Title of Program: Prevention of Intraventricular Hemorrhage: The Evidence from Systematic Reviews

Speakers/Moderators: Roger F. Soll, Matteo Bruschettini, Olga Romantsik

Planning Committee: Jeffrey D. Horbar, Hedge E. Baus-Frank, Roger F. Soll

Date: June 28, 2017

Learning Objectives:

Participants will be presented with evidence from clinical trials and systematic reviews and will be able to evaluate and translate the evidence in the field of neonatology to better serve their practices.

Specifically, evidence for strategies regarding the interventions for the prevention and treatment of intraventricular hemorrhage will be presented and critiqued.

DISCLOSURE:

In the past three years, has anyone in the speakers or scientific committee had a financial interest in anything related to this program?

COMMERCIAL SUPPORT ORGANIZATIONS (if applicable): No Commercial Support

The University of Vermont College of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The University of Vermont designates this live activity for a maximum of 1 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The Basics

- Follow slides on the Internet
- Listen on your phone or speakerphone
- Chat feature - questions anytime
- Your phone will be muted during talks
- Questioner unmuted during Q&A

Use the raised hand icon to queue up for questions

The Basics

Cochrane

Preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health care interventions

Cochrane Neonatal

Prepares and disseminates evidence-based reviews of the effects of therapies in the field of neonatal medicine

Editorial Team

Roger F. Soll
Coordinating Editor

Colleen Ovelman
Managing Editor

Jennifer Spano
Information Specialist

Editorial Team

Michael Bracken
Yale University

Jeffrey Horbar
University of Vermont

Bill McGuire
Hull York Medical School

Gautham Suresh
Baylor University
**Guest Discussants**

Dr. Matteo Bruschettini  
Senior Consultant Neonatologist  
Department of Paediatrics  
Lund University, Skåne University Hospital  

Cochrane Sweden  
Research & Development  
Section for HTA Analysis  
Skåne University Hospital

Dr. Olga Romantsik  
Paediatrician, Fellow in Neonatology, PhD student  
Department of Paediatrics  
Lund University, Skåne University Hospital

---

**Support**

[NIH NICHD Logo]  
[NIH NICHD Logo]

**Disclosure**

Roger F. Soll is the Coordinating Editor of Cochrane Neonatal supported by a contract from the NICHD and President of Vermont Oxford Network

---

**Why These Webinars?**

To develop an understanding of the evidence supplied by systematic reviews in neonatal perinatal medicine (as well as other large well conducted trials) and discuss how this evidence might influence your practice.

---

**Intraventricular hemorrhage**

[Diagram of Intraventricular Hemorrhage]
Intraventricular Hemorrhage

VERMONT OXFORD NETWORK ANNUAL REPORTS 1991-2015

% VLBW INFANTS

0% 10% 20% 30% 40% 50% 60%

1991 1993 1995 1997 1999 2001 2003 2005 2007 2009 2011 2013 2015

% VLBW INFANTS

Intraventricular Hemorrhage

VERMONT OXFORD NETWORK ANNUAL REPORTS 2015

Gestational Age 22 to 25 weeks

% INFANTS (%)

< 24 weeks 24 to 26 weeks 27 to 29 weeks

% INFANTS (%)

Intraventricular hemorrhage

Preterm IVH pathogenesis

<table>
<thead>
<tr>
<th>Intravascular factors (Pressure passive circulation)</th>
<th>Vascular factors</th>
<th>Extravascular factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia/reperfusion</td>
<td>Fragile, invovling capillaries with large diameter lumen</td>
<td>Deficient vascular support</td>
</tr>
<tr>
<td>Fluctuating or increase CBF</td>
<td></td>
<td>Excess fibrinolytic activity</td>
</tr>
<tr>
<td>Increase in cerebral venous pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulation disturbances</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Neonatal risk factors in the pathogenesis of IVH

- Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth (Review)

Roberts D, Brown J, Medley N, Dalziel SR.

Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth.

Objectives: To assess the effects of administering a course of corticosteroids to the mother prior to anticipated preterm birth on fetal and neonatal morbidity and mortality, maternal mortality and morbidity, and on the child in later life.

Selection criteria: We considered all randomized controlled comparisons of antenatal corticosteroid administration (betamethasone, dexamethasone, or hydrocortisone) with placebo, or with no treatment, given to women with a singleton or multiple pregnancy, prior to anticipated preterm delivery (elective, or following spontaneous labor), regardless of other co-morbidity, for inclusion in this review.

Most women in this review received a single course of steroids; however, nine of the included trials allowed for women to have weekly repeats.

Main results: This update includes 30 studies (7774 women and 8158 infants).

Typical RR 0.55 (95% CI 0.40 to 0.76)

Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D.


A possible role for magnesium:

The first report that prenatal magnesium sulphate was associated with a reduction in risk of IVH, from 18.9% to 4.4%, in babies born with a birth weight less than 1500 grams was by Kuban and colleagues in 1992 (Kuban 1992).

Objectives: To assess the effects of magnesium sulphate as a neuroprotective agent when given to women considered at risk of preterm birth.

Selection criteria: Randomized controlled trials of antenatal magnesium sulphate therapy in women threatening or likely to give birth at less than 37 weeks’ gestational age.

For one subgroup analysis, studies were broadly categorized by the primary intent of the study into "neuroprotective intent", or "other intent (maternal neuroprotective - pre-eclampsia)", or "other intent (tocolytic)".

Main results: Five trials (6145 babies) were eligible for this review.

Typical RR 0.96 (95% CI 0.86 to 1.08)
Typical RR 0.83 (95% CI 0.62 to 1.13)

Crowther CA, Crosby DD.
Vitamin K prior to preterm birth for preventing neonatal periventricular haemorrhage.
DOI: 10.1002/14651858.CD000229.pub2.

How the intervention might work

It has been postulated that vitamin K might improve the coagulation status of preterm infants and reduce the frequency of PVH.

As many hemorrhages are thought to originate close to the time of birth, prophylactic antenatal rather than postnatal treatment may be preferable.

Maternally administered vitamin K only crosses the placenta in small amounts with a maternal-fetal gradient of 30:1 (Shearer 1992).

Objectives: To assess the effects of vitamin K administered to women at risk of imminent very preterm birth to prevent PVH and associated neurological injury in the infant.

Selection criteria: Randomized or quasi-randomized trials of vitamin K administered parenterally or orally to women at risk of imminent preterm birth.

Main results: Eight trials were included but only seven (843 women) contributed data to the results.

Typical RR 0.76 (95% CI 0.54 to 1.06)
Authors’ conclusions:

Vitamin K administered to women prior to very preterm birth has not been shown to significantly prevent PVH in preterm infants or improve neurodevelopmental outcomes in childhood.

How the intervention might work

Phenobarbital is a potential neuroprotective agent that might act by preventing ischemic injury or by reducing the fluctuations in blood pressure and cerebral perfusion (Goddard 1987; Wimberley 1982).

Phenobarbital has been suggested as a postnatal treatment and has been the subject of another Cochrane review (Whitelaw 2007). As many hemorrhages are thought to originate close to the time of birth, prophylactic prenatal rather than postnatal treatment may be preferable.

Possible adverse effects for the women of phenobarbital include drowsiness, gastrointestinal upset, and a rash.
Authors’ conclusions:

The evidence in this review does not support the use of prophylactic maternal phenobarbital administration to prevent PVH in preterm infants or to protect them from neurological disability in childhood.

Phenobarbital administration may lead to maternal sedation.

If any future trials are carried out, they should measure neurodevelopmental status at follow-up.

Alfirevic Z, Milan SJ, Livio S.

Caesarean section versus vaginal delivery for preterm birth in singletons (Review).

Planned caesarean delivery for women thought to be in preterm labor may be protective for baby, but could also be quite traumatic for both mother and baby. The optimal mode of delivery of preterm babies for both cephalic and breech presentation remains, therefore, controversial.

**Objectives:** To assess the effects of a policy of planned immediate caesarean delivery versus planned vaginal birth for women in preterm labor.

**Selection criteria:** Randomized trials comparing a policy of planned immediate caesarean delivery versus planned vaginal delivery for preterm birth.

**Data collection and analysis**

**Main results:** We included six studies (involving 122 women) but only four studies (involving only 116 women) contributed data to the analysis.

There were very little data of relevance to the three main (primary) outcomes considered in this review:

- There was no significant difference between planned immediate caesarean section and planned vaginal delivery with respect to birth injury to infant (risk ratio (RR) 0.56, 95% confidence interval (CI) 0.05 to 5.62; one trial, 38 women).
- Birth asphyxia (RR 1.63, 95% CI 0.84 to 3.14; one trial, 12 women).
- The difference between the two groups with regard to perinatal deaths was not significant (0.29, 95% CI 0.07 to 1.14; three trials, 89 women).

**Authors’ conclusions:**

There is not enough evidence to evaluate the use of a policy of planned immediate caesarean delivery for preterm babies. Further studies are needed in this area, but recruitment is proving difficult.
**OUR CHANGING PRACTICE... IS IT EVIDENCE BASED? Cesarean Section**

Demographic, medical, and labor and delivery complications were abstracted from US linked birth and infant death certificate files for 2000-2003.

13,733 neonatal deaths and 106,809 survivors available from the trimmed data set for analysis for the 4-year period.


**RISK OF NEONATAL DEATH:**

- **Gestational Age**
  - 22 weeks: Adjusted odds ratios 0.58 (0.38–0.87)
  - 23 weeks: 0.52 (0.42–0.64)
  - 24 weeks: 0.72 (0.62–0.82)
  - 25 weeks: 0.81 (0.69–0.94)


---

**Delayed cord clamping**

**Introduction**

In the past 50 years, the umbilical cords of babies born preterm have generally been cut soon after birth, so that the newborns can be transferred immediately to the neonatal team. However, there is recent evidence that a delay of clamping by 30 to 60 seconds after birth results in a smoother transition, particularly if the baby begins breathing before the cord is cut.

In both animal and human models, the delay is associated with increased placental transfusion, increased cardiac output, and higher and more stable neonatal blood pressure. There is controversy about how long it is appropriate to delay clamping if the baby is perceived to require resuscitation.


---

**Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes**


---

**Delayed cord clamping**

**Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes**


---

Treatment Recommendation

We suggest delayed umbilical cord clamping for preterm infants not requiring immediate resuscitation after birth (weak recommendation, very-low-quality evidence).

There is insufficient evidence to recommend an approach to cord clamping for preterm infants who do receive resuscitation immediately after birth, because many babies who were at high risk of requiring resuscitation were excluded from or withdrawn from the studies.


Knowledge Gaps

- Results of ongoing large randomized controlled trials
- Comparison of delayed versus immediate cord clamping among preterm infants who receive resuscitation with PPV
- Comparison of delayed cord clamping with cord milking
- Outcome data of high importance, such as long-term neurodevelopment
- Need for resuscitative intervention at delivery
- Hyperbilirubinemia among high-risk populations

Prophylactic Indomethacin

Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants.

Fowlie PW, Davis PG, McGuire W.

Prophylactic Indomethacin

Prophylactic treatment aims to achieve PDA closure prior to the development of shunting and hemodynamic disturbances that are associated with morbidity and mortality but without the need for screening or surveillance using echocardiography. However, universal prophylaxis exposes a substantial proportion of infants in whom PDA closure would have occurred spontaneously to a pharmacological intervention. This is important because, as well as having potential benefits, treatment with prophylactic indomethacin may have harms related to reducing perfusion of essential organs such as reduced cerebral blood flow which may oppose any neurodevelopmental benefits due to possible reduction in the incidence of IVH (Edwards 1990); reduced gastrointestinal perfusion that potentially limits any effect of PDA closure on reducing the risk of NEC (Coombs 1990); and reduced renal perfusion, glomerular filtration and urine output causing fluid and electrolyte disturbances in the early neonatal period (Cifuentes 1979). Indomethacin may also inhibit platelet function and disrupt hemostasis that may cause clinically-important bleeding, e.g. IVH (Friedman 1978).

Types of studies: Randomized or quasi-randomized controlled trials.
Types of participants: preterm infants < 37 weeks gestational age.
Types of interventions: Prophylactic (not guided by knowledge of PDA status) treatment with indomethacin given within 24 hours of birth vs. placebo or no treatment. Specific dose regimens were not pre-specified.

Main results: Nineteen eligible trials in which 2872 infants participated were identified. Most participants were very low birth weight, but the largest single trial restricted participation to extremely low birth weight infants (N = 1202). The trials were generally of good quality.

Meta-analysis of 19 trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Difference (95% CI)</th>
<th>Decreased</th>
<th>Risk</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATENT DUCTUS ARTERIOSUS (7)</td>
<td>-0.27 (-0.32, -0.21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SYMPTOMATIC PDA (14)</td>
<td>-0.24 (-0.28, -0.21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDA LIGATION (8)</td>
<td>-0.05 (-0.08, -0.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fowlie 2010: THE COCHRANE LIBRARY

Long-Term Effects of Indomethacin Prophylaxis in ELBW Infants
Schmidt and colleagues randomly assigned 1202 extremely low birth weight infants to receive either indomethacin (0.1 mg/kg) or placebo intravenously once daily for three days.

The primary outcome was a composite of death, cerebral palsy, cognitive delay, deafness, and blindness at a corrected age of 18 months.

Secondary short-term outcomes were patent ductus arteriosus, pulmonary hemorrhage, chronic lung disease, ultrasonographic evidence of intracranial abnormalities, necrotizing enterocolitis, and retinopathy.

Secondary long-term outcomes were hydrocephalus necessitating the placement of a shunt, seizure disorder, and microcephaly within the same time frame.
Implications for practice: Given the lack of evidence of effect on long term outcomes, the decision to use prophylactic indomethacin will depend on the values that families and clinicians attach to the short term benefits.

In neonatal units without ready access to cardiac diagnostic and therapeutic services, a reduction in symptomatic PDA and a reduction in the need for surgical closure may be considered a greater benefit than in other units with ready access to these services.

Cost implications may need to be considered although economic evaluation of this intervention has been limited to date (TIPP 2001).

Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants.

Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants.

DOI: 10.1002/14651858.CD004213.pub3.

Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants.

Primary objectives

1. To determine the effectiveness and safety of ibuprofen compared to placebo or no intervention in the prevention of PDA in preterm and/or low birth weight infants.

2. To determine the effectiveness and safety of ibuprofen compared to other cyclo-oxygenase inhibitor drugs (indomethacin, mefenamic acid) in the prevention of PDA in preterm and/or low birth weight infants.

Types of studies: Randomized or quasi-randomized controlled trials with or without blinding.

Types of participants: preterm infants < 37 weeks gestational age or low-birth-weight infants (< 2500 grams) in their first 72 hours of life (three days).

Types of interventions: Prophylactic use of ibuprofen for prevention of PDA compared to control infants who received no intervention, placebo, other cyclo- oxygenase inhibitor drugs (indomethacin, mefenamic acid) or rescue treatment with ibuprofen.

Main results: Seven studies (n = 931) comparing prophylactic ibuprofen with placebo/no intervention are included.

Presence of PDA 72 hours after treatment

Typical RR 0.36 (95% CI 0.29 to 0.46);
Typical RD 0.27 (95% CI -0.32 to -0.21); NNT 4 (95% CI 3 to 5).
**Relative Risk and 95% CI**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Difference (95% CI)</th>
<th>0.2</th>
<th>0.5</th>
<th>1.0</th>
<th>2.0</th>
<th>4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYMPTOMATIC PDA (6)</td>
<td>0.27 (-0.33, -0.22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDA LIGATION (3)</td>
<td>-0.04 (-0.06, -0.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NECROTIZING ENTEROCOLITIS (6)</td>
<td>0.00 (-0.03, 0.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEVERE IVH (5)</td>
<td>-0.02 (-0.06, 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PERVENTRICULAR LEUKOMALACIA (4)</td>
<td>0.01 (-0.02, 0.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHRONIC LUNG DISEASE (4)</td>
<td>0.02 (-0.05, 0.08)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MORTALITY (4)</td>
<td>-0.01 (-0.06, 0.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Authors’ conclusions:** Prophylactic use of ibuprofen decreased the incidence of PDA, decreased the need for rescue treatment with cyclo-oxygenase inhibitors and decreased the need for surgical closure.

In the control group, the PDA closed spontaneously by day three in 58% of the neonates.

Prophylactic treatment exposes many infants to a drug that has concerning renal and gastrointestinal side effects without conferring any important short-term benefits and is not recommended.

Until long-term follow-up results are published from the trials included in this updated review, no further trials of prophylactic ibuprofen are recommended.

---

**Ibuprofen for PDA**

**VERMONT OXFORD NETWORK ANNUAL REPORTS 2008-2015**

- **Opioids for neonates receiving mechanical ventilation.**

  Bellù R, de Vaal KA, Zanini R.

Mechanical ventilation is a potentially painful and discomforting intervention widely used in neonatal intensive care units. Newborn babies (neonates) demonstrate increased sensitivity to pain, which may affect clinical and neurodevelopmental outcomes. The use of drugs that reduce pain might be important in improving survival and neurodevelopmental outcomes.

To determine the effect of opioid analgesics (pain-killing drugs derived from opium e.g. morphine), compared to placebo, no drug, or other non-opioid analgesics or sedatives, on pain, duration of mechanical ventilation, mortality, growth and neurodevelopmental outcomes in newborn infants on mechanical ventilation.

Thirteen studies on 1505 infants were included.

Meta-analyses of mortality, duration of mechanical ventilation, and long and short-term neurodevelopmental outcomes showed no statistically significant differences.

Very preterm infants given morphine took significantly longer to reach full enteral feeding than those in control groups (weighted mean difference 2.10 days; 95% confidence interval 0.35 to 3.85).
Neuromuscular paralysis for newborn infants receiving mechanical ventilation.

Cools F, Offringa M.

**Background**
Ventilated newborn infants breathing in asynchrony with the ventilator are potentially at risk for more severe barotrauma and are at risk for complications such as pneumothorax or intraventricular hemorrhage. Neuromuscular paralysis, which eliminates the spontaneous breathing efforts of the infant, creates complete synchronization with the ventilator and may minimize these risks. However, complications have been reported with prolonged neuromuscular paralysis in newborn infants.

**Objectives**
To determine whether routine neuromuscular paralysis compared with no routine paralysis results in clinically important benefits or harms in newborn infants receiving mechanical ventilation.

Ten possibly eligible trials were identified, of which six were included in the review.

All the included trials studied preterm infants ventilated for respiratory distress syndrome and used pancuronium as the neuromuscular blocking agent. In the analysis of the results of all trials, no significant difference was found in mortality, air leak or chronic lung disease.

There was a significant reduction in intraventricular hemorrhage (any grade and severe IVH) and a trend towards less air leak. In the subgroup analysis of trials studying an unselected population of ventilated infants, no significant differences were found for any of the outcomes.
Neuromuscular paralysis

Any Intraventricular Hemorrhage

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Event</th>
<th>Total</th>
<th>Event</th>
<th>Total</th>
<th>Risk Rate</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head midline</td>
<td>64</td>
<td>243</td>
<td>10</td>
<td>25</td>
<td>4.04</td>
<td>1.57</td>
<td>0.28 to 8.98</td>
<td>0.01</td>
</tr>
<tr>
<td>Head rotated</td>
<td>82</td>
<td>327</td>
<td>16</td>
<td>39</td>
<td>1.75</td>
<td>1.14</td>
<td>0.55 to 2.35</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Severe Intraventricular Hemorrhage (Grades 3 and 4)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Event</th>
<th>Total</th>
<th>Event</th>
<th>Total</th>
<th>Risk Rate</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head midline</td>
<td>39</td>
<td>172</td>
<td>8</td>
<td>13</td>
<td>4.17</td>
<td>1.57</td>
<td>0.28 to 8.98</td>
<td>0.01</td>
</tr>
<tr>
<td>Head rotated</td>
<td>53</td>
<td>255</td>
<td>17</td>
<td>49</td>
<td>3.22</td>
<td>1.14</td>
<td>0.55 to 2.35</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Animal Models: One-slide introduction

The principles of the 3Rs — a framework for humane animal research:

1. Replacement: to avoid or replace the use of animals
2. Reduction: to minimize the number of animals used
3. Refinement: to minimize pain, suffering, distress or lasting harm

Can we avoid bestial behaviour in humans who design animal studies?

Head midline position

Head position may affect cerebral hemodynamics and thus be involved indirectly in development of GM-IVH.

Turning the head toward one side may functionally occlude jugular venous drainage on the ipsilateral side and increase intracranial pressure and cerebral blood volume.

Thus, it has been suggested that cerebral venous pressure is reduced and hydrostatic brain drainage improved if the patient is in supine midline position with the bed tilted 30°.

The midline position might be achieved in the supine and, with the use of physical aids, lateral position as well. Midline position should be kept at least when the incidence of GM-IVH is greatest, that is, in the first two to three days of life.

Postnatal Interventions

Head midline position for preventing the occurrence or extension of germinal matrix-intraventricular hemorrhage in preterm infants.

Romantsik O, Calevo MG, Bruschettini M. Head midline position for preventing the occurrence or extension of germinal matrix-intraventricular hemorrhage in preterm infants.


Head midline position

To assess whether head midline position compared with any other head position is more effective in prevention or extension of germinal matrix-intraventricular hemorrhage in infants born at ≤ 32 weeks’ gestational age.

Two randomized controlled trials, for a total of 110 infants, met the inclusion criteria of this review. Both trials compared supine midline head position with the bed at 0° to supine head rotated 90° with the bed at 0°.

Romantsik O, Calevo MG, Bruschettini M. Head midline position for preventing the occurrence or extension of germinal matrix-intraventricular hemorrhage in preterm infants.

Why Animal Models for IVH

- to explore pathophysiology
- to test innovative interventions
- to refine current management


Delayed cord clamping in preterm infants
Outcome: IVH all grades

<table>
<thead>
<tr>
<th>Dr. or reference</th>
<th>Newborn inclusion: days from birth</th>
<th>IVH</th>
<th>Rate A vs B (%)</th>
<th>Mean</th>
<th>Rate B at A (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dean 2006</td>
<td>1/45</td>
<td>1/45</td>
<td>1.75%</td>
<td>5.58</td>
<td>6.30 (0.54, 0.39)</td>
</tr>
<tr>
<td>Milroad 2007</td>
<td>2/16</td>
<td>1/16</td>
<td>25%</td>
<td>0.5</td>
<td>4.63 (0.37, 0.37)</td>
</tr>
<tr>
<td>On 2002</td>
<td>4/8</td>
<td>1/8</td>
<td>59%</td>
<td>4.66</td>
<td>4.60 (0.39, 0.39)</td>
</tr>
<tr>
<td>Pan 2004</td>
<td>1/10</td>
<td>1/10</td>
<td>74%</td>
<td>2.1</td>
<td>4.60 (2.14, 2.14)</td>
</tr>
<tr>
<td>Rupar 2007</td>
<td>2/16</td>
<td>1/16</td>
<td>66%</td>
<td>4.66</td>
<td>4.70 (0.31, 0.31)</td>
</tr>
<tr>
<td>Menez 2005</td>
<td>3/16</td>
<td>1/16</td>
<td>86%</td>
<td>4.66</td>
<td>4.67 (2.14, 2.14)</td>
</tr>
<tr>
<td>Horace 2005</td>
<td>3/16</td>
<td>3/16</td>
<td>86%</td>
<td>4.66</td>
<td>4.67 (2.14, 2.14)</td>
</tr>
<tr>
<td>Fedelt 2005</td>
<td>6/14</td>
<td>1/14</td>
<td>177%</td>
<td>4.67</td>
<td>4.67 (2.14, 2.14)</td>
</tr>
<tr>
<td>Miller 2006</td>
<td>8/14</td>
<td>8/14</td>
<td>222%</td>
<td>4.67</td>
<td>4.67 (2.14, 2.14)</td>
</tr>
<tr>
<td>Mac 2006</td>
<td>5/16</td>
<td>5/16</td>
<td>222%</td>
<td>4.67</td>
<td>4.67 (2.14, 2.14)</td>
</tr>
</tbody>
</table>

Total R% CE: 38% (6.37, 6.37)


Dones 2007: 3/16 GM plasma, 4.66 + 0.39, 4.64 ± 0.39

No trials have assessed neurodevelopment at 2-3 years of age

Delayed cord clamping in preterm infants - other outcomes: need for inotropic; incidence of NEC

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Description</th>
<th>Need for inotropes for low blood pressure</th>
<th>Incidence of NEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-day old preterm infant blood injections into lateral ventricles on P7 and P8 rats</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>2</td>
<td>3-day old preterm infant intraperitoneal glycerol in 2 hours old preterm rabbits</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>


IVH – pathophysiology

• why is extravasated blood in the brain harmful?
• how to prevent its harmful effect on the premature brain?
• how does IVH lead to post-hemorrhagic ventricular dilatation?

Multiple challenges

• developmental brain anatomy and physiology
• limited understanding of the pathogenesis of brain damage
• stable late-preterm/term pups vs sick preterm infants
• differences in hemostatic system in preterm and term newborns
• lack of classification in neuroimaging in animals
• short- and long-term neurodevelopmental outcome (behavioral tests)


Rigorous methodology, e.g. ARRIVE guidelines for reporting; projects such as SYRCLE to promote high-quality systematic reviews of animal studies

Questions/Discussion?

Perhaps you have heard.....

We will no longer receive support from NICHD

Will need to obtain bridging funding and establish a strategy whereby Cochrane Neonatal remains a significant resource for evidence-based medicine in newborn medicine

We will explore all avenues of support and welcome suggestions and thoughts from the Cochrane Neonatal Community, specifically:

• Funder suggestions/contacts
• Testimonials detailing how the work of Cochrane Neonatal has informed your practice, policies, etc. to colleen.ovelman@uvm.edu

Not Ready to Quit!

Upcoming Web Seminar

What has Cochrane Neonatal done for babies!

To be scheduled in September 2017
Housekeeping details!

CME credit?

https://www.surveymonkey.com/r/SZNB7DQ.