Where to go for OB Anesthesia Research?

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Conflicts of Interest

• Holder of the “Baxter UZLeuven Anaesthesia Research Chair 2012 – 2014”
• Co-Holder of the “Noble Gas research fund” supported by Air Liquide.
• Received financial support of the following companies for either research, consultancy or lectures (Active = current or within the last 3 years):
  – Smiths Medical (active).
  – Sintetica (active).
  – Grunenthal (active).
  – Nordic Pharma (active).
  – MSD (active).
  – Janssens Pharmaceutics (active).
  – Heron (active).
  – Halyard (active).
  – Aquettant (active).
  – Aspen (active).
  – AstraZeneca.
  – Glaxo Smith Kline.
  – BBraun.
  – Abbvie.
  – Fresenius.
  – GE.
• **General ideas:**
  – Big Data/electronic record keeping.
  – Meta-Analyses, statistics and (personal) interpretation.

• **Specifics:**
  – Alternatives for neuraxial anesthesia.
  – PDPH.
  – Maintenance of Analgesia: CI-PCEA, PIEB, adjuvants.
  – Use of US in OB Anesthesia.
  – Postoperative analgesia after C-section: new drugs.
  – GA and neurologic development of the fetus/neonate.
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The problems of OB anesthesia research.

- The infrequency of problems.
- Ethics.
- Funding.
- “Recipe” medicine.
- Cultural influence.
- The absence of OB anesthesia subspecialty medicine in many areas of the world – The lack of focus.
- Good research often limited to certain countries.
  - Thus not relative to other areas!
- Focus on “soft” parameters.
Lecture Outline.

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• (OB) Anesthesia is safe.
• But imperfect.
• OB anesthesia carries complications.

• We need better record keeping.
• We need big data – multicenter information.

• A role for OB anesthesia societies such as SOAP, OAA, etc…. !!

• Examples: NAP – project in UK; KK women’s hospital labour ward; ….
If You ask me how?

I haven’t got a clue 😊

I’m an IT nerd …..

But I believe we should initiate this
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A big research network?
• Provide larger grants.

• Initiate research projects:
  – Long term projects.
  – Hard outcome data.
  – Rare complications.
  – ……
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For CSE versus low-dose epidurals, three outcomes were statistically significant. Two of these reflected a faster onset of effective analgesia from time of injection with CSE and the third was of more pruritus with CSE compared to low-dose epidural (average RR 1.80; 95% CI 1.22 to 2.65; 11 trials, 959 women; random-effects, $T^2 = 0.26$, $I^2 = 84\%$). There was no significant difference in maternal satisfaction (average RR 1.01; 95% CI 0.98 to 1.05; seven trials, 520 women; random-effects, $T^2 = 0.00$, $I^2 = 45\%$). There were no data on respiratory depression, maternal sedation or the need for labour augmentation. No differences between CSE and low-dose epidural were identified for need for rescue analgesia, mobilisation in labour, incidence of post dural puncture headache, known dural tap, blood patch for post dural headache, urinary retention, nausea/vomiting, hypotension, headache, the need for labour augmentation, mode of delivery, umbilical pH, Apgar score or admissions to the neonatal unit.

**Authors’ conclusions**

There appears to be little basis for offering CSE over epidurals in labour, with no difference in overall maternal satisfaction despite a slightly faster onset with CSE and conversely less pruritus with low-dose epidurals. There was no difference in ability to mobilise, maternal hypotension, rate of caesarean birth or neonatal outcome. However, the significantly higher incidence of urinary retention, rescue interventions and instrumental deliveries with traditional techniques would favour the use of low-dose epidurals. It is not possible to draw any meaningful conclusions regarding rare complications such as nerve injury and meningitis.
Gabapentin Improves Postcesarean Delivery Pain Management: A Randomized, Placebo-Controlled Trial

Albert Moore, MD,* Joseph Costello, MD,* Paul Wieczorek, MD,* Vibhuti Shah, MD,† Anna Taddio, PhD,§ and Jose C. A. Carvalho, MD, PhD*†

Figure 2. (A) Visual Analog Scale (VAS) scores on movement for gabapentin and placebo groups at each postoperative assessment. Data are presented with inner lines representing mean values, boxes representing 95% confidence intervals, dots representing medians, and error bars representing minimum and maximum values. * indicates significantly lower VAS scores in the gabapentin group (P < 0.001 at 6 hours; P < 0.001 at 12 hours; P = 0.001 at 24 hours; P = 0.02 at 48 hours). (B) Visual Analog Scale (VAS) scores at rest for gabapentin and placebo groups at each postoperative assessment. Data are presented with inner lines representing mean values, boxes representing 95% confidence intervals, dots representing medians, and error bars representing minimum and maximum values. * indicates significantly lower VAS scores in the gabapentin group (P = 0.01 at 6 hours; P = 0.02 at 12 hours; P = 0.2 at 24 hours; P = 0.2 at 48 hours).
p-value

In statistical hypothesis testing, the **p-value** or **probability value** or **asymptotic significance** is the probability for a given statistical model that, when the null hypothesis is true, the statistical summary (such as the sample mean difference between two compared groups) would be the same as or of greater magnitude than the actual observed results.\(^1\) The use of p-values in statistical hypothesis testing is common in many fields of research\(^2\) such as physics, economics, finance, political science, psychology,\(^3\) biology, criminal justice, criminology, and sociology.\(^4\) Their misuse has been a matter of considerable controversy.

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![Diagram of probability distribution showing p-value](image-url)

**A p-value** (shaded green area) is the probability of an observed (or more extreme) result assuming that the null hypothesis is true.
Anesthesiologists: Marc Van de Velde, Barrie Fisher, Francis Bonnet, Narinder Rawal, Stephan Schug, Girish Joshi, Philipp Lirk, Patricia Lavand’Homme, Helene Beloeil, Esther Pogatzki-Zahn, Johan Raeder, Alain Delbos
Surgeons: Henrik Kehlet, Andrew Hill

www.postoppain.org

procedure specific postoperative pain management
• General ideas:
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  – ........
When is an epidural not an option?

- Infection
- Coagulation problems
- Back Surgery
- AS or MS Cardiac Disease
- Raised ICP
- Hypovolemia
- Allergies
Nitrous Oxide for the Management of Labor Pain: A Systematic Review

Frances E. Likis, DrPH, NP, CNM, * Jeffrey C. Andrews, MD, † Michelle R. Collins, PhD, CNM, RN-CEFM, § Rashonda M. Lewis, JD, MHA, †† Jeffrey J. Seroogy, BS, * Sarah A. Starr, MD, || Rachel R. Walden, MLIS, ¶ and Melissa L. McPheeters, PhD, MPH ‡‡

BACKGROUND: We systematically reviewed evidence addressing the effectiveness of nitrous oxide for the management of labor pain, the influence of nitrous oxide on women’s satisfaction with their birth experience and labor pain management, and adverse effects associated with nitrous oxide for labor pain management.

METHODS: We searched the MEDLINE, EMBASE, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases for articles published in English. The study population included pregnant women in labor intending a vaginal birth, birth attendees or health care providers who may be exposed to nitrous oxide during labor, and the fetus/neonate.

RESULTS: We identified a total of 58 publications, representing 59 distinct study populations: 2 studies were of good quality, 11 fair, and 46 poor. Inhalation of nitrous oxide provided less effective pain relief than epidural analgesia, but the quality of studies was predominately poor. The heterogeneous outcomes used to assess women’s satisfaction with their birth experience and labor pain management made synthesis of studies difficult. Most maternal adverse effects reported in the literature were unpleasant side effects that affect tolerability, such as nausea, vomiting, dizziness, and drowsiness. Apgar scores in newborns whose mothers used nitrous oxide were not significantly different from those of newborns whose mothers used other labor pain management methods or no analgesia. Evidence about occupational harms and exposure was limited.

CONCLUSIONS: The literature addressing nitrous oxide for the management of labor pain includes few studies of good or fair quality. Further research is needed across all of the areas examined: effectiveness, satisfaction, and adverse effects. (Anesth Analg 2014;118:153–67)
What do we know?

- Moderate analgesia, worse than epidural, similar then other opioids.

- High risk of respiratory problems:
  - 25% reported incidence of hypoventilation, apnea, etc.
  - Several case reports on CPR, perimortem C-section.
  - High risk of medication errors.

27 apneas in remi-group
9 resulted in saturation < 90%
• Secondary analysis of the 2014 paper.

• Analysis of RR, etCO₂, Pulseoximetry, heart rate and the IPI (integrated pulmonary index: score from 1 - 10).

• **Ability to predict apnea !!**

• **Immediate Early Warning Alerts:** Value below a predetermined threshold >15 seconds.
  RR < 8 bpm
  etCO₂ < 15 mmHg
  Saturation < 92 %

• **Sustained Early Warning Alerts:** if value remained below for a further 10 seconds.
  IPI < or = 4: Immediate attention required.
  IPI = 1: dire condition.

• **Apnea:** etCO₂ < 5 mmHg for 30 seconds.
• 19 women; 160 ± 132 minutes.

• 62 apneas !!!!!
• 331 immediate alerts.
• 271 sustained alerts.

• Low positive predictive value for all parameters: MANY FALSE POSITIVES

• High sensitivity (100%) of RR and IPI to detect apnea.
• Good sensitivity (75%) of etCO₂ to detect apnea.

• LOW sensitivity (15%) of pulseoximetry to detect apnea.
A case series of vital signs-controlled, patient-assisted intravenous analgesia (VPIA) using remifentanil for labour and delivery

W. L. Leong, B. L. Sng, Q. Zhang, N. L. R. Han, R. Sultana and A. T. H. Sia

Summary

Intravenous remifentanil patient-controlled analgesia can be used during labour as an alternative to epidural analgesia. Adverse effects of opioids, including hypoxia and bradycardia, may lead to maternal morbidity and mortality. We devised an interactive feedback system based on a clinical proportional algorithm, to continuously monitor for adverse effects to enhance safety and better titrate analgesia. This vital signs-controlled, patient-assisted intravenous analgesia with remifentanil used a prototype delivery system linked to a pulse oximeter that evaluated maternal oxygen saturation and heart rate continuously. With this system, we detected oxygen saturation < 95% for more than 60 s in 15 of 29 subjects (52%); and heart rate < 60 min⁻¹ for more than 60 s in 7 of 29 subjects (24%) during use. The system automatically responded appropriately by reducing the dosages and temporarily halting remifentanil administration, thus averting further hypoxia and bradycardia.

Table 2 Summary of opioid side-effects and anaesthetic characteristics. Values are number (proportion) or median (IQR [range]).

<table>
<thead>
<tr>
<th>Opioid side-effects</th>
<th>n = 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>SpO₂ &lt; 95% for &gt; 60 s</td>
<td>15 (52%)</td>
</tr>
<tr>
<td>Any SpO₂ &lt; 95%</td>
<td>27 (93%)</td>
</tr>
<tr>
<td>Heart rate &lt; 60 min⁻¹ for &gt; 60 s</td>
<td>7 (24%)</td>
</tr>
<tr>
<td>Any heart rate &lt; 60 min⁻¹</td>
<td>12 (41%)</td>
</tr>
<tr>
<td>Systolic BP &lt; 90 mmHg</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory rate &lt; 8 times.min⁻¹</td>
<td>0</td>
</tr>
<tr>
<td>Sedation score &gt; 1</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>5 (17%)</td>
</tr>
</tbody>
</table>

Anaesthetic characteristics

<table>
<thead>
<tr>
<th>Remifentanil dose, mg</th>
<th>1.95 (0.70–3.07)</th>
</tr>
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<tbody>
<tr>
<td>[0.06–10.21]</td>
<td></td>
</tr>
<tr>
<td>Duration of remifentanil use, min</td>
<td>348 (151–650)</td>
</tr>
<tr>
<td></td>
<td>[31–1430]</td>
</tr>
</tbody>
</table>

Inadequate analgesia | 9 (31%) |
Conversion to epidural analgesia | 1 (3%) |
Maternal pain score at delivery | 8 (7–10 [0–10]) |
Maternal satisfaction | 75% (70–80 [40–100]) |

VPIA Regimen

1 minute bolus bolus
20 µg remifentanil bolus
30 µg remifentanil bolus
40 µg remifentanil bolus
50 µg remifentanil bolus
50 µg remifentanil bolus + 0.025 µg.kg⁻¹.min⁻¹ remifentanil infusion
50 µg remifentanil bolus + 0.050 µg.kg⁻¹.min⁻¹ remifentanil infusion
50 µg remifentanil bolus + 0.075 µg.kg⁻¹.min⁻¹ remifentanil infusion
50 µg remifentanil bolus + 0.100 µg.kg⁻¹.min⁻¹ remifentanil infusion
Stop the pump and alert the attending anaesthetist.
Proceed to the next level when the number of patient demands is 3 or more within the last 15 mins.
Go back to the previous level when the number of patient demands is 2 or less within the last 15 mins.

Figure 1 The VPIA algorithm.
Lecture Outline.

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  – GA and neurologic development of the fetus/neonate.
  – ........
Intracranial subdural haematoma following neuraxial anaesthesia in the obstetric population: a literature review with analysis of 56 reported cases

V. Cuypers, M. Van de Velde, S. Devroe
Department of Anaesthesiology, University Hospitals Leuven, Katholieke Universiteit Leuven, Leuven, Belgium

Fig. 1 Pathophysiological mechanism of post-dural puncture headache and intracranial subdural haematoma
Clinical Trial Network

EPiMAP Obstetrics


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Computer Integrated PCEA (CI-PCEA)

Programmed Intermittent or Automated Mandatory Epidural Boluses (PIEB-PCEA or AMB-PCEA)
Computer-integrated patient-controlled epidural analgesia: a preliminary study on a novel approach of providing pain relief in labour

Sia A T, Lim Y, Ocampo C E

Comparison of computer integrated patient controlled epidural analgesia vs. conventional patient controlled epidural analgesia for pain relief in labour

Y. Lim, A. T. Sia and C. E. Ocampo

1 Associate Consultant, 2 Head of Obstetric Anaesthesia and Senior Consultant, 3 Clinical Fellow, Department of Women’s Anaesthesia, KK Women’s and Children’s Hospital, Singapore

Lim et al. Anaesthesia 2006; 61, 339 – 344.
Sng et al. Anaesth Intens Care 2009; 37, 46 – 53.
Epidural distribution of dye administered via an epidural catheter in a porcine model

I. Mowat¹,* R. Tang¹, H. Vaghadia¹, C. Krebs³, W. R. Henderson² and A. Sawka¹

In conclusion, delivery of dye by bolus injection in a porcine model provided greater spread within the epidural space than delivery by infusion. In clinical terms, this supports the greater efficacy and lower drug requirement offered by a bolus protocol.¹¹ It is reasonable to assume that patients receiving epidural analgesia but who are experiencing pain because of narrow bands of analgesia, might benefit from an additional bolus dose of local anaesthetic rather than an increase in infusion rate alone.

Fig 2 Scatter plot of injection pressures against longitudinal extent of circumferential dye spread. Infusion group in blue. Bolus group in green. Different spinal levels of epidural catheter placement are mid-thoracic (triangles), low-thoracic (crosses) and lumbar (squares).
Intermittent Epidural Bolus Compared with Continuous Epidural Infusions for Labor Analgesia: A Systematic Review and Meta-Analysis

Ronald B. George, MD, FRCPC, * Terrence K. Allen, MBBS, FRCA, † and Ashraf S. Habib, MB, ChB, MSc, MHS, FRCA‡

(Anesth Analg 2013;116:133–44)

Table 2. The Risk of Bias of Included Studies

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</thead>
<tbody>
<tr>
<td>Was the method of randomization adequate?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Was the treatment allocation concealed?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Was the patient blinded to the intervention?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Was the care provider blinded to the intervention?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unsure</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Was the outcome assessor blinded to the intervention?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Was the dropout rate described and acceptable?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all randomized participants analyzed in their allocated group?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Are reports of the study free of suggestion of selective outcome reporting?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Were the groups similar at baseline?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Were co-interventions avoided or similar?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Was the compliance acceptable in all groups?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Was the timing of the outcome assessment similar?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</table>
Epidural neostigmine and clonidine improves the quality of combined spinal epidural analgesia in labour: a randomised, double-blind controlled trial.

Boogmans T¹, Vertommen J, Valkenborgh T, Devroe S, Roofthooft E, Van de Velde M.

Abstract

BACKGROUND: In labour analgesia, the combination of epidural clonidine and neostigmine as adjuvants to local anaesthetics and opioids is under investigation to provide a longer duration of initial spinal analgesia with local anaesthetics and/or opioids.

OBJECTIVES: To evaluate the quality of analgesia with epidural neostigmine and clonidine, added to initial spinal analgesia, and to test the hypothesis that the incidence of breakthrough pain could be reduced and patient satisfaction improved.

DESIGN: Randomised double-blind controlled trial.

SETTING: University Hospital of Leuven in Belgium.

PARTICIPANTS: One hundred healthy, term (≥37 weeks) parturients.

INTERVENTION: All patients received initial spinal analgesia with ropivacaine and sufentanil. Fifteen minutes after spinal injection, 10ml of a solution containing neostigmine 500μg and clonidine 75μg, or 10ml physiological saline alone was injected epidurally. Patient-controlled analgesia with ropivacaine and sufentanil was then made available.

MAIN OUTCOME MEASURES: The incidence of breakthrough pain, patient satisfaction and hourly ropivacaine use.

RESULTS: Ropivacaine use decreased significantly by 32.6% in the neostigmine/clonidine (NC) group [11.6±4.2 vs. 17.2±5.3mgh in the NC group and placebo (P) group, respectively] and a significant difference in breakthrough pain was noted; only 3% in group NC had breakthrough pain compared with 36% in group P. Patient satisfaction was better after 1h in group NC compared with group P (P<0.05) but not different after 24h (visual analogue scale score 97±5 vs. 88±11 mm after 1h; 92±10 vs. 90±14 mm after 24h).

CONCLUSION: The administration of epidural clonidine and neostigmine as adjuvants, following spinal injection of local anaesthetic, improves the quality of analgesia with less ropivacaine consumption, higher patient satisfaction 1h after administration and a decrease in breakthrough pain compared to standard combined spinal and epidural analgesia and patient-
Lecture Outline.

- **General ideas:**
  - Big Data/electronic record keeping.
  - International, multicenter trials & OB Anesthesia Societies.
  - Meta-Analyses, statistics and (personal) interpretation.

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Gastric Ultrasound: A Point-of-care tool for aspiration risk assessment

Editors

Peter Van de Putte, MD
Anesthesiologist • AZ Monica, campus Deurne • Deurne, Belgium

Anahi Perlas, MD
Anesthesiologist • Toronto Western Hospital • Toronto, Canada
Lecture Outline.

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HTX-011

HTX-011, which utilizes our proprietary Biochronomer® drug delivery technology (our-technologies), is under investigation in Phase 3 clinical studies as a long-acting formulation of the local anesthetic bupivacaine in a Dxed-dose combination with the anti-inflammation meloxicam for the prevention of post-operative pain (pain-management). By delivering sustained levels of both a potent anesthetic and an anti-inflammatory agent directly to the site of tissue injury, HTX-011 was designed to deliver superior pain relief while potentially reducing the need for systemically administered pain medications such as opioids, which carry the risks of harmful side effects, abuse, and addiction.

EXPARHEL
(bupivacaine liposome injectable suspension)

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- 3 day analgesic payload – 660 mg
- Consistent drug delivery across 3 days at the site of action
- Safer and targeted instillation method
- Color allows visualization in the surgical field
- Biocompatible and biodegradable
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  – Use of US in OB Anesthesia.
  – Postoperative analgesia after C-section: new drugs.
  – GA and neurologic development of the fetus/neonate.
  – ........
Impact of anaesthetics and surgery on neurodevelopment: an update

R. D. Sanders¹,²,³*, J. Hassell², A. J. Davidson⁴, N. J. Robertson² and D. Ma⁵

Fig 1 Proposed mechanisms of anaesthetic-induced neurodegeneration in the newborn involving the intrinsic and extrinsic apoptotic cell death pathways. Suppression of synaptic signalling is proposed to attenuate neurotrophic survival signals leading to activation of the intrinsic apoptotic cascade. This involves mobilization of the pro-apoptotic protein Bax, which in turn induces cytochrome c (Cyto. C) release from mitochondria, activation of caspase-9, and subsequent induction of caspase 3 cleavage to provoke apoptosis. Anti-apoptotic effectors such as Bcl oppose this pathway. The extrinsic pathway is stimulated by ligands binding to death receptors located on the cell membrane that cause caspase 8 activation, which then cleaves and activates caspase 3. These ligands include cytokines such as TNF-α.
Mechanisms.

Table 1. Anesthetics, their molecular targets and properties

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>GABA-agonism</th>
<th>NMDA-antagonism</th>
<th>Properties</th>
</tr>
</thead>
</table>
| Ketamine           | +            | +++             | - Dose-dependent neuroapoptosis from chronic or repeated (sub)anesthetic dosage in rodents  
|                    |              |                 | - Neuroprotective when used as analgetic in rat model of repetitive neonatal pain. |
|                    |              |                 | - Synergistic neurotoxicity with propofol                                  |
|                    |              |                 | - Causes oligodendrocyte apoptosis                                          |
| Propofol           | +++          | +               | - Neurotoxic from 25% of anesthetic dose                                    |
|                    |              |                 | - Synergistic neurotoxicity with ketamine                                  |
|                    |              |                 | - Less toxic than isoflurane, more toxic than ketamine                       |
|                    |              |                 | - Causes oligodendrocyte apoptosis                                          |
| N₂O                | +            | +++             | - Toxic towards cell organelles                                            |
|                    |              |                 | - Potentiates neurotoxicity of volatile anesthetics in rodents              |
|                    |              |                 | - Neurotoxicity at sub MAC levels                                          |
|                    |              |                 | - Toxicity sevoflurane < isoflurane < desflurane                           |
|                    |              |                 | - Isoflurane toxicity aggravated by noxious stimuli                         |
|                    |              |                 | - Cause oligodendrocyte apoptosis                                          |
| Volatile anesthetics | +++        | +               | - Detrimental towards neurodevelopment                                     |
|                    |              |                 | - Prolonged administration as anti-epileptic drug induces neuroapoptosis    |
| Benzodiazepines    | +++          |                 | - Thiopental induces dose dependent neuroapoptosis, but is less neurotoxic than propofol |
|                    |              |                 | - Potentiates NMDA-antagonist neurotoxicity                                |
| Barbiturates       | +++          |                 | - Neurotoxic at MAC concentrations                                         |
|                    |              |                 | - Neuroprotective properties at sub MAC concentrations against isoflurane neurotoxicity |
| Xenon              |              | +++             | - Thiovaline-induced neuroapoptosis                                         |

GABA: gamma-aminobutyric acid  MAC: Minimal Alveolar Concentration  NMDA: N-methyl-D-aspartate
Mechanisms

Table 1  Salient features of developmental anesthetic neurotoxicity

Apoptotic neuronal death during synaptogenesis\textsuperscript{1}
Suppression of neurogenesis\textsuperscript{10,22}
Morphologically abnormal synapse formation\textsuperscript{16,17}
Altered dendritic spineogenesis\textsuperscript{18,19,117,124}
Impairment of hippocampal long-term potentiation\textsuperscript{1}
Deformation of neuronal and astroglial cytoskeletal protein\textsuperscript{28,29}
Aberrant cell cycle re-entry during neuronal mitosis\textsuperscript{31}
Neuronal mitochondrial dysfunction\textsuperscript{17}
Abnormal intra-neuronal calcium homeostasis\textsuperscript{26,27}


Table 2. Mechanisms of neurotoxicity

| Suppression of neurotrophic signalling leading to apoptosis via the intrinsic pathway |
| Apoptosis via extrinsic pathway |
| Aberrant cell cycle reentry leading to apoptosis |
| Impaired differentiation and synaptogenesis by suppression of Ca\textsuperscript{2+} oscillations |
| Excitotoxicity |
| Oxidative stress and mitochondrial apoptosis induced by radical oxygen species |
| Impaired mitochondrial morphogenesis |
| Impaired cortical neuron polarisation |
| Disturbed axon guidance |
| Dysregulation of intracellular Ca\textsuperscript{2+} levels by inositol 1,4,5-triphosphate receptor overstimulation |
| Neuroinflammation |
| Oligodendrocyte apoptosis |
Recent new data in humans.


Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial

Lancet 2016; 387: 239–50

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 Arup, Pollyanna Hardy, Rodney W Hunt, Michael J Takagi, Gaia Giribaldi, Penelope L Hartmann, Ida Selvo, Neil S Mortan, Britta S von Unger Sterberg, Bruno Guido Locatelli, Niail Wilton, Anne Lynn, Joss J Thomas, David Polaner, Oliver Bagshaw, Peter Szumuk, Anthony R Absalom, Geoff Frawley, Charles Berde, Gillian D Ormrod, Jacki Marmar, Mary Ellen McCann, for the GAS consortium*

Observer blinded, randomized trial
- GA versus Awake Regional (spinal, caudal or combined)
- Inguinal Hernia Repair.
- Infants younger than 60 w postmenstrual age

IQ score at 5 years (not reported now)
- Composite Cognitive score at Age 2 (planned
- Interim analysis)

238 Awake Regional cases
- 294 GA cases

Anesthetists not blinded.
- Parents and observers blinded to group.

Hospital and gestational age at birth were used to stratify randomisation.
It is a secondary outcome for which study was not powered

No differences

Single, < 1 hour sevoflurane anesthesia
- Sibling matched cohort.
- One single anesthetic for inguinal hernia repair before age 3 y
- All children were born at 36 weeks or more.
- Control group: siblings without anesthesia before age 3 y.

- IQ testing at age 10 approximately.
- 105 sibling pairs.

- NO difference in IQ !!!

Conclusions

Among healthy children with a single anesthesia exposure before age 36 months, compared with healthy siblings with no anesthesia exposure, there were no statistically significant differences in IQ scores in later childhood. Further study of repeated exposure, prolonged exposure, and vulnerable subgroups is needed.
Differences neonatal versus fetal brain.

- Timing synaptogenesis.
- Neurogenesis and neuroregeneration:
  - Trophic effects from glutamate and GABA.
- The presence of maternal hormones.
- Plasma increases in oxytocin: effects on GABA signalling.

→ Trimester specific effects ??
Is the fetal brain vulnerable?

- Easy transplacental passage of anesthetizing agents ➔ animal data: measurable concentrations of isoflurane in the fetal brain.
- Sometimes exposure relatively long.
- In animals, minor procedures disrupt brain development.
- Human brain more complex, hence even more vulnerable.
Table 2  Effects of commonly administered maternal anesthetic agents on fetal neurodevelopment in animal models

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Agent</th>
<th>Model</th>
<th>Type of exposure</th>
<th>Dose</th>
<th>Neurodevelopmental effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trimester</td>
<td>Halothane</td>
<td>Mouse</td>
<td>Multiple</td>
<td>1–2%</td>
<td>Impaired learning\textsuperscript{84}</td>
</tr>
<tr>
<td></td>
<td>Isoflurane</td>
<td>Rat</td>
<td>Multiple</td>
<td>1.05%, 6 h/day</td>
<td>No obvious effects\textsuperscript{68}</td>
</tr>
<tr>
<td></td>
<td>Nitrous oxide</td>
<td>Mouse</td>
<td>Multiple</td>
<td>5%, 15%, or 35%</td>
<td>Impaired startle reflex reactivity\textsuperscript{100}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rat</td>
<td>Single</td>
<td>70–75%, 24 h</td>
<td>Encephalocele and hydrocephalus\textsuperscript{77}</td>
</tr>
<tr>
<td>Second trimester</td>
<td>Isoflurane</td>
<td>Guinea pig</td>
<td>Single</td>
<td>0.55%, 4 h</td>
<td>Neuronal apoptosis at multiple brain regions, worse with</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>combination of anesthetics\textsuperscript{89}</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td></td>
<td>Single</td>
<td>1.4%, 4 h</td>
<td>Delayed acquisition of spatial memory, decreased anxiety\textsuperscript{86}</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td></td>
<td>Multiple</td>
<td>1.3%, 2 h</td>
<td>Impaired spatial memory, changes in synaptic ultrastructure\textsuperscript{88}</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td></td>
<td>Single</td>
<td>1.3%, 4 h</td>
<td>Impaired spatial memory, decreased synaptic number\textsuperscript{87}</td>
</tr>
<tr>
<td></td>
<td>Nitrous oxide</td>
<td>Rat</td>
<td>Single</td>
<td>75%, 8 h</td>
<td>Hyperactivity\textsuperscript{99}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mouse</td>
<td>Single</td>
<td>75%, 6 h</td>
<td>Developmental delay and hypoactivity\textsuperscript{125}</td>
</tr>
<tr>
<td></td>
<td>Ketamine</td>
<td>Primate</td>
<td>Single</td>
<td>20–50 mg/kg/h, i.v. 24 h</td>
<td>No change in cell proliferation\textsuperscript{126}</td>
</tr>
<tr>
<td>Third trimester</td>
<td>Isoflurane</td>
<td>Rat</td>
<td>Single</td>
<td>1.3%, 6 h</td>
<td>No effect on learning and memory\textsuperscript{59}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rat</td>
<td>Single</td>
<td>3%, 1 h</td>
<td>Hippocampal neurodegeneration\textsuperscript{90}</td>
</tr>
</tbody>
</table>

Multiple exposures indicate that pregnant animals received the indicated anesthetic agent multiple times during the respective trimester. Only neuroteratogenic effects have been included for clarity. There are no data for the effects of propofol on fetal neurodevelopment in pregnant animal models.
Pitfalls: animal to human data !!!

- Longer exposure in animal studies (1 – 6 hours) + relative to animal gestation (22 days in rodents).
- Lack of cardiorespiratory stability.
  - However, more recent animal studies reaffirm this even with good stability.
- Interspecies differences in neurodevelopment.
- Do we know animal behavior well enough ?
- Animal studies and brain protection= proved not to work in humans !
Neuroprotective strategies.

- Lithium
- Xenon
- Magnesium
- Dexmedetomidine
- Remifentanil
Neuroprotection and neurotoxicity in the developing brain: an update on the effects of dexmedetomidine and xenon

Azeem Alam, Ka Chun Suen, Zac Hana, Robert D. Sanders, Mervyn Maze, Daqing Ma

**Fig. 1.** The mechanism of action of dexmedetomidine. Dexmedetomidine is an agonist of the α-2 adrenoceptor, a transmembrane G-protein coupled receptor. Activation of the α-2 adrenoceptor inhibits adenylyl cyclase, which causes an intracellular decrease of cAMP. This leads to a series of cellular events and many systemic effects, as listed above. Agonism of the α-2 adrenoceptor also causes an activation of the inwardly rectifying potassium channel, leading to an efflux of K⁺ and inhibition of voltage-gated Ca²⁺ channels. This causes membrane hyperpolarization, such as hyperpolarization of the neuronal membrane in the locus coeruleus (LC), which suppresses neuronal firing and ascending noradrenergic activity. Dexmedetomidine also binds to the “I” receptor, which may also be responsible for some of the actions listed above. ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; GTP, guanosine triphosphate; I receptor, imidazoline receptor.
8. Conclusions

Dexmedetomidine and xenon have been found to confer significant neuroprotection in preclinical studies, predominantly exerting their effects via upregulation of the α2A-adrenoceptor and downregulation of NMDA-receptor signaling, respectively, and favorably modulating the ratio of pro-apoptotic to anti-apoptotic proteins.

Preclinical studies demonstrate the ability for both agents to significantly reduce neuroinflammation and neurodegeneration following neurological insult, including perinatal asphyxia and anesthetic-induced neurotoxicity, whilst also having minimal fetotoxic effects. Paradoxically, whilst there is significant preclinical evidence suggesting the neurotoxicity of traditional anesthetics, including nitrous oxide and isoflurane, these agents still remain an important part of any standard anesthetic regimen, although the FDA have recently issued a warning regarding its use in patients under the age of three years. In contrast, despite the significant neuroprotection conferred by dexmedetomidine and xenon in preclinical studies, too few clinical trials have been conducted to confirm these benefits to date. It is important to note that confounding results suggest that both dexmedetomidine and xenon may possess some inherently neurotoxic effects. Further preclinical and well-powered clinical trials are warranted in order to elucidate the reasons for these confounding results, as well as to ascertain the precise short- and long-term effects of dexmedetomidine and xenon on the developing brain.
Original Article
The neuroprotective effects of remifentanil on isoflurane-induced apoptosis in the neonatal rat brain
Bo Pan, Shaoqiang Huang, Shen Sun, Tingting Wang

In conclusion, regardless of the presence of a nociceptive stimulus, inhaled anesthetics were associated with neuronal apoptosis in some brain regions, particularly in the hippocampus. However, remifentanil did not exert neurotoxic effects on the developing brain, and it reduced isoflurane-induced apoptosis. Thus, the anti-apoptosis mechanism of remifentanil requires further investigation.

Figure 3. A specific remifentanil dose reduced isoflurane-induced apoptosis in the hippocampus CA3 region. (A) Representative images of immunofluorescence staining for cleaved caspase-3 in the CA3. Red staining indicates apoptotic (cleaved caspase-3-positive) cells, and green staining indicates neurons in the CA3. Merge: cleaved caspase-3 and NeuN double-labelled neurons (apoptotic neurons). Scale bar = 50 μm. (B) Representative images of TUNEL staining in the CA3. Green staining indicates apoptotic (TUNEL-positive) cells, and blue staining indicates DAPI-stained nuclei. Merge: TUNEL and DAPI double-labelled cells (apoptotic cells). Scale bar = 50 μm. (C, D) Quantification of the number of (C) cleaved caspase-3- and (D) TUNEL-positive cells in the CA3. Sham (n = 10): control group; Iso+I (n = 10): inhaled 1.5% isoflurane with a plantar incision; Iso+Rf5+I (n = 10): inhaled 1.5% isoflurane with a plantar incision and infusion of 5 μg/kg/h remifentanil; Iso+Rf10+I (n = 10): inhaled 1.5% isoflurane with a plantar incision and infusion of 10 μg/kg/h remifentanil; Iso+Rf20+I (n = 10): inhaled 1.5% isoflurane with a plantar incision and infusion of 20 μg/kg/h remifentanil. * P < 0.05 compared with the Sham group. # P < 0.05 compared with the Iso+I group.
Conclusions.

• General ideas:
  – Big Data/electronic record keeping.
  – Meta-Analyses, statistics and (personal) interpretation.

• Specifics:
  – Alternatives for neuraxial anesthesia.
  – PDPH.
  – Maintenance of Analgesia: CI-PCEA, PIEB, adjuvants.
  – Use of US in OB Anesthesia.
  – Postoperative analgesia after C-section: new drugs.
  – GA and neurologic development of the fetus/neonate.

Big data

Role of Societies

Specific, good research protocols with HARD outcomes!