Delirium, anesthesia, and the manipulation/management of perioperative stress

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Disclosures

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  Research Center Pilot Program

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Purpose

• Describe the stress response to surgery

• Discuss the effect of anesthesia on the stress response
  – Is postoperative delirium related to the neuroendocrine stress response to surgery?
  – Is it possible to reduce the incidence of delirium through anesthetic choice?
Hypothalamic-Pituitary Adrenal Axis Control


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A normal ultradian rhythm of both cortisol (blue) and ACTH (green)

Stressors during the rising phase can result in different outcomes: exaggerated response during the rising phase, relative refractory during the falling phase

Stress and surgery/anesthesia

• Begins with anxiety
• Salivary cortisol increases 50% after preoperative information session
• Increases with pain and inflammation
• Magnitude varies by surgery and anesthetic type

Miluk-Kolasa 1994
Stress Response: laparoscopic vs. minilap vs. laparotomy

Marana J Am Gynecol Laparosc 2003
Anesthesia is a cocktail

IV Amnestic + Analgesic + Gas = General

IV Amnestic + Analgesic + Nerve block = Regional
Stress response and anesthetic gases

- minimally suppress cortisol response
- Some gases suppress catecholamines more than others
IV Anesthetics: propofol vs. gas

Marana et al. 2010
Robust phenomenon in the elderly: serum cortisol by anesthetic

N=56

Deiner S., Abstract, AGS 2013
Neuraxial anesthesia vs. general anesthesia and catecholamines

Fig. 1. Plasma norepinephrine (A) and epinephrine (B) concentrations before induction of anesthesia (P), at skin closure (C), and 1, 6, 12 and 18 h after lower extremity revascularization. Data from patients receiving general anesthesia and parenteral morphine analgesia (GA) are contrasted with data from patients receiving epidural bupivacaine anesthesia and epidural fentanyl analgesia (RA). **P < 0.01; *P < 0.05 compared with RA group. Data are mean ± SEM.

Breslow MJ et al Anesthesiology 1993
Combination general anesthesia plus epidural

Shavit et al J Neuroimmune Pharm 2006
Connection between stress response and delirium

Mechanism behind the stress response and delirium

Cunningham et al. Brain, Behavior, and Immunity 2013
Delirium and anesthesia

• Zhang metaanalysis
  – review of RCTs prior to August 2012
  – 198 articles – 38 RCTs
• Inconsistence in definition of delirium
  – Use of a variety of measures
  – DSM, CAM, DRS, NEECHAM Confusion Scale
• Issue- different types of surgery
38 articles included

1 controlled hypotension (marked vs. mild)

9 anesthesia:
   4 neuroaxial anesthesia (NA) vs. general anesthesia (GA) *
   4 anesthetics
   1 depth of sedation during spinal anesthesia

5 postoperative analgesia
   3 epidural analgesia vs. intravenous analgesia *
   1 additional fascia iliaca compartment block vs. standard analgesia
   1 morphine vs. placebo

3 postoperative sedation (alpha-2 adrenergic receptor agonists vs. standard) *
   2 dexmedetomidine vs. routine sedatives *
   1 additional clonidine vs. routine sedatives

4 acetylcholinesterase inhibitors vs. placebo *

6 antipsychotics vs. placebo *
   3 typical antipsychotics (haloperidol) vs. placebo *
   3 atypical antipsychotics (olanzapine or risperidone) vs. placebo *

2 anticonvulsants (gabapentin or pregabalin) vs. placebo *

1 sleep restoration using diazepam/flunitrazepam/pethidine vs. standard

2 sleep restoration using bright light vs. standard *

1 psychological intervention vs. standard

1 music vs. standard

2 multicomponent intervention vs. standard *

1 histamine H₂ receptor blockers (cimetidine vs. ranitidine)
Studies comparing delirium between different types of general anesthesia

• Comparison of 2 general anesthetics: gas vs. total intravenous anesthesia

• Mixed results
  – Nishikawa et al 2004: higher DRS and trend toward increased incidence for propofol (16%) vs. sevoflurane (0%) (but NS)
  – Monk et al 2011 propofol vs. isoflurane in major ortho surgery no difference (12.6% vs. 13.6%)
  – Royse et al 2011 propofol vs. desflurane in cardiac surgery - no difference (7.9% vs. 13.2%)
Delirium and neuraxial vs. general anesthesia

Neuraxial= epidural or spinal

- 4 Randomized controlled trials
- Each study used a different maintenance anesthetic
  - halothane, isoflurane, propofol
Pooled RR of POD = .99 CI .65 to 1.5
Incidence approximately 17%

Zhang et al Critical Care 2013
Deiner 2013 AGS Abstract 2013

• Study design: Prospective cohort study

• Subjects: >68 years old for major elective noncardiac surgery. Identified by the computerized scheduling system at Mount Sinai Hospital

• Outcomes: Delirium, POCD, postoperative complications
  • Measured at screen, 3 and 6 months.

• Predictors:
  • Primary: anesthetics technique (GS vs. TIVA),
  • Secondary: serum norepineprine, epinephrine, cortisol
• Delirium was not different in the PACU (Gas 3.2% vs. TIVA 8.1% p=.62)
• Opposite trend in the postoperative period (Gas 19.4% vs. TIVA 12.5% p=.41).
  – 30% reduction, but would have needed 476/arm for significance
  – Consistent with Royce’s findings
Model to Predict Delirium: diabetes, serum norepinephrine, surgical duration

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unit</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical Duration</td>
<td>1 hour</td>
<td>1.46</td>
<td>0.92-2.32</td>
</tr>
<tr>
<td>Norepi Time 2</td>
<td>100 pg/ml</td>
<td>1.20</td>
<td>1.01-1.42</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1= yes</td>
<td>4.51</td>
<td>1.01-20.14</td>
</tr>
</tbody>
</table>

Deiner et al,
Confounding issues

• Pain
  – Treatment of pain
• Hypothermia, shivering
• Depth of anesthesia
  – Sedation given with regional anesthesia
• Adjuvant agents may not be inert: steroids, ketamine
• Immediate postoperative delirium = inadequate emergence?
Conclusion

• Do anesthetics suppress the stress response to surgery (yes, some more than others)

• Is delirium related to stress? (likely)

• Is it possible to reduce the incidence of delirium through anesthetic choice (maybe)
Thank you

NIA GEMSSTAR R03
American Geriatrics Society Jahnigen Program
Alzheimer’s Disease Research Center
Icahn School of Medicine at Mount Sinai Research Staff
Results of the cognitive tests in patients after a sevoflurane- or propofol-based anaesthesia during on-pump cardiac surgery in patients with and without cerebral desaturation.

Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision--MAC BAR

Table 5. Comparison of MAC with MAC EI and MAC BAR*

<table>
<thead>
<tr>
<th></th>
<th>MAC₆₀†</th>
<th>MAC₄₅</th>
<th>MAC EI₆₀④⑤</th>
<th>MAC EI₆₀④⑥</th>
<th>MAC BAR₆₀⑦</th>
<th>MAC BAR₄₅</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>1.0 MAC</td>
<td>1.2 MAC</td>
<td>1.3 MAC</td>
<td>1.7 MAC</td>
<td>1.5 ± 0.1 MAC</td>
<td>2.1 MAC</td>
</tr>
<tr>
<td></td>
<td>0.74 ± 0.03 per cent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.0 MAC</td>
<td>1.1 MAC</td>
<td>1.4 MAC</td>
<td>1.9 MAC</td>
<td>1.6 ± 0.1 MAC</td>
<td>2.5 MAC</td>
</tr>
<tr>
<td></td>
<td>1.68 ± 0.04 per cent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.13 ± 0.1 mg/kg plus 60 per cent N₂O</td>
<td>1.5 mg/kg plus 60 per cent N₂O</td>
</tr>
</tbody>
</table>

“If adverse effects of surgery are related to the neuroendocrine stress that surgical manipulations induce, the hypothesis the less anesthetic the better may be wrong.”

Roizen et al Anesthesiology 1981
Spinal (regional anesthesia) blocks the adrenergic response to incision

**Table 4. Preincision Plasma Norepinephrine Concentrations**

<table>
<thead>
<tr>
<th></th>
<th>Age-adjusted MAC Level</th>
<th>Preincision Plasma Norepinephrine Concentration (pg/ml)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enflurane plus 60 per cent N₂O</td>
<td>1.3 MAC</td>
<td>292 ± 117</td>
</tr>
<tr>
<td></td>
<td>1.6 MAC</td>
<td>282 ± 171</td>
</tr>
<tr>
<td></td>
<td>1.9 MAC</td>
<td>360 ± 172</td>
</tr>
<tr>
<td>Halothane plus 60 per cent N₂O</td>
<td>1.0 MAC</td>
<td>415 ± 186</td>
</tr>
<tr>
<td></td>
<td>1.3 MAC</td>
<td>393 ± 276</td>
</tr>
<tr>
<td></td>
<td>1.6 MAC</td>
<td>441 ± 247</td>
</tr>
<tr>
<td></td>
<td>1.9 MAC</td>
<td>515 ± 310</td>
</tr>
<tr>
<td>Morphine plus 60 per cent N₂O</td>
<td>0.4 mg/kg</td>
<td>308 ± 200</td>
</tr>
<tr>
<td></td>
<td>0.9 mg/kg</td>
<td>330 ± 139</td>
</tr>
<tr>
<td></td>
<td>1.4 mg/kg</td>
<td>324 ± 100</td>
</tr>
<tr>
<td>Spinal anesthesia T10 level</td>
<td>T4 level</td>
<td>255 ± 150</td>
</tr>
<tr>
<td></td>
<td>T4 level</td>
<td>235 ± 135</td>
</tr>
</tbody>
</table>

* Values are means ± SD.

Roizen et al Anesthesiology 1981