Up-date in anesthetic neurotoxicity

Jurgen C. de Graaff
Department Pediatric Anesthesia
Wilhelmina Children's Hospital

BAPA-SKA Refresher course
16 Januari 2015
Heverlee

Is anaesthesia dangerous for children?
Established Neurotoxins

- Alcohol → Fetal alcohol syndrome

www.FASproject.nl
Creeley and Olney Anesth Analg 2010;110 442-8

Established Neurotoxins

- Alcohol → Fetal alcohol syndrome

- Antiepileptic drugs → Fetal malformations
  - Phenytoin → Developmental delay
  - Phenobarbital → Microcephaly
  - Benzodiazepine

Creeley and Olney Anesth Analg 2010;110 442-8
Established Neurotoxins

- Alcohol → Fetal alcohol syndrome
- Antiepileptic drugs → Fetal malformations
  - Phenytoin
  - Phenobarbital
  - Benzodiazepine
- Anesthetic drugs → ?
  - Nitrous oxide
  - Ketamine
  - Isoflurane/Sevoflurane
  - Propofol
  - Midazolam

Creeley and Olney Anesth Analg 2010;110:442-8

Anaesthetic neurotoxicity?

- Non-clinical research
- Clinical Research
Patho-physiological mechanism

- NMDA receptor antagonist
  - Ketamin
  - Nitrous oxide
  - Reduced synaptogenesis
  - Apoptosis: programmed cell death
- GABA-agonist:
  - Propofol
  - Barbiturate
  - Benzodiazepine
  - Inhalation anesthetics: Sevoflurane, isoflurane,
  - Higher concentration intracellular calcium
  - GABA-activation:
    - Hyperpolarization
    - Toxic concentration calcium

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Early Exposure to Common Anesthetic Agents Causes Widespread Neurodegeneration in the Developing Rat Brain and Persistent Learning Deficits

Vesna Jevtovic-Todorovic,1 Richard E. Hartman,2 Yukitoshi Izumi,1 Nicholas D. Benshoff,2 Krikor Dikranian,3 Charles F. Zorumski,1 John W. Olney,2 and David F. Wozniak2

1Department of Anesthesiology, University of Virginia Health System, Charlottesville, Virginia 22908, and Departments of 2Neurology and 3Psychiatry, Washington University School of Medicine, St. Louis, Missouri 63110
Early Exposure to Common Anesthetic Agents Causes Widespread Neurodegeneration in the Developing Rat Brain and Persistent Learning Deficits

- Triple cocktail (P7 rat pups)
  - Midazolam
  - Isoflurane
  - Nitrous oxide

- Histological changes
  - Neurodegeneration

- Functional changes
  - Morris water maze
  - Radial arm maze

*Jevtovic-Todorovic et al, J Neurosci, 2003*

Pathophyiological mechanism

**Apoptosis: programmed cell death**

Control Ketamine
Ikonomidou Science 1999

Control N2O+Mida+Isoflurane
Jevtovic-Todorovic J Neurosci 2003
Morris Water Maze

A Radial Arm Maze
Neonatal Exposure to Sevoflurane Induces Abnormal Social Behaviors and Deficits in Fear Conditioning in Mice

Maiko Satomoto, M.D.,† Yasushi Sato, Ph.D.,‡ Katsuo Tenu, M.D., Ph.D.,† Hideki Miyao, M.D., Ph.D.,§ Kunio Takishima, Ph.D.,‖ Masaaki Ito, M.D., Ph.D.,§ Junko Inaki, M.D., Ph.D.,**

A Control
B 3% Sevo
dhc
cp
C Control
D 3% Sevo
cp

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Neonatal Exposure to Sevoflurane Induces Abnormal Social Behaviors and Deficits in Fear Conditioning in Mice

Maiko SatoMoto, M.D.,† Yasushi Satoh, Ph.D.,‡ Katsuo Terui, M.D., Ph.D.,§ Hideki Miyao, M.D., Ph.D.,§ Kunio Takishima, Ph.D.,¶ Masataka Ito, M.D., Ph.D.,¶ Juniko Inaki, M.D., Ph.D.,**

** Of Mice and Men: Should We Extrapolate Rodent Experimental Data to the Care of Human Neonates?**

Salvatore G. Soriano, M.D.,* Kanwaljit J. S. Anand, M.B.B.S.,
D. P. Hall, Cynthia R. Bovaghi, M.S., Paul R. Hickey, M.D.,
* Children’s Hospital Boston and Harvard Medical School, Boston,
Comment: Humans are not rats!

Problem with rodent experimental paradigm

- Duration exposure to drugs
  - 7 rat days \(\approx\) 27 human months
  - 6 hour anesthesia \(\approx\) 1 month
- Lack of precise physiological monitoring
  - High etCO2
  - End-organ perfusion
  - Varying anaesthetic depth
    - Target-controlled infusions
    - MAC values
- Interspecies variation
  - Dose-response
  - Drug metabolism
  - Peak susceptibility
Ketamine-Induced Neuronal Cell Death in the Perinatal Rhesus Monkey

Creeley BJA 2013 & Brambrink Anesthesiology 2010
### Anaesthesia neurotoxicity?

#### Experimental research:

- >900 publications experimental studies
- All anesthetic drugs
- Dose and duration dependent
- Window vulnerability
- Period?
  - Younger age
  - <2-3 year?
- Clinical proof?
Anaesthetic neurotoxicity?

- Experimental research
- Clinical research:
  - RCT: almost impossible
  - epidemiological

Early Exposure to Anesthesia and Learning Disabilities in a Population-based Birth Cohort

Robert T. Waldie, M.D., Ph.D.,* Randall P. Flick, M.D., M.P.H.,† Junj Sprung, M.D., Ph.D.,† Stanica K. Katakic, M.D.,§ William J. Barbanal, M.D.,Christopher Melkerson, M.D.,‡ Stephen J. Gluck, M.D.,‡,* Danell R. Schroeder, M.S.,‡* Amy L. Weaver, M.S.,†† David O. Warner, M.D.††

- birth cohort study: (n=5,357)
- 593 children received anesthesia before age 4 yr
- Learning Disabilities
  - 1 anesthesia: (HR 1.0; 95% CI, 0.79–1.27)
  - 2 anesthetics (n = 100): HR 1.59; 95% CI, 1.06–2.37
  - > 2 anesthetics (n = 44) HR 2.60; 95% CI, 1.60–4.24
- Risk LD increased with longer cumulative duration of anesthesia exposure
Cumulative percentage of learning disabilities diagnosis by the age at exposure

Wilder et al., 2009

Cognitive and Behavioral Outcomes After Early Exposure to Anesthesia and Surgery
Randall P. Flick, Slavica K. Katusic, Robert C. Colligan, Robert T. Wilder, Robert G. Voigt, Michael D. Olson, Juraj Sprung, Amy L. Weaver, Darrell R. Schroeder and David O. Warner

- Cohort study Rochester Minnsota
- Exposed to anesthesia n= 350
- Controls: n= 700
- Multivariate analysis
  - Learning disabilities: LD
  - Emotional and behavior disorders: IEP-EBD
  - Speak and language: IEP-SL
- Multiple exposures:
  - LD: HR 2.12 (1.26-3.54)
  - IEP-EBD: 0.00
  - IEP-SL: 4.76 (2.48 – 9.12)
Anesthesia and Cognitive Performance in Children: No Evidence for a Causal Relationship

Meike Bartels,* Robert R. Althoff,** and Dorret I. Boomsma¹

¹ Department of Biological Psychology, VU University Amsterdam, The Netherlands
² Departments of Psychiatry and Pediatrics, University of Vermont, Burlington, Vermont, United States of America
* Both authors contributed equally to the manuscript

Twin Research and Human Genetics Volume 12 Number 3 pp. 246-253

• Netherlands Twin Registry: data on anesthesia administration and learning abilities and disabilities for 1,143 monozygotic twin pairs
• Parents of the twins reported on anesthesia/surgery before age 3 and again between ages 3 -12 years.
• Near age 12, educational achievement and cognitive problems were assessed with standardized tests (CITO) and teacher ratings
• Twins who were exposed to anesthesia before age 3 had significantly lower educational achievement scores and significantly more cognitive problems than twins not exposed to anesthesia.
• The unexposed co-twin from discordant pairs did not differ from their exposed co-twin
Bartels et al 2009: educational achievement

Limitations Bartels et al 2009:

- Relative small group: <3 yr
  - CITO: 61 boy twin, 49 girls
  - Cognitive problems: 29 boys & 27 girls
- Only learning problems
- Type and duration surgery and anesthesia is unknown
• Birth cohort Denmark: 1986-1990:
  – Hernia repair n= 2689
  – Controls: n= 14575
• Exclusion: congenital malformations
• School performance
• Exposed – control group: 7.68 – 7.83
  – (Difference: 0.15; 95% CI: 0.10 – 0.21)
• Correction:
  – Congenital malformations: NS

Summary clinical research

• Wilder (Anesthesiology 2009) +
• Sprung (Anesthesiology 2009) -
• DiMaggio (J Neuroanesthe 2009) +
• Bartels (Twin Res 2009) -
• DiMaggio (A&A 2011) +
• Flick (Pediatrics 2011) +
• Laign (J Paed Child Heal 2011) +
• Hansen (Anesthesiology 2011) -
• Sprung (Mayo Proc 2012) +
• Block (Anesthesiology 2012) +
• Ing (pediatrics 2013) +
• Ing (J Neurosurg Anesth 2014) +
• Conclusion ?
Anaesthetic neurotoxicity?

- Experimental research
- Clinical research: Epidemiological
- Clinical research: Randomized clinical trial

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, Nicole Diasio, Jurgen C de Graeff, Dawid K Wiblinger, Liam Doris, Graham Bell, Robyn Staggott, David C Bellinger, Tibor Schuster, Sarah J Arrows, Pollyanna Hardy, Rodney W Hewitt, Michael J Takagi, Gaius Girnbachl, Piers Lopez, Martin Jadae, Idai S Mufunye, Britta von Ungern-Stamberg, Bruno Guido Locatelli, Niell Milson, Anne Lynn, Issy J Thomas, David Polener, Oliver Boghina, Peter Szmul, Anthony R Alhakim, Geoff Fraley, Charles Birse, Gillian D Ormond, Judi Marmar, Mary Ellen McCann, for the GAS consortium

Anaesthetics, infants, and neurodevelopment: case closed?

THE LANCET
16 January, 2016; 229-238
**Study design:**
compare children who undergo surgery with anesthesia with a control group (no anesthesia)

<table>
<thead>
<tr>
<th></th>
<th>ANESTHESIA</th>
<th>Local ANESTHESIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>groups</td>
<td>330</td>
<td>330</td>
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</tbody>
</table>

**Aim**

- To determine if general anaesthesia in infancy is “safe”
- Question: Does general anaesthesia and awake-regional anaesthesia in infancy have the same neurodevelopmental outcome?
Rationale

- Spinal and GA accepted techniques for infant inguinal hernia repair
- Infants probably most at risk
- Duration is short but most anaesthetics in children are short
- No reason to think spinal anaesthesia is injurious

- If we find equivalence then we can assume the majority of general anaesthetics in children are “safe”

Randomized Clinical Trial GAS-study:
General vs. regional anaesthesia

- Randomized, assessor blinded, multisite equivalence trial
  - Hernia repair (< 60 post conceptional age = 4 month)
  - Spinal vs. General anesthesia
  - Neuropsychological development at age 2 & 5 yrs

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<tbody>
<tr>
<td>Recruit</td>
<td>x</td>
<td>x</td>
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<td>Yr 2 assessment</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>x</td>
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<tr>
<td>Yr 5 assessment</td>
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<td>x</td>
<td>x</td>
<td>x</td>
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</tr>
</tbody>
</table>
Sites Involved in the GAS study

- **Australia and New Zealand:**
  - Royal Children's Hospital, Melbourne
  - Monash Medical Centre, Melbourne
  - Cabrini Hospital Melbourne
  - Casey Hospital Melbourne
  - Women's and Children's, Adelaide
  - Princess Margaret Hospital, Perth
  - Starship Children's Hospital, Auckland

- **USA:**
  - Children's Hospital, Boston
  - Children's Memorial Hospital Chicago
  - Dartmouth Hitchcock Medical Centre
  - Vanderbilt Children's Hospital, Nashville
  - The University of Iowa Hospital
  - Children's Medical Centre, Dallas
  - Children's Hospital of Philadelphia
  - Seattle Children's Hospital
  - The Children's Hospital, Denver
  - The University of Vermont/Pfleger Allen Health Care in Burlington, Vermont

- **UK:**
  - Royal Hospital for Sick Children, Glasgow
  - Bristol Royal Hospital for Children
  - Birmingham Children's Hospital NHS Trust
  - Royal Belfast Hospital for Sick Children
  - Royal Liverpool Children's NHS Alder Hey Hospital
  - Sheffield Children's Hospital

- **Italy:**
  - Gaslini Hospital for Children, Genoa
  - Buzzi Children's Hospital, Milan
  - Ospedali Riuniti, Bergamo

- **The Netherlands:**
  - Wilhelmina Children's Hospital, University Medical Centre Utrecht, The Netherlands
  - Universitair Medisch Centrum Groningen

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RA

- **Awake Spinal**
  - Bupivacaine or levobupivacaine 0.5% 0.2 ml/kg (min 0.5 ml)
  - +/- caudal or ilioinguinal block
  - No sedation

- **Awake Caudal**
  - Bupivacaine 2.5mg/kg
  - No sedation
GA

- Up to 8% Sevoflurane in oxygen/air
- No nitrous oxide, No opioids
- Facemask or ETT +/- NDNMB
- Mechanical or spontaneous ventilation
- Caudal or ilio-inguinal block

Neurodevelopmental outcomes

- Primary outcome:
  - WPPSI-III Full Scale IQ score at 5 years

- Secondary outcomes
  - Bayley III at 2 years
  - MacArthur Bates at 2 years
  - Diagnosis of CP or other neurologic or behavioural disorders
Bayley-III

- 5 scores
  - Cognitive
  - Motor
  - Language
  - Social emotional
  - Adaptive behaviour

- Composite score normalised to each country
  - Mean 100
  - SD 15

Analysis

- Primary: As per protocol
- Secondary: Intention to treat

- Adjusted for gestational age at birth
- Multiple imputation
- Complete case
Demographic data

<table>
<thead>
<tr>
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<th>GA Arm ITT (N=358)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, Male</td>
<td>232 (81%)</td>
<td>304 (85%)</td>
<td>294 (82%)</td>
<td>306 (86%)</td>
</tr>
<tr>
<td>Chronological age at surgery (days)</td>
<td>68±9 (31)</td>
<td>71±1 (32)</td>
<td>70±1 (32)</td>
<td>71±0 (32)</td>
</tr>
<tr>
<td>Post menstrual age at surgery (days)</td>
<td>317±2 (32)</td>
<td>319±7 (32)</td>
<td>318±3 (33)</td>
<td>319±5 (32)</td>
</tr>
<tr>
<td>Weight of child at surgery (kg)</td>
<td>4±2 (1±1)</td>
<td>4±3 (1±1)</td>
<td>4±2 (1±1)</td>
<td>4±3 (1±1)</td>
</tr>
<tr>
<td>Mean (SD) Post menstrual age at birth (days)</td>
<td>248±2 (29)</td>
<td>248±6 (27)</td>
<td>248±3 (29)</td>
<td>248±6 (27)</td>
</tr>
<tr>
<td>Prematurity (Born &lt; 37 weeks gestation)</td>
<td>160 (56%)</td>
<td>195 (55%)</td>
<td>198 (55%)</td>
<td>196 (55%)</td>
</tr>
<tr>
<td>Birth Weight (kg)</td>
<td>2±3 (0±9)</td>
<td>2±3 (0±9)</td>
<td>2±4 (0±9)</td>
<td>2±3 (0±9)</td>
</tr>
<tr>
<td>Z score for birth weight</td>
<td>-0.68 (1±3)</td>
<td>-0.69 (1±3)</td>
<td>-0.66 (1±2)</td>
<td>-0.69 (1±3)</td>
</tr>
<tr>
<td>Mode of delivery of birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalic vaginal</td>
<td>135 (47%)</td>
<td>157 (44%)</td>
<td>168 (47%)</td>
<td>157 (44%)</td>
</tr>
<tr>
<td>Breech vaginal</td>
<td>1 (&lt;1%)</td>
<td>6 (2%)</td>
<td>3 (1%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Compound vaginal</td>
<td>2 (1%)</td>
<td>4 (1%)</td>
<td>3 (1%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>49 (52%)</td>
<td>189 (53%)</td>
<td>185 (51%)</td>
<td>191 (53%)</td>
</tr>
<tr>
<td>Mother exposed to nitrous oxide during delivery</td>
<td>48 (18%)</td>
<td>62 (18%)</td>
<td>61 (18%)</td>
<td>62 (18%)</td>
</tr>
<tr>
<td>Maternal education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed tertiary studies</td>
<td>150 (52%)</td>
<td>171 (48%)</td>
<td>181 (51%)</td>
<td>171 (48%)</td>
</tr>
<tr>
<td>Continuing tertiary studies</td>
<td>50 (17%)</td>
<td>67 (19%)</td>
<td>68 (19%)</td>
<td>67 (19%)</td>
</tr>
<tr>
<td>Completed year 11 or 12</td>
<td>62 (22%)</td>
<td>83 (23%)</td>
<td>77 (22%)</td>
<td>84 (24%)</td>
</tr>
<tr>
<td>Did not complete year 11</td>
<td>25 (9%)</td>
<td>33 (9%)</td>
<td>32 (9%)</td>
<td>34 (10%)</td>
</tr>
</tbody>
</table>
### Anaesthesia data

<table>
<thead>
<tr>
<th></th>
<th>RA Arm APP (N=287)</th>
<th>GA Arm APP (N=356)</th>
<th>RA Arm ITT (N=361)</th>
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<tbody>
<tr>
<td><strong>Median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose level</td>
<td>5.4 (4.7-6.1)</td>
<td>5.5 (4.8-6.4)</td>
<td>5.4 (4.7-6.2)</td>
<td>5.5 (4.8-6.4)</td>
</tr>
<tr>
<td>(mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/100 ml)</td>
<td>10.3 (2.1)</td>
<td>10.2 (2.0)</td>
<td>10.3 (2.1)</td>
<td>10.2 (2.0)</td>
</tr>
<tr>
<td>Need for fluid bolus for hypotension</td>
<td>15 (5%)</td>
<td>59 (17%)</td>
<td>21 (6%)</td>
<td>59 (17%)</td>
</tr>
<tr>
<td>Duration of surgery (mins)</td>
<td>26.0 (19.0-35.0)</td>
<td>28.0 (20.0-40.0)</td>
<td>28.0 (20.0-38.0)</td>
<td>28.0 (20.0-40.0)</td>
</tr>
<tr>
<td>Sevoflurane exposure (mins)</td>
<td>NA</td>
<td>54.0 (41.0-70.0)</td>
<td>42.0 (31.0-62.5)</td>
<td>54.0 (41.0-70.0)</td>
</tr>
<tr>
<td>End tidal sevoflurane concentration (%)</td>
<td>NA</td>
<td>2.6 (0-7)</td>
<td>2.3 (0-8)</td>
<td>2.6 (0-7)</td>
</tr>
<tr>
<td>Total concentration x hours</td>
<td>NA</td>
<td>2.6 (1-1)</td>
<td>1.9 (1-0)</td>
<td>2.6 (1-1)</td>
</tr>
<tr>
<td>Any significant apnoea to 12hrs postop</td>
<td>6 (2%)</td>
<td>15 (4%)</td>
<td>10 (3%)</td>
<td>15 (4%)</td>
</tr>
</tbody>
</table>

### At 2 years

<table>
<thead>
<tr>
<th></th>
<th>RA Arm APP (N=287)</th>
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<th>RA Arm ITT (N=361)</th>
<th>GA Arm ITT (N=358)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corrected age at assessment (weeks)</strong></td>
<td>108.9 (13-0)</td>
<td>108.9 (9-8)</td>
<td>108.7 (12-5)</td>
<td>108.9 (9-8)</td>
</tr>
<tr>
<td>Number of anaesthetics since</td>
<td>1</td>
<td>34 (14%)</td>
<td>36 (12%)</td>
<td>42 (14%)</td>
</tr>
<tr>
<td>Child had a head injury that involved the loss of consciousness</td>
<td>7 (3%)</td>
<td>4 (1%)</td>
<td>7 (2%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Child had an acquired brain injury</td>
<td>1 (0%)</td>
<td>1 (0%)</td>
<td>1 (0%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Child had febrile seizures</td>
<td>8 (3%)</td>
<td>9 (3%)</td>
<td>10 (3%)</td>
<td>9 (3%)</td>
</tr>
<tr>
<td>Child had other seizures</td>
<td>1 (&lt;1%)</td>
<td>4 (1%)</td>
<td>1 (&lt;1%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>The child has had an intervention for neurodevelopmental issues</td>
<td>46 (19%)</td>
<td>55 (18%)</td>
<td>54 (18%)</td>
<td>55 (18%)</td>
</tr>
<tr>
<td>Speech Therapy</td>
<td>22 (9%)</td>
<td>27 (9%)</td>
<td>28 (9%)</td>
<td>27 (9%)</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>22 (9%)</td>
<td>27 (9%)</td>
<td>26 (8%)</td>
<td>27 (9%)</td>
</tr>
<tr>
<td>Occupational Therapy</td>
<td>9 (4%)</td>
<td>12 (4%)</td>
<td>12 (4%)</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>Psychology</td>
<td>11 (&lt;1%)</td>
<td>6 (2%)</td>
<td>1 (&lt;1%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Developmental medicine/early intervention</td>
<td>8 (3%)</td>
<td>7 (2%)</td>
<td>9 (3%)</td>
<td>7 (2%)</td>
</tr>
</tbody>
</table>
### Composite scores

<table>
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<th></th>
<th>RA Arm APP</th>
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<th>RA Arm ITT</th>
<th>GA Arm ITT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive, Composite Score</td>
<td>98.6 (14.2)</td>
<td>98.2 (14.7)</td>
<td>98.6 (14.2)</td>
<td>98.2 (14.6)</td>
</tr>
<tr>
<td>Language, Composite Score</td>
<td>94.6 (15.4)</td>
<td>94.0 (15.6)</td>
<td>94.9 (15.5)</td>
<td>94.0 (15.6)</td>
</tr>
<tr>
<td>Motor, Composite Score</td>
<td>98.3 (13.2)</td>
<td>97.9 (13.4)</td>
<td>98.9 (13.5)</td>
<td>97.8 (13.4)</td>
</tr>
<tr>
<td>Social Emotional, Composite Score</td>
<td>97.4 (19.0)</td>
<td>95.4 (18.3)</td>
<td>97.4 (19.2)</td>
<td>95.4 (18.3)</td>
</tr>
<tr>
<td>Adaptive Behaviour Composite Score</td>
<td>93.1 (15.6)</td>
<td>94.3 (14.7)</td>
<td>93.4 (16.1)</td>
<td>94.3 (14.7)</td>
</tr>
<tr>
<td>MacArthur Bates Percentile Score</td>
<td>32.4 (27.9)</td>
<td>34.7 (28.7)</td>
<td>33.6 (28.0)</td>
<td>34.7 (28.7)</td>
</tr>
</tbody>
</table>
Summary

• Just under an hour of anaesthesia in infancy does not cause clinically significant adverse neurodevelopmental outcome compared to awake regional anaesthesia, as measured at 2 years of age.

Limitations

• Duration of exposure – just under an hour

• 2 year outcome measure
  – Imperfect predictor of future function
  – No measure of higher executive function

• Single exposure
Implications

• Strongest evidence to date that just under an hour of anaesthesia in infancy does not cause clinically significant adverse neurodevelopmental outcome

• Tip the balance of evidence toward not avoiding “brief” general anaesthesia in infancy?

What now?

• Increasing number of experimental studies suggest that anaesthesia at younger age is toxic for the brain.

• Clinical (epidemiological) studies are inconclusive

• RCT < 1h anesthesia
  – 2YR no difference
  – 5YR is ongoing. Results 2018

• Clinical practice?
Clinical problem

- Cardiac & noncardiac congenital abnormalities:
  - Oesophageal atresia / Duodenal atresia
  - Anorectal malformations
  - Hirschsprung
  - Gastrochisis, omphalocele
  - Congenital hydronephrosis
  - Choanal atresia

⇒ Surgery & Anaesthesia inevitable!
⇒ Long procedures: toxic?

- Hernia repair: safe?

- Doubtful indications:
  - Cleft lip & palate?
  - Orchidopexy?
  - BAHA?

⇒ Postpone surgery?

What now?

- Nothing has been proven yet
  - Children are not rats
  - Time is not comparable

- Surgery without anesthesia is not possible
- Continue as before

OR

- Anesthesia might be toxic; There is no smoke without fire!
- Be restrictive
- Strickt indication
- Use locoregional techniques
- Fast surgery techniques and surgeon
Discuss with parents and other caretakers the risks and benefits of procedures requiring anesthetics or sedatives, as well as the known health risks of not treating certain conditions.

Stay informed of new developments in this area.

Recognize that current anesthetics and sedatives are necessary for infants and children who require surgery or other painful and stressful procedures.

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European Society of Anaesthesiology

The NEW ENGLAND JOURNAL of MEDICINE

Perspective
Anesthetic Neurotoxicity — Clinical Implications of Animal Models
Rob A. Rappaport, M.D., Santhananimal Sassoth, M.D., Sharon Mika, M.D., Alex S. Evans, M.D., and Nowzady A. Orulu, M.D., Ph.D.

UMC Utrecht
Parents and caregivers should discuss the risks, benefits, and timing of surgery and procedures requiring anesthetics and sedative drugs. Surgeries and procedures requiring anesthetic and sedative drugs that could reasonably be delayed should possibly be postponed because of the potential risk to the developing brain of infants, toddlers, and preschool children.

When surgeries and procedures are required using current standard of care anesthetics, consider participating in a study to help identify better anesthetic and sedative practices and/or drugs that have the least effect on the developing brain.

THE 10 Ns

1. NO FEAR
2. NORMATIENSON
3. NORMOCARDIA
4. NORMOVOLEMIA
5. NORMOXEMIA
6. NORMOCARBIA
7. NORMONATREMIA
8. NORMOGLYCEMIA
9. NORMOTHERMIA
10. NO PAIN