SEDATION FOR SMALL PROCEDURES

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SEDATION in newborns

- How and when
- How to evaluate
- How to dose
Pain in babies may cause later harm

Study in newborn rats suggests early trauma re-wires nervous system

July 27 — Newborns who have painful, but often life-saving, medical procedures in the early weeks of life may have a lower pain threshold in later years, according to a new animal study released Thursday.
Long term effects of pain

Taddio et al. Lancet 1995

Figure: Pain response during HIB injection in circumcised and uncircumcised boys
Why use sedation:

Pain or distress?

Both need to be prevented and treated

Discussion about short and long term effects of pain and distress is more important
Stress

Analgesia

Pain

Inflammation

Stressful procedures

Oxidative stress

Sedation
What do we know?

Neonatal distress / pain:

- Decrease in white and grey matter  
  Brummelte, 2012
- Epigenetic changes (SLC6A4)  
  Provenzi, 2015
- Worse cognitive and motor development  
  Grunau, 2009
- Less visual/perceptive skills  
  Doesburg, 2013
- Thinner cortex and decrease in cerebellar volume  
  Ranger, 2013 & 2015
- Changed reaction to stress  
  Grunau, 2013
- More internalising behavior  
  Ranger, 2014
But what about the negative effects of sedative and analgesic drugs?
How to use sedation?

Examples:

- Intubation
- INtubation SUrfactant Extubation (INSURE)
- Mininally Invasive Surfactant Therapy (MIST)
Premedication for Endotracheal Intubation in (premature) Neonates
POLAND: 
no consensus about medication

Survey all 30 tertiary NICUs

10% always use premedication,

40% use premedication before intubation only sometimes, in case of technical difficulties of active term newborns.

15,5% never use any sedation or analgesia before intubation.

Used drugs:
- midazolam (11 units, 35%),
- analgesics (10 units, 33,3%) (morphine, fentanyl, or pethidine)
- phenobarbitone (4 units, 13,3%),
- muscle relaxants (6,6%)
Endotracheal intubation: evidence

Neonatal elective intubation more successful if pre-treated

Evidence for morphine, atropine and suxamethonium vs placebo
(Oei et al 2002)

Untreated intubation probably harmful for the newborn infant

Premedication prevents acute physiological changes
(VanLooy et al 2008)
Endotracheal intubation seriously painful intervention
(Simons et al 2003)

No consensus about treatment regimen

Wide variability in treatment protocols among centres
(Kumar et al 2008 / Simon et al 2004)
Use of premedication increases; no consensus about medication

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Routine medication</th>
<th>Protocol</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>1998</td>
<td>37%</td>
<td>14%</td>
<td>Whyte et al. 2000, Arch Dis Child Fetal Neonatal Ed.</td>
</tr>
<tr>
<td>UK</td>
<td>1999</td>
<td>34%</td>
<td>?</td>
<td>Hancock et al. 2000, Arch Dis Child Fetal Neonatal Ed.</td>
</tr>
<tr>
<td>Australia</td>
<td>1999</td>
<td>67%</td>
<td>?</td>
<td>Hancock et al. 2000, Arch Dis Child Fetal Neonatal Ed.</td>
</tr>
<tr>
<td>Italy</td>
<td>2005</td>
<td>13%</td>
<td>?</td>
<td>Lago et al. 2005, Paediatr Anesth</td>
</tr>
<tr>
<td>USA</td>
<td>2006</td>
<td>44%</td>
<td>24%</td>
<td>Sarkar et al. 2005, J of Perinatology</td>
</tr>
<tr>
<td>France</td>
<td>2007</td>
<td>74%</td>
<td>60%</td>
<td>Walter-Nicolet et al. 2007, Archives de Pediatrie</td>
</tr>
<tr>
<td>UK</td>
<td>2007</td>
<td>90%</td>
<td>76%</td>
<td>Chaudary et al. 2009, Pediatric Anesth</td>
</tr>
<tr>
<td>UK</td>
<td>2007</td>
<td>93%</td>
<td>82%</td>
<td>Kelleher et al. 2009, Arch Dis Child Fetal Neonatal Ed.</td>
</tr>
</tbody>
</table>
What do we need?

Adequate ways to measure the level of sedation

Adequate drugs and dosages
# How to evaluate sedation

## Intubation Readiness Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Motor reaction to stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Spontaneous movement</td>
</tr>
<tr>
<td>2</td>
<td>Movement in reaction to slight touch</td>
</tr>
<tr>
<td>3</td>
<td>Movement in reaction to firm stimulus</td>
</tr>
<tr>
<td>4</td>
<td>No movement</td>
</tr>
</tbody>
</table>

EVALUATION OF AN INTUBATION READINESS SCORE TO ASSESS NEONATAL SEDATION BEFORE INTUBATION

Ellen de Kort et al. *Neonatology* in press
How to evaluate sedation

<table>
<thead>
<tr>
<th>FACIAL EXPRESSION</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peaceful</td>
<td>Distressed expression</td>
<td>Distressed expression, may cry</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May grimace slightly</td>
<td>Chin drop</td>
</tr>
<tr>
<td>BREATHING PATTERN</td>
<td>Calm effortless breathing</td>
<td>Slightly strained breathing</td>
<td>Strained breathing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breathing pauses</td>
<td>Fast breathing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Apneas</td>
</tr>
<tr>
<td>TONE OF EXTREMITIES</td>
<td>Normal tone</td>
<td>Varied tone</td>
<td>Tense or flacid</td>
</tr>
<tr>
<td>HAND/FOOT ACTIVITY</td>
<td>Relaxed</td>
<td>Slightly clenched</td>
<td>Tightly clenched</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May try to grasp</td>
<td>Fingers/toes spread</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hand on face</td>
<td>Flaccid</td>
</tr>
<tr>
<td>LEVEL OF ACTIVITY</td>
<td>Calmly awake</td>
<td>Occasional motor restlessness</td>
<td>Persistent motor restlessness</td>
</tr>
<tr>
<td></td>
<td>Calmly asleep</td>
<td></td>
<td>Exhausted</td>
</tr>
</tbody>
</table>

Kleberg Agneta, Astrid Lindgren Children’s Hospital, Stockholm, Sweden
Larsson Björn A, Astrid Lindgren Children’s Hospital, Stockholm, Sweden
Lundqvist Pia, Department of Health Sciences, Lund University, Sweden
Adequate drugs?

**Opioids**
- Morphine
- Remifentanil
- Fentanyl
- Sufentanil
- Sufentanil
- Fentanyl

**Muscle relaxants / neuromuscular blockers**
- Rocuronium
- (Cis)atracurium
- Succinylcholine
- +/- Atropine

**Hypnotic / sedative drugs**
- Propofol
- Ketamine
- Midazolam
- Clonidine
- Phenobarbital
- Thiopental
Adequate drugs?

Short onset of action: (semi) urgent intubation

Fast recovery: INSURE to enable extubation

Persistent breathing of newborn: MIST

... without any negative effects on the developing newborn!
# Traditional drugs

## Opioid + muscle relaxant (+ atropine)

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine + vecuronium</td>
<td></td>
</tr>
</tbody>
</table>
  - ‘Gold-standard’ therapy  
  - Extensive experience  
  - Unwarranted Pk/Pd properties (relatively long $T_{\text{max}}$ and $T_{1/2}$) |
| Fentanyl + rocuronium / succinylcholine |  
  - Sedation?  
  - Preferable Pk/Pd properties (relatively long $T_{\text{max}}$ and $T_{1/2}$) |
## Midazolam

### Benzodiazepine
- Short acting
- Sleep inducing
- Easy to use (even nasal route directly after birth)

### On-label for sedation in the NICU
- No loading dose
- Maintenance dose:  
  - <32 weeks: 0.03 mg/kg/hr
  - >32 weeks: 0.06 mg/kg/hr

### Disadvantages
- ?
Midazolam

Disadvantages

Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Neonatal Outcome and Prolonged Analgesia in Neonates.

Anand KJ¹, Barton BA, McIntosh N, Lagercrantz H, Pelusa E, Young TE, Vasa R.
Propofol

Relatively new drug in neonatal care

- Lipid soluble sedative / hypnotic agent
- Extensively used in older children and adults

Advantages

- Easy to use
- Rapidly acting

Disadvantages

- Lack of extensive knowledge in preterm newborns
- Safety unknown (propofol infusion syndrome?)
- Probable hypotensive side effect
- No analgesic effect
Propofol Compared With the Morphine, Atropine, and Suxamethonium Regimen as Induction Agents for Neonatal Endotracheal Intubation: A Randomized, Controlled Trial

Satish Ghanta, MBBS, MD, Mohamed E. Abdel-Latif, MBBS, MRCPCH, MPH, MScEpi, Kei Lui, MBBS, FRACP, MD, Hari Ravindranathan, MBBS, MD, John Awad, MBBS, FANZCA, FJFICM, Julee Oei, MBBS, FRACP

Pediatrics 2007

RCT: N = 33 vs N = 30

Conclusion:
Propofol is more effective, more rapid in action and easier to use compared to morphine, atropine and suxamethonium.
Propofol as an induction agent for endotracheal intubation can cause significant arterial hypotension in preterm neonates

LARS WELZING

Neonates received 1 mg/kg propofol before intubation for INSURE procedure
Clinical evaluation of propofol as sedative for endotracheal intubation in neonates

SHP Simons (ssimons@erasmusmc.nl), R van der Lee, Irwin KM Reiss, MM van Weissenbruch

1. Division of Neonatology, Department of Pediatrics, Erasmus MC Sophia Children’s Hospital, Rotterdam, The Netherlands
2. Department of Neonatology, AMC Emma Children’s Hospital, Amsterdam, The Netherlands
3. Department of Neonatology, VU Medical Center Amsterdam, Amsterdam, The Netherlands

Hypotension in 39% of patients
Propofol dose finding

De Kort et al. PAS Toronto 2018
Propofol dose finding

- With increasing dose (1.0 $\rightarrow$ 2.5 mg/kg), sedation improves

- But also higher risk for side-effects

- Adequate dose in individual patient can not be predicted
Propofol

Thewissen et al. Pediatr Res. 2018
Ketamine

<table>
<thead>
<tr>
<th>NMDA receptor antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Often used in pediatric anesthesia</td>
</tr>
<tr>
<td>Short duration of action</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Studies on safety are lacking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential adverse effects on the developing central nervous system</td>
</tr>
<tr>
<td>Induction of neuronal cell death</td>
</tr>
<tr>
<td>If used in painful situations it might be neuroprotective(!?)</td>
</tr>
</tbody>
</table>
Comparative trials...
Comparative trials...

Propofol (+ atropine) vs Atracurium + Sufentanil (+ atropine)

N=173

Prolonged desaturation = Underpowered for other conclusions

Durrmeyer et al. JAMA 2018
MIST

Sedation during minimal invasive surfactant therapy: a randomised controlled trial

RCT
Newborns 26-36 weeks
MIST
Propofol vs no-premedication

Dekker et al. ADC 2018
MIST

Sedation during minimal invasive surfactant therapy: a randomised controlled trial

<table>
<thead>
<tr>
<th></th>
<th>Propofol</th>
<th>vs</th>
<th>no-premedication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comfort scores &lt;14</td>
<td>76%</td>
<td></td>
<td>22%</td>
</tr>
<tr>
<td>Desaturation &lt; 85%</td>
<td>91%</td>
<td></td>
<td>69%</td>
</tr>
<tr>
<td>Nasal ventilation</td>
<td>93%</td>
<td></td>
<td>47%</td>
</tr>
</tbody>
</table>

Dekker et al. ADC 2018
sedatives in neonates?

*Use guidelines +

*Think about the basics ....
hepatic

Body composition

Formula dependent

renal

Kearns et al, NEJM 2003
ALLEGAEERT, SIMONS. ET AL. EUR J PHARMACEUTICAL SCIENCES 2017
AUTOMATED MULTIMODAL ASSESSMENT
OF INFANTS PAIN / DISTRESS

Facial expression  Body movements  Physiological data  Crying sounds

AUTOMATED ANALYSIS
‘movement tracking’

total pain score
thresh

Continuous pain monitoring

Abstract, PAS meeting San Fransisco 2017
Multi model assessment

General observations: body movements, sleep state, crying

‘Emotional’ behavior: facial expression

Specific flexor muscle EMG activity

Cortical neural activity with NIRS and EEG

Cardiovascular and respiratory responses: heart rate, $pO_2$

Hormonal responses: cortisol

Heel lance
Sedation: personalized medicine!

In general for all sedation and analgesia:

The amount and intensity of treatment depends on the specific patient and the specific condition.

It needs to be titrated to the individual's needs.

With the Child

Analgesic treatment should be individualized according to:

- The child’s pain
- Response to treatment
- Frequent reassessment
- Modification of plan as required
Thank you very much for your attention!

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