Updates in the Anesthetic Management of the Neonate

Lynn D. Martin, MD, FAAP, FCCM

Professor of Anesthesiology & Pediatrics (Adjunct)
Director, Department of Anesthesiology & Pain Medicine
Seattle, Washington

UNIVERSITY OF WASHINGTON
SCHOOL OF MEDICINE

Children's
Hospital & Regional Medical Center

ACCME Disclaimer

No financial relationships with any commercial interests

Objectives

- Review *"new"* controversies in anesthetic care of the neonatal
  - Oxygen toxicity
  - Anesthetic-related neurotoxicity
- Discuss new anesthetic alternatives for neonates

Oxygen Paradox

- Elixir of Life
  - Considered universally beneficial
  - Administered without thought
- Limits Lifespan
  - Dose (high concentration) toxicity
  - Duration toxicity

Neonatal Oxygen Toxicity

- Retinopathy of prematurity (ROP) – 1940s
- Bronchopulmonary dysplasia (BPD) – 1960s
- Oxygen most prescribed ‘drug’ in neonates

Silverman WA: *Pediatrics* 2004; 113: 394-6

Oxygen Toxicity-Neonatal Resuscitation

- Review neonatal resuscitation - 21% v 100% O_2
  - No difference
    - HR response, acid-base status
    - 28 day outcome, APGAR score
  - Air beneficial
    - Shorter time to first cry ($p < 0.05$)
    - Shorter duration positive pressure ventilation ($p < 0.01$)
  - Mortality *trend* (air - 6.9% v oxygen - 8.2%)

Niermeyer S, *et al*: *J Maternal Fetal Neonatal Med* 2004; 15: 75-84

Cochrane Systemic Review

- Reduction in mortality without harm seen in resuscitation with air (RR 0.71, 0.54-0.94; NNT 20)
- Insufficient evidence at present to recommend a policy for use of air over oxygen
- If air used for initial resuscitation gas, supplementary oxygen should be available

Tan A, *et al*: *Cochrane Database of Systemic Reviews* 2005; (2): CD002273

2005 AHA Neonatal Resuscitation Guidelines

- Clinicians may begin resuscitation with less than 100% oxygen or air
- If air resuscitation used, supplementary oxygen available within 90 seconds if no improvement
- Supplemental oxygen recommended whenever positive-pressure ventilation indicated
- Free-flow oxygen used for centrally cyanotic spontaneous breathing infants

AHA/AAP: *Pediatrics* 2006; 117: e1029-38

2005 ILCOR Neonatal Guidelines

- Air is as effective as 100% O2 for resuscitation
- Growing concerns regarding potential adverse effects of 100% oxygen
- Insufficient evidence to specify optimal oxygen concentration for resuscitation
- Supplemental oxygen should be considered with persistent central cyanosis

ILCOR: *Pediatrics* 2006; 117: e978-88

100% O2 Neonatal Resuscitation

- Increases mortality & myocardial/kidney injury

  (Saugstad OD: *Biol Neonate* 2005; 87: 27-34)

- Delays recovery (5 minute APGAR, first cry/breath) & increased oxidative stress @ 4 wks

  (Vento M, *et al*: *J Pediatr* 2003; 142: 240-6)

Antioxidant System

- Antioxidant system compromised in prematurity

  O'Donovan D, *et al*: *Mol Genet Metab* 2000; 71: 352-8

- Markers oxidative stress elevated at 28 days

  Niermeyer S, *et al*: *J Maternal Fetal Neonatal Med* 2004; 15: 75-84

- O_2 stress can cause heart/kidney injury

  Vento M, *et al*: *Am J Respir Crit Care Med* 2005; 172: 1-6

Oxygen and Neonatal Anesthesia

Standard Practice

- Minimum FiO_2 is 30% (air/oxygen mixture)
- If air not available, 100% O_2 acceptable with precautions
    1. Limit high FiO_2 < 6-8 hours duration
    2. Maintain alveolar volume
    3. Contraindicated invulnerable groups (premature, CLD, patients receiving chemotherapy)

Baum J: *Curr Opin Anaesthesiol* 2004; 17: 513-6

Neonatal Respiratory Mechanics

- Small FRC, high closing volume, & unstable alveoli cause 20% reduction dynamic compliance
  - Marcus RJ, *et al*: *Paediatr Anaesth* 2002; 12: 579-84
- Loss of FRC / dependent atelectasis
  - Hedenstierna G, *et al*: *Br J Anaesth* 1990; 64: 507-14
  - Hatch D, *et al*: *Br J Anaesth* 1992; 68: 398-410
- Denitrogenation (FRC loss; V/Q mismatch)
  - Ragg P, *et al*: *Anaesth Intensive Care* 2004; 32: 723
- Effects resolve with recruitment maneuver
  - Marcus RJ, *et al*: *Paediatr Anaesth* 2002; 12: 579-84
  - Tusman G, *et al*: *Anesthesiology* 2003; 98: 14-22

Lung Volume During Anesthesia

- Absorption atelectasis with high FiO_2
  - Induction

    Edmark L, *et al*: *Anesthesiology* 2003; 98: 28-33

    Reber A, *et al*: *Anaesthesia* 1996; 51: 733-7
  - Maintenance

    Hedenstierna G, *et al*: *J Clin Monit* 2000; 16: 329-35

    Rothen H, *et al*: *Lancet* 1995; 345: 1387-91
  - Emergence

    Loeckinger A, *et al*: *Anesth Analg* 2002; 95: 1772-6

Respiratory Adverse Events

- ASA closed claims (infants high risk)
  - Morray JP, *et al*: *Anesthesiology* 1993; 78: 461-7
  - Jimenez N, *et al*: *Anesth Analg* 2007; 104: 147-53
- POCA (infants at risk)
  - Morray JP, *et al*: *Anesthesiology* 2000; 93; 6-14
  - Bhananker SM, *et al*: *Anesth Analg* 2007; 105: 344-50
- Single Center Studies (infants highest risk)
  - Braz LG, *et al*: *Pediatri Anesth* 2006; 16: 860-866
  - Braz LG, *et al*: *Pediatr Anesth* 2006; 16: 860-6
  - Flick RP, *et al*: *Anesthesiology* 2007; 106: 226-37

Summary

- Newborns at risk from oxidative stress
- Anesthesiologists must study their use of oxygen in their neonatal practice
- Answers needed:

  Is it possible to identify infants at risk?

  How long are infants at risk for oxidative injury?

  Can strategies be developed to minimize oxidative stress?

  What is optimal PaO_2 and SpO_2?

  Is it possible to ensure optimal oxygen delivery?

  What is threshold (concentration/duration) to alter therapy?

Van der Walt J: *Pediatr Anesth* 2006; 16: 1205-12

Use of Anesthetic Agents in Neonates and Young Children

R. Daniel Mellow, PhD
Arthur F. Simone, MD, PhD
Bob A. Rappaport, MD

Anesth Analg 2007; 104: 509-20

Receptor Activity of Anesthetic Agents

Agent	NMDA antagonist	GABA-mimetic	Opioid agonist
Volatile anesthetic			
Isoflurane	-/0	+++	0
Desflurane	-/0	+++	0
Sevoflurane	-/0	+++	0
Injectable anesthetic			
propofol/etomidate	0	+++	0
benzodiazepines	0	+++	0
ketamine	- - -	-/0	0
Medical gases			
NO_2/xenon	- - -	+++	0
Opioid analgesics			
morphine	-/0	0	+++
methadone	- - -	0	+++
fentanyl	-/0	0	+++
Other			
ethanol	- - -	+++	0

Neurotoxicity

- MK-801 (NMDA antag) 0.5 mg/kg IP Q 8h x 3
- Ketamine 20 mg/kg SC x 7 over 9 hours
- Apoptotic neurodegeneration in developing brain of rat
- Age-related sensitivity

    High 0-7 postnatal day

    Decrease 7-21 postnatal day

Ikonomidou C, *et al*: *Science* 1999; 283: 70-4

Jevtovic-Todorovic V, *et al*: *J Neurosci* 2003; 23: 876-82

7 day old Sprague-Dawley Rats		
Treatment	**Neuroapoptosis**	**Behavioral**
NO_2 50, 75 or 150%	None	Not evaluated
Midaz 3, 6,& 9 mg/kg IP	None	Not evaluated
Isoflurane 0.75, 1 7 1.5 %	Dose-dependent	Not evaluated
Midaz 9 mg/kg + ISF 0.75%	Increased v ISF alone	Not evaluated
NO_2 75%, midaz 9 mg/kg IP + ISF 0.75%	Greater than double cocktail	Persistent memory/learning loss

Developing Rodent CNS

- Sensitive to:
  - NMDA-antagonist
  - GABAergic agonist
- Combination has greater effect
- Associated with behavior changes

Wang C, *et al*: *Neuroscience* 2005; 132: 967-77

- PND1 Rat Forebrain Culture
  - Ketamine dose (0.1, 1, 10, 20 μM) x 24 hr
    - No effect with O.1 & 1 μM
    - Apoptotic cell death in cortical cells 10 & 20 μM
  - Ketamine duration 10 μM x (2, 6, 12, 24, 48 hr)
    - Cell death noted after 6 or more hours

Wang C, *et al*: *Toxicol Sci* 2006; 91: 192-201

- PND3 rhesus monkey cortical culture
  - Ketamine dose (0.1, 1, 10, 20 μM) x 12 hrs
    - Apoptotic cell death with 10 & 20 μM
  - Ketamine duration 10 μM for 2, 6, 12, 24 hr
    - Cell death seen after 6 or more hours
  - Ketamine injury 10 μM for 24 hr detection (exam 2, 6, 12, 24 hr after washout)
    - Viability decreased at 6, 12, and 24 hr

National Center for Toxicology Research

- Effects seen *in vivo* and *in vitro*
  - Not related to physiologic (O_2, CO_2, BP) changes
- Effects not isolated to rodent species

Do these results occur in humans?

K J S Anand: *Anesthesiology* 2007; 107: 2-4

- Limitations of available laboratory studies
  - Neuronal Development
    - postnatal day 7 rats equal to 16-22 wk gestation human
  - Prolonged exposure
    - Equivalent to days of drug administration
  - Huge dose of drug
    - Log order increase above clinical doses

Koch *et al*: *Anesthesiology* 2008; 108: 122-9

- Paradoxical effects of midazolam in neonatal rats
  - Dose-dependent reduction withdrawl to touch/pain
  - Lack of sedation
    - Day 3: baseline-3.2 ± 0.8 s vs. 15 min-3.9 ± 0.5 s ($p>0.05$)
    - Day 10: baseline-1.4 ± 0.1 s vs. 15 min-20 ± 0 s ($p<0.001$)
    - Day 21: baseline-0.5 ± 0 s vs. 15 min-19.2 ± 2 s ($p<0.001$)

Kain *et al*: *Anesthesiology* 2007; 107:545-52

- Midazolam effectiveness in humans
  - Age-dependent (lower in young)
    - <4 yr 24.7% vs. 8.1% non-responders (p=0.001)
  - Emotionality higher in no-responders

What is safe in neonates?

- Volatile gases?
- Benzodiazepines?
- Ketamine?

Regional Anesthesia

Spinal Anesthesia

- Recorded experience from 1998-2005
- 505 patients; 31% born <35 wks gestation
- 96% success rate
- Average 1.41 attempts per patient
- Bupivacaine 0.66 ± 0.16 mg/kg
- IV sedation needed for 28%

Kacho *et al*: *Pediat Anesth* 2007; 17:647-53

Ropivacaine Spinal

- Fifty neonates < 55 wk undergoing BIH
- ED50 – 0.50 (0.39-0.63) mg/kg
- ED95 – 10.8 (0.70-1.67) mg/kg
- Duration motor block 60 minutes (51.5-68.5 minutes)

Frawley *et al*: *Pediati Anesth* 207; 17: 126-32

Combined Spinal-Epidural Anesthesia

- Twenty four neonates undergoing abdominal surgery
- Bupivacaine 1 mg/kg spinal
- Thoracic (T5-10) caudal catheter (x-ray confirmation)
- Success rate of 85%

Somri *et al*: *Pediati Anesth* 207; 17: 1059-65

Epidural Anesthesia

- Prospective, randomized comparison of ultrasound vs. standard LOR
- Patients less than 6 months of age

Willschke *et al*: *Br J Anaesth* 2006; 97: 200-7

	Ultrasound	Control	P-value
Patients (n)	19	13	--
Age (months)	2.3 (0.1-6)	2.5 (0.1-5)	--
Weight (kg)	3.6 (**0.9**-7.2)	4.7 (**0.8**-6.9)	--
Thoracic puncture	16	11	--
Lumbar puncture	3	2	--
Time required (minutes)	2.9 (1.4)	2.7 (1.8)	--
% punctures with one or more bone contacts	21	54	<0.01
Successful puncture & anesthesia (%)	100	100	--

Internal Jugular vs Subclavian CVC

	Internal Jugular	Subclavian
Body weight (kg)	2.2 (0.58-4.5)	2.8 (0.8-4.5)
Postconceptional age (wk)	37 (26-44)	38 (26-44)
Duration (days)	10 (3-68)	10 (2-62)

Breschan *et al*: *Anesthesiology* 2007; 107: 946-53

Internal Jugular vs Subclavian CVC

	Internal Jugular	Subclavian	P
Infection	20 (0.09-0.23)	5 (0.01-0.11)	<0.01
Suspected infection	7 (0.02-0.12)	4 (0.01-0.1)	0.38
Thrombosis	1 (0.002-0.04)	2 (0.002-0.06)	0.43
Obstruction	8 (0.027-0.12)	1 (0.002-0.05)	< 0.05

Breschan *et al*: *Anesthesiology* 2007; 107: 946-53

Ultrasound Guided CVP Placement

- Randomized clinical trial
- Ultrasound location vs. real-time imaging
- 60 neonates enrolled (all < 7.5 kg)

Hosokawa *et al*: *Anesthesiology* 2007; 107: 720-4

Ultrasound Guided CVP Placement

	Location (n=27)	Real-time (n=33)	P
Puncture attempts			
1st attempt	14 (34-69)	23 (53-83)	0.19
<3 attempts	20 (53-83)	33 (89-100)	<0.01
Complications	2 (2-23)	0 (0-10)	0.20

Hosokawa *et al*: *Anesthesiology* 2007; 107: 720-4

Summary

- “First Do No Harm”
- Pediatric Anesthesiologists must lead the research evaluating potential “toxicity” of our care
  - Oxygen
  - Inhalational and IV anesthetics
- Advances in regional anesthesia potentially provide new options

Children's Hospital & Regional Medical Center