr>
<td>Other CLD</td>
<td>3/1 (95% CI)</td>
<td>3/1 (95% CI)</td>
<td>3/1 (95% CI)</td>
</tr>
<tr>
<td>NEC</td>
<td>13/2 (95% CI)</td>
<td>15/2 (95% CI)</td>
<td>20/4 (95% CI)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4/1 (95% CI)</td>
<td>6/1 (95% CI)</td>
<td>8/1 (95% CI)</td>
</tr>
<tr>
<td>IVH</td>
<td>15/2 (95% CI)</td>
<td>15/2 (95% CI)</td>
<td>20/3 (95% CI)</td>
</tr>
<tr>
<td>IVH &gt; Grade 2</td>
<td>5/2 (95% CI)</td>
<td>6/1 (95% CI)</td>
<td>10/1 (95% CI)</td>
</tr>
<tr>
<td>ROP</td>
<td>5/1 (95% CI)</td>
<td>7/1 (95% CI)</td>
<td>9/1 (95% CI)</td>
</tr>
<tr>
<td>ROP &gt; Grade 2</td>
<td>2/1 (95% CI)</td>
<td>4/1 (95% CI)</td>
<td>4/1 (95% CI)</td>
</tr>
<tr>
<td>Bayley MDI</td>
<td>2/1 (95% CI)</td>
<td>2/1 (95% CI)</td>
<td>2/1 (95% CI)</td>
</tr>
<tr>
<td>Bayley PDI</td>
<td>1/1 (95% CI)</td>
<td>1/1 (95% CI)</td>
<td>1/1 (95% CI)</td>
</tr>
<tr>
<td>WPPSI</td>
<td>1/1 (95% CI)</td>
<td>1/1 (95% CI)</td>
<td>1/1 (95% CI)</td>
</tr>
<tr>
<td>Severe DD</td>
<td>4/1 (95% CI)</td>
<td>3/1 (95% CI)</td>
<td>4/1 (95% CI)</td>
</tr>
<tr>
<td>HSI</td>
<td>3/1 (95% CI)</td>
<td>3/1 (95% CI)</td>
<td>3/1 (95% CI)</td>
</tr>
</tbody>
</table>

#### Indomethacin PO/IV Prophylaxis

<table>
<thead>
<tr>
<th>Ductal Patency</th>
<th>Odds Ratio (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1/5 (95% CI)</td>
<td>2/7 (95% CI)</td>
<td>5/8 (95% CI)</td>
</tr>
<tr>
<td>BPD</td>
<td>1/5 (95% CI)</td>
<td>1/2 (95% CI)</td>
<td>5/8 (95% CI)</td>
</tr>
<tr>
<td>Death or BPD</td>
<td>1/5 (95% CI)</td>
<td>1/2 (95% CI)</td>
<td>2/4 (95% CI)</td>
</tr>
<tr>
<td>Other CLD</td>
<td>1/5 (95% CI)</td>
<td>1/2 (95% CI)</td>
<td>2/4 (95% CI)</td>
</tr>
<tr>
<td>NEC</td>
<td>1/5 (95% CI)</td>
<td>2/7 (95% CI)</td>
<td>5/8 (95% CI)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1/5 (95% CI)</td>
<td>4/2 (95% CI)</td>
<td>4/7 (95% CI)</td>
</tr>
<tr>
<td>IVH</td>
<td>1/5 (95% CI)</td>
<td>1/2 (95% CI)</td>
<td>5/8 (95% CI)</td>
</tr>
<tr>
<td>IVH &gt; Grade 2</td>
<td>1/5 (95% CI)</td>
<td>1/2 (95% CI)</td>
<td>4/7 (95% CI)</td>
</tr>
<tr>
<td>ROP</td>
<td>1/5 (95% CI)</td>
<td>2/7 (95% CI)</td>
<td>3/15 (95% CI)</td>
</tr>
</tbody>
</table>

#### Indomethacin PO/IV Prophylaxis

<table>
<thead>
<tr>
<th>Ductal Patency</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>5/8 (95% CI)</td>
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<tr>
<td>BPD</td>
<td>5/8 (95% CI)</td>
</tr>
<tr>
<td>Death or BPD</td>
<td>2/4 (95% CI)</td>
</tr>
<tr>
<td>Other CLD</td>
<td>2/4 (95% CI)</td>
</tr>
<tr>
<td>NEC</td>
<td>2/4 (95% CI)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4/7 (95% CI)</td>
</tr>
<tr>
<td>IVH</td>
<td>5/8 (95% CI)</td>
</tr>
<tr>
<td>IVH &gt; Grade 2</td>
<td>4/7 (95% CI)</td>
</tr>
<tr>
<td>ROP</td>
<td>3/1 (95% CI)</td>
</tr>
</tbody>
</table>

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Benitz WE. J Perinatol 2010
Which treatment approach for PDA?

Lack of evidence of benefits of treatment

- Bose CL & Laughon MM ADC 2007
- Benitz WE J Perinatol 2010

Pooled results of treatment for PDA

Benitz WE. J Perinatol 2010
1. Pharmacological treatment

- Prophylactic or late treatment?
- Indomethacin or ibuprofen?
- Higher-, prolonged dosing?
- Oral administration?

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**Cyclooxygenase inhibiting selectivity**

*Figure 2.* Concentrations of Various Drugs Required to Inhibit the Activity of Cyclooxygenase-1 and Cyclooxygenase-2 by 50 Percent (IC$_{50}$) in Assay of Whole Blood. Each point is the mean of three or four values.$^{14}$ $^{19}$ Drugs plotted below the diagonal line indicating equivalence are more potent inhibitors of cyclooxygenase-2 than drugs plotted on or above the line. 6-MNA denotes 6-methoxy-2-naphthylacetic acid.

FitzGerald GA. New Engl J Med 2001
Metaanalysis of treatment of PDA

<table>
<thead>
<tr>
<th></th>
<th>Indomethacin*</th>
<th>Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>n</td>
<td>97</td>
<td>956</td>
</tr>
<tr>
<td>PDA</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Duration of FiO₂</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Oliguria</td>
<td>↑ minimal</td>
<td></td>
</tr>
</tbody>
</table>

* Early symptomatic treatment
Cooke, Cochrane, 2002
Ohlsson, Cochrane, 2010

Metaanalysis ibuprofen vs indomethacin for PDA

- **Similar closure of PDA**  
  n = 956  19 studies  
  RR 0.94 (95% CI 0.76 – 1.17)

- **Less NEC with ibuprofen**  
  n = 865  15 studies  
  RR 0.68 (95% CI 0.47 - 0.99)

- **Less renal insufficiency with ibuprofen**
  - No differences for other neonatal outcomes: mortality, BPD, IVH, infections, intestinal perforation, ...

Ohlsson et al., Cochrane, 2010
Gastrointestinal side effects of NSAIDs

Hierarchy of gastric damage due to NSAIDs in volunteer endoscopy studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>pKa</th>
<th>Lanza Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>2000</td>
<td>3.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Naproxen</td>
<td>1000</td>
<td>4.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>100</td>
<td>4.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>150</td>
<td>4.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>2400</td>
<td>4.7</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>1200</td>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>75</td>
<td>5.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Fenbufen</td>
<td>1000</td>
<td>5.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Nimesulide</td>
<td>200</td>
<td>6.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Placebo</td>
<td>700</td>
<td>7.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>500</td>
<td>8.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>800</td>
<td>9.6</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Additional risks of NSAID treatment of PDA in preterm infants

- **Spontaneous ileal perforation (SIP)**
  indomethacin + ibuprofen

- **Increased bleeding tendency**
  indomethacin
  - Corazza MS et al. J Pediatr 1984

- **Elevated unbound bilirubin levels**
  ibuprofen
  - Ambat MT et al. J Perinatol 2008
  - Diot C et al. Early Hum Dev 2010

- **Pulmonary hypertension**
  ibuprofen
  - Gournay. Lancet. 2002;359:1486
Impact of NSAIDs on cerebral perfusion

Indomethacin induced changes in cerebral circulation:
- Cerebral blood flow ↓
- Cerebral blood volume ↓
- Cerebral oxygen delivery ↓


Evolution of PDA treatments over time

Infants <32w or <1500g receiving PDA treatment (Belgium 2001-2008)

NIC college 2009 Belgium
1. Pharmacological treatment

- Prophylactic or late treatment?
- Indomethacin or ibuprofen?
- Higher-, prolonged-, or additional courses?
- Intravenous or oral route?

Conventional NSAID dosing (per kg) for PDA

<table>
<thead>
<tr>
<th>Indomethacin</th>
<th>Age</th>
<th>1st dose</th>
<th>2nd dose</th>
<th>3rd dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 48 h</td>
<td>0,2 mg</td>
<td>0,1 mg</td>
<td>0,1 mg</td>
</tr>
<tr>
<td></td>
<td>2 – 7 d</td>
<td>0,2 mg</td>
<td>0,2 mg</td>
<td>0,2 mg</td>
</tr>
<tr>
<td></td>
<td>&gt; 7 d</td>
<td>0,2 mg</td>
<td>0,25 mg</td>
<td>0,25 mg</td>
</tr>
</tbody>
</table>

| Ibuprofen    | q 24 h:| 10 mg   | 5 mg     | 5 mg     |
Prolonged indomethacin courses

Five trials, n = 431
No significant effect on: PDA closure, re-treatment, reopening, ligation rate, CLD, IVH, mortality

Prolonged course
– increased risk of NEC (RR 1.87 95%CI 1.07- 3.27)
– lower proportion of infants with diminished urine output

Authors’ conclusions
Prolonged course does not appear to have a significant benefit. Reduction of transient renal impairment does not outweigh the increased risk of NEC.

Herrera C et al. Cochrane Database of Systematic Reviews. 2006

Multiple courses: indomethacin versus ibuprofen


*Percentage calculated on number of patients who underwent ECHO after each dose of drug.
†Percentage calculated on total number of patients in each treatment group.
‡2nd course of therapy was open-label.

p-values: not significant
Additional doses of ibuprofen in <28 w infants

<table>
<thead>
<tr>
<th></th>
<th>Ibuprofen group (n = 60)</th>
<th>Indomethacin group (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at start of treatment (hours)</td>
<td>8 (4–21)</td>
<td>8 (3–24)</td>
</tr>
<tr>
<td>Doses of medicine (number)</td>
<td>1 (1–6)</td>
<td>2 (1–6)</td>
</tr>
<tr>
<td>PDA closed after 1 dose</td>
<td>32 (53.3)</td>
<td>31 (52.5)</td>
</tr>
<tr>
<td>2 doses</td>
<td>10 (16.7)</td>
<td>11 (18.6)</td>
</tr>
<tr>
<td>3 doses</td>
<td>3 (5)</td>
<td>3 (5.1)</td>
</tr>
<tr>
<td>4 doses</td>
<td>2 (3.3)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>5 doses</td>
<td>2 (3.3)</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>6 doses</td>
<td>4 (6.7)</td>
<td>4 (6.8)</td>
</tr>
<tr>
<td>Total PDA closed</td>
<td>53 (88.3)</td>
<td>52 (88.1)</td>
</tr>
<tr>
<td>Reopening rates</td>
<td>9 (15)</td>
<td>8 (13.5)</td>
</tr>
<tr>
<td>Ligation rates</td>
<td>4 (6.7)</td>
<td>5 (8.5)</td>
</tr>
</tbody>
</table>

*Values are median (range) or number (%). Percentages were calculated on total number of infants in each treatment group. There were no significant differences between the groups.

Su BH. Arch Dis Child Fetal Neonatal Ed 2008

Double-dosed second ibuprofen course

Decobert F et al. 2008
Effectiveness of additional ibuprofen courses

1. Lago 2002  
   N=25  
   <1500 g  
   48 % closure

2. Su 2008  
   N=15  
   <1100 g  
   50 % closure

3. Decobert 2008  
   N=25  
   <800 g  
   10 % closure

4. Richards 2009  
   N=80  
   <1000 g  
   41 % closure

5. Munshi 2009  
   N=67  
   <750 g  
   21 % closure

1. Pharmacological treatment

- Prophylactic or late treatment?
- Indomethacin or ibuprofen?
- Higher-, prolonged-, or additional courses?
- Intravenous or oral route?
Oral ibuprofen

Randomized trials (n=295)
2. n=36 versus oral indo  Fakhraee SH et al.  Dang Dai Er Ke Za Zhi 2007; 9(5):399
7. n=23 versus indo IV  Akissi
8. n=20 versus oral indo  Pourarian
9. n=64 versus ibu IV  Cherif

Non-randomized observational studies (n=175)
2. n=22 PDA on day 2  Heyman E et al.  Pediatrics 2003; 112:e354
5. n=80 oral ibu only  Manjunath

Pharmacokinetics of oral ibuprofen

Plasma ibuprofen concentration after single oral dose 10 mg/kg (mean ± SEM)

Sharma PK. J Clin Pharmacol 03
Oral Ibuprofen

Other reports

Comments
- Limited number of patients, statistical bias!
- Not blinded, no systematic control group
- Infants of larger gestational ages
- Rates of NEC are twice that of ibuprofen IV
  46/281 (16 %) versus 27/356 (8%)

3. Surgical ligation

- Adverse effects
- How to reduce ligation rates?
- When to go for ligation?
Ligation of PDA

**Metaanalysis of ligation studies**

**Prophylactic PDA ligation for prevention of mortality and morbidity in <1000g or <28w**

n = 84. 1 trial.

Reduction of stage II-III Nec

**CONCLUSION**

Prophylactic ligation **did not** decrease mortality or BPD in ELBW infants, it is not indicated

**Surgical vs medical treatment with cyclooxygenase inhibitors for symptomatic PDA in preterms**

n = 154. 1 trial. Gersony 1983

Increase in pneumothorax and ROP stage III and IV

**CONCLUSION**

Data are **inconclusive** to prefer surgical ligation or medical treatment as initial treatment for symptomatic PDA.

Mosalii R et al. 2008 Cochrane Databases  Malviya M et al. 2008 Cochrane Database Syst Rev
Pooled results of ligation studies

<table>
<thead>
<tr>
<th>Prophylactic ligation</th>
<th>Ligation for symptomatic PDA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ductal Patency</td>
</tr>
<tr>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>BPD</td>
</tr>
<tr>
<td></td>
<td>Death or BPD</td>
</tr>
<tr>
<td></td>
<td>Ox @ 28 days</td>
</tr>
<tr>
<td></td>
<td>Ox @ 36 wks</td>
</tr>
<tr>
<td></td>
<td>NEC</td>
</tr>
<tr>
<td></td>
<td>SIP</td>
</tr>
<tr>
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<td>Sepsis</td>
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<td></td>
<td>IVH</td>
</tr>
<tr>
<td></td>
<td>IVH</td>
</tr>
<tr>
<td></td>
<td>IVH &gt; Grade 2</td>
</tr>
<tr>
<td></td>
<td>PVL</td>
</tr>
</tbody>
</table>

Benitz WE. J Perinatol 2010

Surgical ligation of PDA

SHORT TERM adverse effects

Noori S. J Pediatr ’07  
Acute deterioration of myocardial function (n=23)

McNamara J. J Thac Cardiovasc Surg 10:  
Impaired left ventricular systolic performance, particularly in <1000g infants (n=46).

Lemmers P. ADC ’10  
Important cerebral desaturations during ligation, persisting until 24 h after surgery (n=20)
Cerebral effects of ligation of the ductus

Patients
n = 20
GA 24.7- 30.4 w
BW 630-1540 g

Methods
Near infrared spectroscopy (NIRS) before, during and 24h after ligation:
- Regional cerebral oxygen saturation (rScO2)
- Cerebral fractional tissue oxygen extraction (cFTOE)
- amplitude-integrated EEG (aEEG)

Results
- Very low regional oxygen saturations (rScO2) may occur during surgery
- Only 24h after surgery saturations above preclipping values
Left recurrent laryngeal nerve

Truong MT. Otolaryngol Head Neck Surg 2007

Left recurrent laryngeal nerve injury

Patients
n = 60, clip ligated PDA

GA (w) 25 (23 - 27)
BW (g) 725 (510 - 910)
Age (d) 20 (5 - 41)

Methods
Flexible fiberoptic laryngoscopy in those with suspected of left vocal cord paralysis. Compared with outcomes: respiratory, feeding, neurodevelopment up to 18-22m

Results
40 % of the surviving 55 had LVCP.

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Suspicion of unilateral left vocal cord paralysis (LVCP)
- Unable to wean
- Stridor, hoarse, absent cry
- Cardiorespiratory distress with initiation of feedings
Left recurrent laryngeal nerve injury

**Table 2** Medical morbidities and developmental outcomes of infants with and without LVCP

<table>
<thead>
<tr>
<th></th>
<th>LVCP n (%)</th>
<th>No LVCP n (%)</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>Respiratory outcomes</strong></td>
<td></td>
<td></td>
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<tr>
<td>Reactive airway disease</td>
<td>19 (86)</td>
<td>11 (33)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>18 (82)</td>
<td>13 (59)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total days of mechanical ventilation</td>
<td>44 ± 24</td>
<td>29 ± 16</td>
<td>0.008</td>
</tr>
<tr>
<td>Aspiration</td>
<td>17 (77)</td>
<td>1 (33)</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Feeding and Growth Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrostomy tube insertion</td>
<td>14 (64)</td>
<td>2 (6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nissen fundoplication</td>
<td>9 (41)</td>
<td>1 (3)</td>
<td>0.001</td>
</tr>
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Left recurrent laryngeal nerve injury

**Table 3** LVCP as predictor of morbidity, adjusted for gestational age and severe IVH

<table>
<thead>
<tr>
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<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>Respiratory outcomes</strong></td>
<td></td>
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<tr>
<td>Reactive airway disease</td>
<td>14.9 (3.2, 70.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>5.5 (1.4, 21.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Aspiration</td>
<td>6.4 (0.3, 127)</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Feeding and growth outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrostomy tube</td>
<td>47.8 (4.5, 502)</td>
<td>0.001</td>
</tr>
<tr>
<td>Nissen fundoplication</td>
<td>18.4 (1.7, 223)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Neurodevelopmental outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurodevelopmental impairment</td>
<td>0.7 (0.1, 3.5)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; LVCP, left vocal cord paralysis.

*Intraventricular hemorrhage (Grade 3 or 4).

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Adverse effects of ligation of PDA

SHORT TERM
- Hypotension, myocardial dysfunction (30 %)
- Chylothorax, laryngeal (1.7 - 67%) and phrenic nerve injury
- Respiratory deterioration, pulmonary edema, pneumothorax
- Cerebral effects

MEDIUM - LONGTERM
- Retinopathy of prematurity
- Bronchopulmonary dysplasia
- Necrotizing enterocolitis
- Neurodevelopmental impairment
- Feeding difficulties

Surgical ligation of PDA

LONG TERM adverse effects

Camm EJ. Pediatr Res 04: Baboon model indicated highest incidence of cerebral injury in those with ligation (n = 22)

Kabra NS. J Pediatr 07: Neurosensory impairment, increased risk of BPD, ROP after ligation in ELBW from TIPP (n = 426)

Chorne N. Pediatrics 07: Association between ligation & chronic lung disease, not with neuro-impairment after risk adjustment for GA (n = 446, < 28w)

Madan JC. Pediatrics 09: Poor short- and longterm outcome after primary or secondary ligation (n=2838)
Outcomes after surgical ligation

145 ELBW infants
Ligated PDA after failure or contraindications of indomethacin treatment
Review of medical records - 1987 - 2005

GA (w) 25.5 (24 - 36)
BW (g) 838 (450 - 1000)
Age (d) 14.1 (+/- 1.8)

Results
Postoperative complications in 10:
(6 bleeding, pneumothorax, left vocal cord paralysis, left phrenic nerve injury, Lymphatic leak...)

Conclusion  Ligation is safe with minimal associated morbidity

How to reduce PDA ligation rates ?

Optimize pre- and postnatal factors
- Antenatal steroids
- No indomethacin tocolysis
- Restricted fluid intake
- Caffeine treatment
Antenatal indomethacin increases ligation

Retrospective cohort study - 157 infants < 30 wk GA

<table>
<thead>
<tr>
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<th>Antenatal indo n = 79</th>
<th>Controls n = 78</th>
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<tbody>
<tr>
<td>PDA</td>
<td>68 % (54/79)</td>
<td>67 % (52/78)</td>
</tr>
<tr>
<td>PDA closed with indo</td>
<td>41 % (22/54)</td>
<td>65 % (34/52)</td>
</tr>
<tr>
<td>Ligation</td>
<td>59 % (32/54)</td>
<td>35 % (18/52)</td>
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Conclusion

Antenatal indomethacin exposure is associated with an increased rate of therapy failure and more ligation

Soraisham AS et al. J Obstet Gynaecol Can 2010

How to reduce PDA ligation rates?

Optimize pre- and postnatal factors
- Antenatal steroids
- No indomethacin tocolysis
- Restricted fluid intake
- Caffeine treatment
- Increased Peep, less HFOV

Echocardiographic assessment
- Avoid treatment of hemodynamically non-significant shunts
- Shunt assessment to guide additional dosing / doses

Conservative treatment approach
- Most ducts will close spontaneously
- There is no evidence of increased mobidity caused by PDA
Conservative approach after indomethacin prophylaxis failure

Design
comparison of 2 strategies after prophylactic indomethacin

Results
2nd epoch: decreased ligation (72% vs 100%; p<0.05), less NEC.
Similar BPD, sepsis, ROP, neurologic injury, death

Conclusion
Conservative approach might have benefits

Effect of implementing a clinical and echocardiographic staging system

Ligation rates at the Hospital for Sick Children, Toronto between 2005-2009, after implementing an echocardiographic staging system for treatment of PDA
When to call the surgeon?

1. **Do not start PDA treatment before end of 1st week**
   - Allow time for spontaneous closure
   - Supportive therapy (fluid, dopamine, respiratory support)

2. **Try first the pharmacological approach**
   - Repeated doses, guided by echocardiography
   - Postpone treatment if signs of infection/inflammation

3. **Ligation as last rescue**
   - When PDA not hemodynamically important: no surgery
   - Perform on site if possible, pre-operative stabilization
   - Postoperative assessment (cardiocirculatory, larynx,….)
Conclusions

Pharmacological treatment

1. Prophylaxis with indomethacin reduces IVH/cPVL, and need for ligation of PDA

2. Few arguments for prophylactic ibuprofen

3. Both indomethacin and ibuprofen are effective in closing PDA, but effects on morbidity = ?

4. Ibuprofen seems to have better safety profile

Conclusions

Adapted dosing, courses and route

1. Enteral route is not advisable for now

2. Prolonged indomethacin dosing is not convincingly effective

3. Additional courses of ibuprofen and indomethacin do improve final PDA closure rates

4. Higher ibuprofen dosing has not yet been shown to be safe
Conclusions

Surgical ligation

1. Carries many short- and longterm side effects

2. Need for ligation can be reduced by optimizing ante- and postnatal factors

3. Conservative and echography-guided treatment may avoid surgery

What really makes science grow is new ideas, including false ideas

Sir Karl Popper 1963