neonatal analgosedation
on what we know and how we act?

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Pain in babies may cause later harm

Study in newborn rats suggests early trauma rewires 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.
Figure: Pain response during HIB injection in circumcised and uncircumcised boys
Data not available for cry on 1 infant. p=0.02 for cry, p=0.01 for behavioural pain score.

Taddio et al. JAMA 2002
Influence of
on the development of

Anna Taddio^a,b,

Venipuncture
PIPP Scores

Treatment Group

Sucrose Placebo

Low (≤ 4) High (≥ 5)

**

VAS Pain Scores

Group

Sucrose Placebo

Low (≤ 4) High (≥ 5)

*

Cry Duration

Group

Sucrose Placebo

Low (≤ 4) High (≥ 5)


Figure 1 Key sites of developmental transition in infant pain pathways. The areas of the nervous system are indicated where developmental changes and plasticity impact pain detection and treatment. (1) The epithelial innervation is vulnerable and sensitive to injury. (2) The primitive reflex pathways undergo considerable postnatal development, and some reflex pathways are diffuse and poorly tuned, which may contribute to hyperalgesia before secondary hyperalgesia. (5) Endogenous opioid systems in the medulla oblongata and brainstem are unbalanced. (6) Extensive structural remodeling occurs, but little is known of the development of these structures into early adulthood. (7) The somatosensory cortex is established early in life, but little is known of activation in the somatosensory cortex before term.

**early insult rewires pain circuits**

Maximal effect in rats: 6-9 days *(Anand & Scalzo 2000)*

No effect in rats: 14 days *(Ruda et al. 2000)*

Rat - Human
0 day - 24 wks GA
7 days - full-term
14 days - 1-year-old
If a procedure is painful in adults, it should be considered painful in newborns, even if they are preterms.
not ‘only’ human ethical aspects
also hard short and longterm clinical outcome data
Venipuncture Is More Effective and Less Painful Than Heel Lancing for Blood Tests in Neonates

Björn A. Larsson, MD*; Gunnilla Tannfeldt, RN*; Hugo Lagercrantz, MD, PhD‡; and Gunnar L. Olsson, MD, PhD*
The 3 P’s of Helping your Baby during Vaccinations
A Parent’s Guide: Babies up to 1 year old

Vaccine injections can be painful and stressful for babies and parents, but you can really make a difference.

For your baby’s next vaccine injection, plan with your health care provider to:
1) Apply topical anaesthetics to numb the skin – these are medicines you can buy at a pharmacy without a prescription.
2) Give your baby sugar water for comfort – make sugar water at home or at the clinic by mixing 1 teaspoon of sugar with 2 teaspoons of water.
3) Distract your baby – choose an age-appropriate item to bring.

Read the 3 P’s of vaccination pain management below and combine these strategies to improve pain relief.
For more information and a video, visit the SickKids (The Hospital for Sick Children, Toronto, Canada) website: www.aboutkidshealth.ca/pain-free-injections.

STEP 1: PHARMACOLOGICAL (PAIN MEDICINE)

TOPOCAL ANALGESICS
- Available products: lidocaine (Maxeran™), tetracaine (Anistop™), lidocaine/prilocaine (EMLA™).
- Apply to either the upper outer part of the leg (infants less than 1 year), or upper arm (infants 1 year old). 30 to 60 minutes before injection – check product instructions.
- May cause temporary reddening or whitening of skin – this is normal. If there is a rash, talk to your doctor – it could be an allergic reaction.
- Avoid acetaminophen (Tylenol™), ibuprofen (Advil™), ice and cold sprays before injection – they have not been proven to reduce injection pain. After injection, acetaminophen or ibuprofen may be used to relieve fever or discomfort.

STEP 2: PHYSICAL (BODY POSITION AND ACTIVITY)

HOLD
- Hold your baby close during injection – in a hug or on your lap. This feels good and helps your baby stay still.
- Avoid holding your baby too tightly – this can increase pain and distress.

BREASTFEED
- Start breastfeeding your baby before injection and continue during and after injection.
- If 1 injection is planned, position your baby to expose 1 leg; expose both legs for 2 or more injections.
- If the baby cannot be breastfed, offer a bottle or pacifier starting before injection and continue during and after injection.

STEP 3: PSYCHOLOGICAL (THOUGHTS AND BEHAVIOURS)

DEEP BREATHS
- Stay calm and use your normal speaking voice. This helps your baby stay calm – babies look to their parents for how to act and feel.
- If you are nervous, take a few slow, deep breaths to calm yourself before and during injection – breathe so your stomach expands, not your chest. You can do this while holding your baby.

DISTRACT
- Help keep your baby’s attention away from the injection.
- Distractions you can use: rocking, cuddling, singing, talking, sucking (breastfeeding or pacifier). Distract with objects or toys (bubbles, pop-up books, rattles) when your baby is calm enough to do so; otherwise, distress can be increased.

These are scientifically proven ways of reducing pain in babies during vaccine injections. Think about what worked and plan ahead to make the next vaccination less painful.

treatment

maturational aspects
unexplained variability

assessment

pain scales
intersubjectivity

prevention

relevant
limited

individualized approach
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, pO2

Heel lance

Hormonal responses: cortisol

Figure 2 Methods of assessing infant pain. In the absence of language, infant pain is assessed by a number of different physiological methods. Some of these methods are integrated into current clinical pain assessment tools. The neurophysiological techniques EMG, EEG and NIRS are not used for routine pain assessment but are increasingly being used in research studies of infant pain. Abbreviations: EMG, electromyogram; NIRS, near-infrared spectroscopy; pO2, partial pressure of oxygen.
A multifaceted model of the components of pain.
INVITED COMMENTARY

Calming minds or killing pain in newborn infants?

S Lindahl

Department of Anaesthesiology and Intensive Care, Karolinska Hospital and Institute, Stockholm, Sweden


Fig 2. Pain evaluation with DAN scale (0 to 10) during venepuncture in 150 newborns randomised to six equal sized groups, with values for individual infants, median values, and interquartile ranges (for 30% sucrose and pacifier lower quartile coincides with median value).
Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomised controlled trial

Rebecca Slater, Laura Cornelissen*, Lorenzo Fabrizi*, Debbie Patten, Jan Yoxen, Alan Worley, Stewart Boyd, Judith Meek†, Maria Fitzgerald†
Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomised controlled trial

Rebecca Slater, Laura Cornelissen, Lorenzo Fabrizi, Debbie Patten, Jan Yoxen, Alan Worley, Stewart Boyd, Judith Meek, Maria Fitzgerald

<table>
<thead>
<tr>
<th></th>
<th>Sucrose (N=20)</th>
<th>Sterile water (N=24)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nociceptive-specific brain activity (mean weight)</td>
<td>0.10 (0.04-0.16)</td>
<td>0.08 (0.04-0.12)</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline heart rate (bpm)</td>
<td>132.6 (124.3-140.9)</td>
<td>131.8 (122.2-141.5)</td>
<td>0.90</td>
</tr>
<tr>
<td>Mean baseline oxygen saturation (%)</td>
<td>99.4% (98.8-100.1)</td>
<td>97.4% (95.0-99.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>Baseline behavioural score (from PIPP)</td>
<td>1.3 (0.8-1.7)</td>
<td>1.3 (0.8-1.8)</td>
<td>0.91</td>
</tr>
<tr>
<td>PIPP score</td>
<td>5.8 (3.7-7.8)</td>
<td>8.5 (7.3-9.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Latency to change in facial expression (s)</td>
<td>3.8 (1.3-6.4)</td>
<td>3.5 (1.0-6.1)</td>
<td>0.86</td>
</tr>
<tr>
<td>Facial non-responders</td>
<td>7/20 (35%)</td>
<td>0/24 (0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean nociceptive reflex withdrawal activity (µV)</td>
<td>36.11 (24.20-48.02)</td>
<td>30.82 (18.51-43.13)</td>
<td>0.49</td>
</tr>
<tr>
<td>Mean latency to nociceptive reflex withdrawal activity (ms)</td>
<td>363.3 (256.4-470.1)</td>
<td>413.5 (262.0-564.9)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Data are mean (95% CI) or n/N (%). bpm=beats per min. PIPP=premature infant pain profile.
AIM 1: To increase pain assessment in all babies from 30% to 70% by end of cycle 2.

AIM 2: We will improve the use of bundling and sweet solution for babies undergoing painful procedures from 5% to 60%.

Pain Management for Infants

Why use bundling?
Bundling decreases pain during painful procedures.
treatment

maturational aspects
unexplained variability

assessment

pain scales
intersubjectivity

prevention

relevant
limited

individualized approach
Figure 1. Stepwise approach to neonatal analgesia.
analgesics in neonates

maturational changes in

body composition
renal function
liver function
### Neonatal formulary\(^{12}\)

<table>
<thead>
<tr>
<th>Method</th>
<th>Loading dose</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral</strong></td>
<td>24 mg/kg</td>
<td>12 mg/kg/dose&lt;br&gt;q4h in ≥ 32 wk PMA, q8h in &lt; 32 wk</td>
</tr>
<tr>
<td><strong>Rectal</strong></td>
<td>36 mg/kg</td>
<td>24 mg/kg, q8h in term neonates&lt;br&gt;No advice in preterm neonates</td>
</tr>
<tr>
<td><strong>Intravenous</strong></td>
<td>20 mg/kg, irrespective of age&lt;br&gt;15 mg/kg, q6h in term cases&lt;br&gt;12.5 mg/kg, 31–36 wk PMA&lt;br&gt;10 mg/kg, ≤ 30 wk PMA</td>
<td></td>
</tr>
</tbody>
</table>

### Dutch formulary\(^{13}\)

<table>
<thead>
<tr>
<th>Method</th>
<th>Loading dose</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral</strong></td>
<td>Not sufficiently supported by clinical evidence&lt;br&gt;60 mg/kg/d, &gt; 32 wk PMA&lt;br&gt;30 mg/kg/d, 28–32 wk PMA</td>
<td></td>
</tr>
<tr>
<td><strong>Rectal</strong></td>
<td>30 mg/kg, &lt; 32 wk PMA&lt;br&gt;20 mg/kg, 28–32 wk PMA&lt;br&gt;20 mg/kg, q8h in term neonates&lt;br&gt;20 mg/kg, q12h in preterm neonates</td>
<td></td>
</tr>
<tr>
<td><strong>Intravenous</strong></td>
<td>Off label in preterm neonates&lt;br&gt;20 mg/kg, irrespective of age&lt;br&gt;10 mg/kg, max 40 mg/kg/d, in term cases&lt;br&gt;10 mg/kg, max 30 mg/kg/d, 31–36 wk PMA&lt;br&gt;10 mg/kg, max 20 mg/kg/d, &lt; 31 wk PMA</td>
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PMA = postmenstrual age (in weeks).
Fig. 1. Changes occurring in percentages of body fat and water stores along the continuum of age [16].

Ref: Rakhmanina et al, 2006
distribution volume: hydrophylic drugs
Figure 3  A typical concentration profile for neonates of 28–44 weeks’ prematurity given a paracetamol loading dose of 20 mg/kg (black continuous line) or not given a loading dose (grey continuous line), followed by a maintenance dose of 10 mg/kg every 6 h. A mean concentration of 11 mg/l is achieved.
the route matters

Anderson et al. Anesthesiology 1999;90:411-21

rectal route

oral route

Biodisponibility 0.54
the route matters

Solid box = 50th centile
Values outside the 97.5% centile are shown individually

Anderson et al. Anesthesiology 1999;90:411-21
together is better?

Effect of Intravenous Paracetamol on Postoperative Morphine Requirements in Neonates and Infants Undergoing Major Noncardiac Surgery: A Randomized Controlled Trial

Ilse Ceelie, MD, PhD
Saskia N. de Wildt, MD, PhD
Monique van Dijk, MSc, PhD
Margreet M. J. van den Berg, MD
Gerbrich E. van den Bosch, MD
Hugo J. Duivenvoorden, PhD
Tom G. de Leeuw, MD
Ron Mathôt, PharmD, PhD
Catherijne A. J. Knibbe, PharmD, PhD
Dick Tibboel, MD, PhD

The treatment of pain in young children has improved after the publications by Anand et al. in 1987 that made clear that neonates have well-developed nociceptive pathways and therefore are capable of experiencing pain. Because untreated pain is both an unwanted experience and ultimately may lead to adverse consequences, opioids were introduced and have been used ever since. Opioid therapy, however, is associated with adverse effects, in particular respiratory depression. Re-

Importance Continuous morphine infusion as standard postoperative analgesic therapy in young infants is associated with unwanted adverse effects such as respiratory depression.

Objective To determine whether intravenous paracetamol (acetaminophen) would significantly (>50%) reduce morphine requirements in neonates and infants after major surgery.

Design, Setting, and Patients Single-center, randomized, double-blind study conducted in a level 3 pediatric intensive care unit in Rotterdam, the Netherlands. Patients were 71 neonates or infants younger than 1 year undergoing major thoracic (noncardiac) or abdominal surgery between March 2008 and July 2010, with follow-up of 48 hours.

Interventions All patients received a loading dose of morphine 30 minutes before the end of surgery, followed by continuous morphine or intermittent intravenous paracetamol up to 48 hours postsurgery. Infants in both study groups received morphine (boluses and/or continuous infusion) as rescue medication on the guidance of the validated pain assessment instruments.

Main Outcome Measures Primary outcome was cumulative morphine dose (study and rescue dose). Secondary outcomes were pain scores and morphine-related adverse effects.

Results The cumulative median morphine dose in the first 48 hours postoperatively was 121 (interquartile range, 99-264) μg/kg in the paracetamol group (n = 33) and 357 (interquartile range, 220-605) μg/kg in the morphine group (n = 38), P < .001, with a between-group difference that was 66% (95% CI, 34%-109%) lower in the paracetamol group. Pain scores and adverse effects were not significantly different between groups.

Conclusion and Relevance Among infants undergoing major surgery, postoperative use of intermittent intravenous paracetamol compared with continuous morphine resulted in a lower cumulative morphine dose over 48 hours.

Trial Registration trialregister.nl Identifier: NTR1438

JAMA. 2013;309(2):149-154
together is better?
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The NEW ENGLAND JOURNAL of MEDICINE

Defining Safe Use of Anesthesia in Children
Bob Rappaport, M.D., R. Daniel Mellon, Ph.D., Arthur Simone, M.D., Ph.D., and Janet Woodcock, M.D.
Mind numbing: Anesthesia in baby rats stunts brain development.

Common general anesthetics given at an early age may cause brain damage and other neurologic problems.
<table>
<thead>
<tr>
<th>Institution/Organization</th>
<th>Description</th>
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<tbody>
<tr>
<td>Odense University Hospital (Denmark) and the Danish Registry Study Group</td>
<td>A nationwide epidemiologic study comparing the educational achievement of all children who have undergone a surgical procedure before the age of 1 with that of a general-population control group.</td>
</tr>
<tr>
<td>Columbia University</td>
<td>A prospective cohort study of children who had exposure to an anesthetic before the age of 3 and their siblings who were not exposed. The two groups will be followed for neurodevelopmental outcomes.</td>
</tr>
<tr>
<td>International collaboration of institutions from Australia, the United States, Canada, Italy, the United Kingdom, and the Netherlands</td>
<td>Prospective, randomized, investigator-blinded, controlled clinical trial to assess the effects of general anesthesia using sevoflurane versus neuraxial anesthesia using bupivacaine on neurocognitive function in infants over 26 weeks’ gestational age. Children will be followed with evaluations of neurocognitive development at 2 and 5 years of age.</td>
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Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial

Andrew J Davidson, Nicola Disma, Jurgen C de Graaff, Davinia E Withington, Liam Dorris, Graham Bell, Robyn Stargatt, David C Bellinger, Tibor Schuster, Sarah J Arnup, Pollyanna Hardy, Rodney W Hunt, Michael J Takagi, Gaia Giribaldi, Penelope L Hartmann, Ida Salvo, Neil S Morton, Britta S von Ungern Sternberg, Bruno Guido Locatelli, Niall Wilton, Anne Lynn, Joss J Thomas, David Polaner, Oliver Bagshaw, Peter Szmuk, Anthony R Absalom, Geoff Frawley, Charles Berde, Gillian D Ormond, Jacki Marmor, Mary Ellen McCann, for the GAS consortium*

Findings Between Feb 9, 2007, and Jan 31, 2013, 363 infants were randomly assigned to receive awake-regional anaesthesia and 359 to general anaesthesia. Outcome data were available for 238 children in the awake-regional group and 294 in the general anaesthesia group. In the as-per-protocol analysis, the cognitive composite score (mean [SD]) was 98·6 (14·2) in the awake-regional group and 98·2 (14·7) in the general anaesthesia group. There was equivalence in mean between groups (awake-regional minus general anaesthesia 0·169, 95% CI −2·30 to 2·64). The median duration of anaesthesia in the general anaesthesia group was 54 min.

Interpretation For this secondary outcome, we found no evidence that just less than 1 h of sevoflurane anaesthesia in infancy increases the risk of adverse neurodevelopmental outcome at 2 years of age compared with awake-regional anaesthesia.
Treatment
Maturational aspects affect drug dose (pharmacokinetics)
Changes in practices affect primary outcome variables (pharmacodynamics)

Assessment
Pain scales
Intersubjectivity
Hetero-assessment

Prevention
Growing evidence on effectiveness of non-pharmacological modalities

Individualized approach
Combination of unit specific guidelines and the individual needs of the newborn