1. Anesthetic neurotoxicity

- Growing concern about the effects of anesthesia in the developing brain
- Learning disabilities, ADHD, etc.
- Younger age and cumulative dose
- Animal data: apoptosis, synaptic development
- Lacks verification in humans (confounding)

Anesthetic neurotoxicity — Clinical Implications of Animal Models

More specifically, since the original statement was released, new studies have confirmed that commonly used anesthetics and sedatives that either increase inhibitory or excitatory amino acid (GABA and glutamate receptors, e.g., propofol, midazolam, ketamine, thiopental, and isoflurane or block excitatory glutamate receptors, e.g., ketamine cause profound neurotoxic effects in laboratory animals. The reversible anesthetic propofol, most commonly used to induce a rapid loss of consciousness, causes apoptosis of neurons and nigrostriatotectal neurons in the brains of fetal and neonatal animals. Similarly, thiopental used in adult human infants with spread apoptosis in the normal prenatal brain. The glutamate re-
Anesthetic neurotoxicity

• ...while the concern is a FAD...

FUTURE

• Whether real or not, we will be hearing a lot more about this
• Efforts to minimize exposure among pediatric surgeons will increase
• “the seed of doubt has been planted”
**Ophthalmic Technology Assessment**

**Rebound Tonometry in Children**

A Report by the American Academy of Ophthalmology

Scott R. Lashner, MD, Michelene B. Amin, MD, Angela A. Belfiore, MD, MPH, Michael F. Chang, MD, Josep L. Jiménez, MD, Michael H. Yang, MD

• FDA approved since 2007 and endorsed by the AAO in 2013 as accurate way of measure IOP in children <18 (normal and glaucoma)
• DOES NOT REQUIRE TOPICAL ANESTHESIA
• Good GAT correlation (+2-3 mmHg)
• Solid P: +/- 1.8 mmHg SD
  – flashing P indicates higher SD (>3.5 mmHg)

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**2. VEGF blockers for ROP**

- **BEAT-ROP 2011**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Zone I ROP (N=64)</th>
<th>Zone II Posterior ROP (N=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intravitreal Bevacizumab (N=31)</td>
<td>Conventional Laser Therapy (N=33)</td>
</tr>
<tr>
<td>Recurrence of ROP (primary outcome) — no. of patients (%)</td>
<td>6%</td>
<td>42%</td>
</tr>
</tbody>
</table>

---

**Late recurrence concern with IVB**

**Significant Treatment Failure With Intravitreous Bevacizumab for Retinopathy of Prematurity**

- **Less myopia**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Bevacizumab</th>
<th>Laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes, No.</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Patients, No.</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>476 (462 to 619)</td>
<td>685 (440 to 1000)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>24.8 (1.2)</td>
<td>25.1 (1.9)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>25.1 (20 to 27)</td>
<td>26.4 (22 to 29)</td>
</tr>
<tr>
<td>Follow-up time, mo</td>
<td>10.5 (2.7)</td>
<td>11.5 (1.9)</td>
</tr>
<tr>
<td>Mean</td>
<td>10.5</td>
<td>11.3</td>
</tr>
</tbody>
</table>

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*JAMA Ophthalmology, June 2012*
Bevacizumab (Avastin) for retinopathy of prematurity: Wrong dose, wrong drug, or both?

Robert L. Avery, MD

Journal of AAPOS Volume 16 Number 1 / February 2012

Systemic absorption

**All patients had received LASER**

T Sato, Am J Ophthal, 2011

*Lee S. IOVS 2011;52:ARVO E-abstract 3165

Which anti-VEGF?

<table>
<thead>
<tr>
<th></th>
<th>Ranibizumab</th>
<th>Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>48 KDa</td>
<td>149 KDa</td>
</tr>
<tr>
<td>Intravitreal half-life</td>
<td>2.88 days (0.5 mg)</td>
<td>4.32 days (1.25 mg)</td>
</tr>
<tr>
<td>Serum half-life</td>
<td>2 hours</td>
<td>20 days (60 days)</td>
</tr>
<tr>
<td>Decrease Serum VEGF</td>
<td>1-3 weeks 15%</td>
<td>7+ weeks 60%</td>
</tr>
<tr>
<td>Cost</td>
<td>$1,986.29</td>
<td>$64.62</td>
</tr>
<tr>
<td>Regulatory</td>
<td>Not FDA approved for ROP</td>
<td>Not FDA approved for ROP Has only RCT</td>
</tr>
</tbody>
</table>
Ranibizumab appears safer

Pre-injection

Post-injection

40 days after Lucentis injection

INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT FOR RETINOPATHY OF PREMATURENESS

Comparison Between Ranibizumab and Bevacizumab

Table 3. Refractive Errors and Biometry of the ROP Patients at a Corrected Age of 1 Year After Bevacizumab or Ranibizumab Treatment

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab</th>
<th>Ranibizumab</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrected age at examination, mean (95% CI), months</td>
<td>12.5 (11.9 to 13.2)</td>
<td>12.3 (11.5 to 13.1)</td>
<td>0.196</td>
</tr>
<tr>
<td>AXL, mean (95% CI), mm</td>
<td>20.0 (19.0 to 21.9)</td>
<td>20.2 (19.4 to 21.0)</td>
<td>0.912</td>
</tr>
<tr>
<td>BC, mean (95% CI), dipters</td>
<td>-0.3 (-0.8 to 1.1)</td>
<td>+0.1 (-0.4 to 0.3)</td>
<td>0.251</td>
</tr>
<tr>
<td>Anterior chamber depth, mean (95% CI), mm</td>
<td>2.8 (2.6 to 3.0)</td>
<td>2.8 (2.7 to 2.9)</td>
<td>0.334</td>
</tr>
</tbody>
</table>

Presence of high myopia (DSE ≤ -0.6 D) %

Bevacizumab: 14.6%

Ranibizumab: 0%

0.033
IVRani vs. IVBeva

- Chen 2015 (Retina): 72 eyes, no difference
- Wong 2015 (Retina): 83% (5/6) vs. 0% reactivation
- Baumal 2015 (OSLIR): 100% reactivation (8/8)
- Bedda 2014: 12.5% recurrence rate
- Jang 2010: Bilateral RD 1 month after full regression
- Zhou 2014: 45% recurrence (10/22)
- De Alba/Rivera (WOC 2016): 100% recurrence (7/7)

VEGF blockers for ROP

- Despite lack of long term and safety studies
- “the horse is out of the barn”

FUTURE

- We will see (hopefully) more information about optimal VEGF agent, combined treatments and guidelines for follow-up

3. Oral levodopa for amblyopia

- Started as treatment in 1995
- No evidence that there is a deficiency in the brain in children with amblyopia
- Dopamine plays a role in retinal function and central visual processing (Brandies et al 2008)
- Several studies show some improvement in vision (1.1 log) as initial treatment for amblyopia
A Randomized Trial of Levodopa as Treatment for Residual Amblyopia in Older Children

- RCT, placebo controlled, as adjunctive treatment to patching in children 7-12 yo with VA 20/50-400
- Strabismic or anisometropic amblyopia
- Dose 0.76 mg/kg levo/carbidopa TID +patching for 16 weeks

Editorial

What Is Next in Amblyopia Treatment?
Creig Hoyt, MD, MA - San Francisco, California

In reference to levodopa as an adjunct therapy for the treatment of amblyopia, it should persuade us that it is time to move on. Twenty-five years of study has not produced a convincing body of data to justify its clinical use as it has been used in amblyopia treatment. Make no mistake, there remains plenty of work to be done to improve our treatment of amblyopia.
Dopamine for amblyopia

- Need to expand our armamentarium for the treatment of amblyopia

4. Atropine to halt myopia progression

“the myopia epidemic”

| N A T U R E | V O L 5 1 9 | 1 9 M A R C H 2 0 1 5 |

THE MYOPIA BOOM
SHORT-SIGHTEDNESS IS REACHING EPIDEMIC PROPORTIONS. SOME SCIENTISTS THINK THEY HAVE FOUND A REASON WHY.
Interventions to retard myopic progression

- Muscarinic antagonists
  - ATROPINE, Pirenzepine
- Progressive addition lenses (PALs)
- Orthokeratology
- Bifocal glasses
- Bifocal soft contact lenses
- Environmental interventions
- Combinations

Atropine

- Night topical atropine 1%
- Slows progression of low and moderate myopia and axial elongation
- Placebo eyes progressed -1.20 D (±0.69)
- Treated eyes progressed -0.38 D (±0.92)
- After treatment is stopped, treated eyes had a higher rate of myopic progression

Chua et al. Ophthalmology 2006;113:2285-2291
Low dose Atropine

- ATOM 1 (atropine for the treatment of myopia)
- ATOM 2: compared 0.01% vs. 0.1% vs. 0.5%
  - Dose response in progression in first 2 years
  - Higher dose faster effect, lower dose takes 8-24m
  - Higher rebound effect in higher doses, almost none in lower doses
  - Dilation and accommodation minimally affected by 0.01%
  - Decreases myopia progression by 50% (0.5 vs. 1 D/yr)
  - 10% do not respond
  - Need to slow taper

Atropine to halt myopia progression

Thank you!
dealbaa@vision.ucsf.edu
Telemedicine for ROP

- Potential to expand the evaluation and management options available for ROP surveillance.
- Combination of factors has fueled interest in TM:
  - Scarcity of qualified ophthalmologists willing to provide screening
  - Complex coordination of services and tracking
  - Inadequate reimbursement
  - Decentralization of neonatal care to community hospitals
- Barriers: variability in image interpretation, insufficient evidence, high implementation cost

Telemedicine for ROP

- Systematic review 11 studies (total of 486 references)
- Level I evidence that telemedicine is accurate
  - Sensitivity 76*-100% (*outlier 57%)
  - Specificity 87*-97% (*outlier 37%)
- Not more harmful or stressful that indirect ophthalmoscopy
Telemedicine for ROP

- Useful adjunct but not replacement of ophthalmoscopy
- “the pace of implementation of TM for ROP evaluation in the ophthalmic community has outstripped the pace of systematic evaluation of the approach.”

Future

- Need to define roles, protocols, training
- Expand on the available technology (smart phones?)