Postoperative Delirium

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Objectives

• Explore risk factors and advice for preoperative screening
• Provide some recommendations for perioperative care
• Identify novel techniques currently under investigation
Why Do I Care?
Why Should We Care?

• Aging population
  • Statistics Canada Estimates by 2036, 23-25% of population will be ≥ 65 yo
  • Estimated 1/3 of people ≥ 65 will receive anesthetic in any year

• New onset delirium increases length of stay by average of 8 days
  • This prolongation was not seen in patients with admitting diagnoses of delirium

• Medical and Surgical patients showed increased RR 1.95 of mortality, OR 2.41 institutionalization


What is Delirium

• DSM V Characterizes it based on 5 criteria
  I. Disturbance in attention and awareness
  II. Fluctuant, developing over short time period
  III. Disturbance in cognition
  IV. Disturbances are not explained by pre-existing diagnosis
  V. Evidence of medical problem, medication side effect, or substance intoxication/withdrawal

• May be hyperactive or hypoactive
  • Mix of both
Pathophysiology

• Inflammation and stress
  • Leads to release of inflammatory mediators including interleukin-1, TNFα, interferon
  • Increases permeability of blood-brain barrier
  • Leads to altered neurotransmission, drug trapping

• Cholinergic and dopaminergic activity implicated
  • Anticholinergics can precipitate delirium, cholinesterase inhibitors can treat
  • Antipsychotic agents working via dopamine may provide benefit

• Extremely Multifactorial
Pathophysiology

• The INTUIT Study: Investigating Neuroinflammation Underlying Postoperative Cognitive Dysfunction

• Ongoing observational prospective cohort

• Evaluating monocyte chemoattractant protein 1 in CSF pre and postoperatively up to 1 yr

• Assess for delirium postop day 1-5, cognitive function up to 1 yr

## Risk Factors

### Patient
- AGE
- \(\sigma\)
- Dehydration/malnutrition
- Depression
- Dementia
- Polypharmacy
- Metabolic derangements
- Disease states
  - Hypoxia
  - Febrile
  - Anemia
  - Shock

### Procedure
- Type of OR
  - Hip Fracture, vascular, cardiothoracic
- Emergent vs Urgent vs Elective
- Duration of OR (?)
- Physical restraints
- Urinary Catheters

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Prediction Tools

- 0 = 1-2% risk of delirium
- 1-2 = 8-19%
- ≥3 = 45-55%

<table>
<thead>
<tr>
<th>Variable</th>
<th>Criteria</th>
<th>Points</th>
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</thead>
<tbody>
<tr>
<td>Cognitive impairment</td>
<td>TICS score &lt; 30</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 70</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Physical impairment</td>
<td>SAS Class IV (unable to perform 3 METs)</td>
<td>1</td>
</tr>
<tr>
<td>Laboratory abnormality</td>
<td>Sodium &lt; 130 or &gt; 150 mmol·L⁻¹</td>
<td>1</td>
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<tr>
<td></td>
<td>Potassium &lt; 3.0 or &gt; 6.0 mmol·L⁻¹</td>
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<tr>
<td></td>
<td>Glucose &lt; 3.3 or &gt; 16.7 mmol·L⁻¹</td>
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<tr>
<td>Aortic aneurysm surgery</td>
<td>Yes</td>
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<tr>
<td>Non-cardiac thoracic surgery</td>
<td>Yes</td>
<td>1</td>
</tr>
</tbody>
</table>

TICS = telephone interview for cognitive status (a score < 30 indicates minimal cognitive impairment);⁴⁹ SAS = specific activity scale;⁵⁰ METs = metabolic equivalents (Class IV is equivalent to exercise tolerance ≤ 2 METS); 0 points = 1-2% incidence of delirium; 1-2 points = 8-19% incidence of delirium; ≥ 3 points = 45-55% incidence of delirium

Prediction Tools

1. Rapidity of onset of the insult
2. Severity of the insult
3. Preoperative health status

Noimark D. Predicting the onset of delirium in the postoperative patient. Age Ageing 2009; 38: 368-73.

Table 2 Patient-specific predictors of delirium\textsuperscript{20}

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Criteria for increased risk</th>
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<tbody>
<tr>
<td>Age</td>
<td>Increasing age</td>
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<tr>
<td>ASA physical status</td>
<td>ASA $\geq$ III</td>
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<tr>
<td>Sex</td>
<td>Male</td>
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<tr>
<td>Cognitive impairment</td>
<td>Dementia</td>
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<tr>
<td></td>
<td>MMSE $&lt; 24$</td>
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<tr>
<td></td>
<td>Poor executive function</td>
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<tr>
<td></td>
<td>Attention deficits</td>
</tr>
<tr>
<td>Depression</td>
<td>Presence of preoperative depression</td>
</tr>
<tr>
<td>Smoking</td>
<td>Preoperative smoking</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Presence of multiple comorbidities</td>
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<tr>
<td></td>
<td>Risk factors for vascular disease</td>
</tr>
<tr>
<td>Medications</td>
<td>Three or more medications</td>
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<td></td>
<td>Anticholinergic effect</td>
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<tr>
<td>Alcohol</td>
<td>Alcohol use</td>
</tr>
<tr>
<td>Functional status</td>
<td>Inability to perform activities of daily living</td>
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<td>Visual or hearing</td>
<td>Visual or hearing impairment</td>
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<tr>
<td>Laboratory abnormalities</td>
<td>Anemia (inconsistent)</td>
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<tr>
<td></td>
<td>Hypoalbuminemia</td>
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<tr>
<td></td>
<td>Electrolyte abnormalities (inconsistent)</td>
</tr>
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<td></td>
<td>Renal insufficiency</td>
</tr>
</tbody>
</table>

ASA = American Society of Anesthesiologists; MMSE = Mini-Mental Status Examination
How do we diagnose? When?

• POD 1-3 highest occurrence
• Do we recognize and diagnose delirium?

• Limited utility for anesthesiologist
  • Lack of follow-up
  • Role for connectcare?
Confusion Assessment Method

1. Acute onset and fluctuating
2. Inattention
3. Disorganized thinking
4. Altered LOC

Delirium = Must have 1 and 2, and then one of 3 or 4.
Has been adapted for ventilated patients in ICU
Note: MMSE noted to be least accurate in large systematic review for predicting delirium

Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium?: value of bedside instruments. JAMA 2010; 304: 779-86.
So I’ve identified my patient at risk, now what?
Preoperatively

- **Consult geriatrician?**
- RCT for 126 patients admitted for hip fracture
  - Recommended ≥ 24 hr preop
  - Instituted protocol for preventive supportive measures including rehydration, restoration of electrolytes, med reconciliation, analgesia strategy, and plan for early mobilization postop
  - Delirium in 32% pts with early geriatric consult vs 50% in control group
  - Obvious limitation meeting patients *immediately* preop
    - Role for PAC?

Early Geriatric Consultation

- RCT comparing patients randomized to geriatric unit postop vs conventional orthopedic unit post hip fracture repair
- Incidence reduced 20%
- Duration reduced by 5 days

Geriatric Consultation

Bottom line

- Unlikely feasible to get geriatrics involved preop
- Determine what they do to optimize, do it ourselves?
- Modify the modifiable RFs

Ounce of prevention = Pound of cure
Haldol

- RCT comparing prophylactic Haldol 72 hours preop vs placebo
  - Haldol 0.5mg PO TID 72 hours both pre and post op
  - No difference in incidence of delirium, both 6.4 days mean reduction in duration of delirium, and subsequently 5.5 days mean reduction in hospital stay
  - Both groups had preop geriatric consultation

Haldol

- Randomized prospective study with 201 patients ≥75yo going for major abdominal or orthopedic surgery
- Postop Day: 0-5 received Haldol 5mg IV via slow infusion
- Incidence of severe delirium was 18.2% in haldol group compared to 32% in control
- No difference in duration of delirium
- No adverse events at high dose of 5mg

Haldol

• Efficacy of low dose (0.5mg) IV haldol in RCT for 135 patients post major thoracic surgery (noncardiac)

• Found no efficacy for incidence nor duration of POD

• May be dose dependent

Haldol

• Useful for patients at risk, and appears to be safe even at high doses.
• Unclear ideal dose
  • Relationship for prophylaxis of POD *appears* to be dose-dependant
### Table 1. Study, Patient, and Treatment Characteristics of Included Randomized Controlled Trials

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Hakim et al.,[6] 2012 (Egypt)</td>
<td>101</td>
<td>DBPCT parallel</td>
<td>Age ≥65 y, male: 68.3% On-pump cardiac surgery NYHA class III or IV: 62.4% MMSE score ≥ 25 ICU setting All patients had subsyndromal delirium prior to randomization</td>
<td>RIS: n = 51, 0.5 mg bid until incidence of delirium PLA: n = 50</td>
<td>ICDSC ≥ 3 every 8 h DSM-IV-TR</td>
<td>Incidence of delirium: RIS &gt; PLA Duration of delirium: RIS &gt; PLA Severity of delirium: RIS &gt; PLA (highest score on the ICDSC) Length of ICU stay: RIS &gt; PLA Length of hospital stay: RIS &gt; PLA</td>
<td>Switched to standard treatment (RIS up to 4 mg/d and HAL as needed)</td>
</tr>
<tr>
<td>Kalisvaart et al.,[14] 2005 (Netherlands)</td>
<td>430</td>
<td>DBPCT parallel</td>
<td>Mean age: 79.1 y, male: 20.2% Orthopedic (hip) surgery APACHE II mean score = 13.4 MMSE mean score = 24.7 Non-ICU setting</td>
<td>HAL: n = 212, 0.5 mg tid until postoperative day 3 PLA: n = 218</td>
<td>DSM-IV-TR CAM</td>
<td>Incidence of delirium: HAL &gt; PLA Duration of delirium: HAL &gt; PLA Severity of delirium: HAL &gt; PLA (maximum DRS-R-98 score) Length of hospital stay: HAL &gt; PLA</td>
<td>Switched to standard treatment (HAL and/or lorazepam) when delirium was diagnosed</td>
</tr>
<tr>
<td>Kaneko et al.,[2] 1999 (Japan)</td>
<td>80</td>
<td>Nonblind parallel</td>
<td>Mean age: 72.8 y, male: 64.1% Gastrointestinal surgery Cognitive impairment: 7.7% Non-ICU setting</td>
<td>HAL: n = 40, 0.5 mg IV until postoperative day 5 PLA (normal saline): n = 40</td>
<td>DSM-III-R</td>
<td>Incidence of delirium: HAL &gt; PLA</td>
<td>Switched to standard treatment (HAL and/or lorazepam) when delirium was diagnosed</td>
</tr>
<tr>
<td>Larsen et al.,[16] 2010 (United States)</td>
<td>495</td>
<td>DBPCT parallel</td>
<td>Mean age: 73.7 y, male: 65.7% Orthopedic surgery (knee and hip joint replacement) ASA class ≥ 3: 42.0% No dementia Non-ICU setting</td>
<td>OLA: n = 243, 5 mg twice perioperative administration PLA: n = 252</td>
<td>DSM-III-R MMSE DRS-R-98 CAM</td>
<td>Incidence of delirium: OLA &gt; PLA Duration of delirium: OLA &gt; PLA Severity of delirium: OLA &gt; PLA (maximum DRS-R-98 score) Length of hospital stay: OLA &gt; PLA</td>
<td>Continued blind treatment and additional standard treatment (nonpharmacologic and/or HAL/OLA as needed) when delirium was diagnosed</td>
</tr>
<tr>
<td>Prakanrattana and Praapatraokul,[15] 2007 (Thailand)</td>
<td>126</td>
<td>DBPCT parallel</td>
<td>Mean age: 61.0 y, male: 58.7% On-pump cardiac surgery NYHA class III or IV: 33.3% ICU setting</td>
<td>RIS: n = 63, 1 mg when regained consciousness from surgery PLA: n = 63</td>
<td>CAM-ICU</td>
<td>Incidence of delirium: RIS &gt; PLA Length of ICU stay: RIS &gt; PLA Length of hospital stay: RIS &gt; PLA</td>
<td></td>
</tr>
<tr>
<td>Wang et al.,[17] 2012 (China)</td>
<td>457</td>
<td>DBPCT parallel</td>
<td>Mean age: 74.2 y, male: 63.0% Noncardiac surgery ASA class ≥ 3: 38.7% ICU setting</td>
<td>HAL: n = 229, 0.5 mg IV within 1 h after enrollment, followed by 0.1 mg/h for 12 h PLA: n = 228</td>
<td>Richmond Agitation Sedation Scale CAM-ICU</td>
<td>Incidence of delirium: HAL &gt; PLA Time to onset of delirium: HAL &gt; PLA Length of ICU stay: HAL &gt; PLA Length of hospital stay: HAL &gt; PLA</td>
<td>Continued blind treatment and additional standard treatment (nonpharmacologic and/or IV HAL 0.5–1.0 mg every 20 min) when delirium was diagnosed</td>
</tr>
</tbody>
</table>

[^4]: In Outcome Measures column, boldface indicates primary outcome measure of each study, “<” indicates superiority of experimental drug to placebo, and “=” indicates no significant difference between 2 groups.
Atypical Antipsychotics

- Olanzapine has FDA black box warning for sudden death (stroke) in patients with dementia
- Multiple small studies investigating Risperidone, limited benefit
- Risperidone may be better tolerated than Olanzapine due to less anticholinergic and antihistaminic effects
- Dosing?

- **No role for atypical antipsychotics in these patients**
Anticholinesterase Inhibitors - Donepezil

No difference in postoperative delirium in multiple studies evaluating donepezil

• No role for donepezil


Does Opioid Choice Matter?

• Systematic review (2006) of 3 RCTs and 3 Observational Studies suggests no difference
  • Avoid Meperidine because of its anticholinergic properties

Does Opioid Choice Matter?

**Figure 1**: Incidence of delirium episodes in the recovery room in patients who received either remifentanil or fentanyl intraoperative opioid anaesthesia during elective surgery. 

**Figure 2**: Incidence of delirium episodes on the first post-operative day in patients who received either remifentanil or fentanyl intraoperative opioid anaesthesia during elective surgery.

**Observational Study**

Does Opioid Choice Matter?

- Limited evidence to suggest a difference
- Potentially harm with using Remifentanil in at risk patients

- No!
GA vs Regional

- Large systematic review of 104 studies in elderly (≥60 yo) patients for hip fracture repair
- No difference in primary outcome of postoperative delirium
- Very Limited evidence to suggest any mortality benefit, shortened length of stay, reduction in adverse events, or earlier mobilization

Effect of regional versus general anaesthesia on postoperative delirium in elderly patients undergoing surgery for hip fracture: a systematic review
BMJ Open 2018;8:e020757.
Gabapentin

• Very small, poorly powered trial of 21 patients going for spine surgery suggested a dramatic statistically significant reduction in POD

• Leung et al (2017) conducted double-blinded RCT with 697 patients, stratified for surgery type, anesthetic technique, and preoperative risk via CAM
  • NO difference in incidence or duration of POD
  • Slight reduction in postop opioid requirements

• No role for gabapentin to prevent POD

Ketamine

- Avidan et al (2017) found in large multicenter DB-RCT no benefit to subanesthetic dose of ketamine intraop
  - may have found to be harmful via postop dissociative experiences, nightmares etc
- Hovaguimian et al (2018) meta analysis also revealed no benefit, low quality evidence

- Avoid ketamine if possible


Dexamethasone

• If primarily due to inflammation, preventing inflammatory processes should prevent postoperative delirium?

• Evidence of delirium reduction in patients undergoing CABG

• Very few studies on Dex for postoperative delirium

• Dexamethasone likely useful in these patients

TIVA vs Inhalational

• Radtke et al (2010) found no statistical difference in incidence of delirium in PACU or on ward postoperative day 1 in 1002 patients
  • Limitation= observational cohort study

• Miller et al (2018) comprehensive systematic review of 28 RCTs including 4507 patients undergoing noncardiac surgery
  • Found no significant difference in rates of POD or POCD

• Tanaka et al (2017) DB-RCT of 100 obese patients going for elective TKR with femoral catheter in situ
  • no difference between Desfluorane vs Propofol maintenance in terms of POD, POCD

• NO Difference between TIVA vs Inhalational Anesthetic
Fluods

• Fasting Duration significant for incidence of delirium in observational study


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Recovery room (n = 910)</th>
<th>Ward (n = 862)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Delirium (n = 100)</td>
<td>No delirium (n = 810)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.8 ± 16.2</td>
<td>50.1 ± 17.0</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>45 (45.0%)</td>
<td>380 (46.9%)</td>
</tr>
<tr>
<td>ASA PS 1 and 2</td>
<td>66 (66.0%)</td>
<td>623 (76.9%)</td>
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<tr>
<td>ASA PS 3 and 4</td>
<td>34 (34.0%)</td>
<td>187 (23.1%)</td>
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<tr>
<td>Preoperative fasting (fluids) (h)</td>
<td></td>
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<tr>
<td>2–6</td>
<td>11 (11.0%)</td>
<td>209 (25.8%)</td>
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<tr>
<td>&gt;6</td>
<td>89 (89.0%)</td>
<td>601 (74.2%)</td>
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<tr>
<td>Preoperative fasting (solids) (h)</td>
<td></td>
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<tr>
<td>6–12</td>
<td>36 (10.0%)</td>
<td>325 (90.0%)</td>
</tr>
<tr>
<td>&gt;12</td>
<td>64 (11.7%)</td>
<td>485 (88.3%)</td>
</tr>
<tr>
<td>Anaesthetic</td>
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<tr>
<td>Inhalative</td>
<td>56 (56.0%)</td>
<td>423 (52.2%)</td>
</tr>
<tr>
<td>Intravenous</td>
<td>44 (44.0%)</td>
<td>397 (47.8%)</td>
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<tr>
<td>Opioid</td>
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<tr>
<td>Fentanyl</td>
<td>65 (65.0%)</td>
<td>413 (51.0%)</td>
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<tr>
<td>Remifentanil</td>
<td>35 (35.0%)</td>
<td>397 (49.0%)</td>
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<tr>
<td>Fentanyl dosage (µg kg⁻¹ h⁻¹)</td>
<td>4.0 ± 3.0</td>
<td>3.9 ± 2.8</td>
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<tr>
<td>Duration of surgery (min)</td>
<td>93.2 ± 63.0</td>
<td>77.5 ± 57.8</td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
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<tr>
<td>Intraabdominal and intrathoracic</td>
<td>28 (19.2%)</td>
<td>118 (80.8%)</td>
</tr>
<tr>
<td>Other</td>
<td>72 (9.4%)</td>
<td>692 (90.6%)</td>
</tr>
</tbody>
</table>

Data were expressed as mean ± SD, except for categorical data as number and percentage; P values are with respect to χ² test or Mann–Whitney U test. ASA PS, American Society of Anaesthesiologists physical status.
Fluids

• Dehydration known modifiable risk factor for POD,
• Consider fasting time

• Euvolemia, preop rehydration
• Electrolyte correction
Observational cohort study (2016) of 727 patients receiving GA with planned ICU disposition, Age ≥18 yo
• Duration of EEG Suppression recorded
• CAM assessment for delirium twice daily for postop day 1-5
• Follow-up at 30 days for QoL, functionality, cognitive abilities assessed using validated scoring systems
• POD in 26% of patients
Factors that predict POD:

- Duration of Burst Suppression
- EtMAC
- Blood Transfusion
Figure 2. This descriptive figure depicts the univariable relationships between these 2 electroencephalogram parameters and incident delirium. There is no control for covariates in this descriptive figure. A, Incidence of delirium among patients who experienced no electroencephalogram suppression \((n = 71)\) and among patients who experienced electroencephalogram suppression \((n = 548)\) divided into quartiles based on duration of electroencephalogram suppression. B, Incidence of delirium among patients who never experienced bispectral index <20 \((n = 362)\) and among patients who experienced bispectral index <20 \((n = 257)\) divided into quartiles based on duration of bispectral index <20. Error bars represent 95% confidence intervals around the incidence of delirium in each group.
EEG Monitoring

• Prolonged burst suppression predicted postoperative delirium in Day 1-5 in ICU
• Higher EtMAC corresponded to higher burst suppression ratios
• Prolonged burst suppression found to have no effect on QoL or cognitive impairment, but significant impact on functional independence at 30 days

• Limitation: Observational
EEG Monitoring

- Single-center RCT of 1232 patients undergoing major surgery with GA
- EEG-Guided group
  - POD 26% (vs 23% for Usual Care Group)
  - Significantly lower EtMAC (0.69 vs 0.8)
  - Reduced duration of burst suppression (median 7 mins vs 13 mins)
  - More undesirable movement (22.3% vs 15.4%)
  - No difference in MAP, PONV, serious adverse events
  - Lower 30 day mortality (0.65% vs 3.07%)
  - No awareness

EEG Monitoring

Bottom Line

• Unclear
Does MAP Matter?

- No correlation between lower map values (≤90% preoperative values) and incidence of POD in elderly patients with GA for noncardiac surgery
- RCT Pilot Trial, 101 patients

MAP > 55mmHg

- Ongoing Multicenter DB-RCT of 322 patients randomized to MAP targets 60-70mmHg vs 80-90mmHg to assess for POD from Day 1-7
- Willingham et al (2014) found 3x higher risk of 90 day postop all cause mortality associated with combo of burst suppression + MAP < 55mmHg

At present, unclear but stands to reason keep these patients tightly within 20% of preoperative values

Hu A, Qiu Y, Zhang P, et al. *Comparison of the effect of high versus low mean arterial pressure levels on clinical outcomes and complications in elderly patients during non-cardiothoracic surgery under general anesthesia: study protocol for a randomized controlled trial*. Trials. 2017;18(1);554.

Dexmedetomidine

• Could prevent inflammatory ramp up
• Has analgesic and sedative effects
• Opioid-sparing
• Resembles natural sleep patterns

• “Magic Bullet” for Postoperative Delirium
  -Anne Donovan in CJA Jan 2019
Dexmedetomidine

- Evidence is inconsistent
- RCT of 143 pts undergoing thoracic surgery running Sevo with Dexmedetomidine vs Sevo alone
  - Dexmed (0.5µg•kg⁻¹•hr⁻¹) started at induction, terminated at OR end-time
  - Assessed for rates of emergence agitation, postoperative delirium to Postop Day 3.
  - RRR 0.62 in emergence agitation, no difference for POD
  - Reduction in serum catecholamines
  - Increase in cytokines

Dexmedetomidine

• Systematic review of 18 studies including 3309 patients, 9 cardiac (8 on pump) and 9 noncardiac surgeries
• Found firm evidence of reduction in POD in all patient populations
• Insufficient evidence for length of stay, mortality benefit
• Dosage and timing unclear
• Tailor to type of procedure and postop disposition plan

Duan X, Coburn M, Rossaint R et al. Efficacy of perioperative dexmedetomidine on postoperative delirium: systematic review and meta-analysis with trial sequential analysis of randomised controlled trials. BJA. 2018;121(2):384-397
Dexmedetomidine

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>DEX group</th>
<th>Control group</th>
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<td>Events</td>
<td>Total</td>
<td>Total</td>
<td>Weight</td>
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<td></td>
<td></td>
<td></td>
<td>M.H.</td>
<td>Random, 95% CI</td>
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<tr>
<td>Balkanay O 2015</td>
<td>0</td>
<td>60</td>
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<td>1</td>
<td>43</td>
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<td>32</td>
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<td>Shiahb 2009</td>
<td>13</td>
<td>152</td>
<td>22</td>
<td>147</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>646</td>
<td>655</td>
<td>42.3%</td>
<td>0.41 [0.26, 0.63]</td>
</tr>
</tbody>
</table>

Total events: 45
Heterogeneity: Tau² = 0.05; Ch² = 9.01, df = 9 (P = 0.34); I² = 11%
Test for overall effect: Z = 4.07 (P < 0.0001)

2 non-cardiac surgery

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>DEX group</th>
<th>Control group</th>
<th>Odds ratio</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M.H.</td>
<td>Random, 95% CI</td>
</tr>
<tr>
<td>Chang J 2017</td>
<td>0</td>
<td>29</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>Deiner S 2017</td>
<td>34</td>
<td>189</td>
<td>35</td>
<td>201</td>
</tr>
<tr>
<td>Guo Y 2015</td>
<td>6</td>
<td>78</td>
<td>21</td>
<td>78</td>
</tr>
<tr>
<td>Huang F 2014</td>
<td>2</td>
<td>54</td>
<td>5</td>
<td>54</td>
</tr>
<tr>
<td>Liu Y 2016</td>
<td>15</td>
<td>99</td>
<td>43</td>
<td>99</td>
</tr>
<tr>
<td>Ma P-P 2013</td>
<td>2</td>
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<td>11</td>
<td>30</td>
</tr>
<tr>
<td>Su X 2016</td>
<td>32</td>
<td>350</td>
<td>79</td>
<td>350</td>
</tr>
<tr>
<td>Wan Lu 2011</td>
<td>4</td>
<td>102</td>
<td>31</td>
<td>98</td>
</tr>
<tr>
<td>Yang X 2015</td>
<td>2</td>
<td>39</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>977</td>
<td>1039</td>
<td>57.7%</td>
<td>0.33 [0.18, 0.59]</td>
</tr>
</tbody>
</table>

Total events: 97
Heterogeneity: Tau² = 0.44; Ch² = 24.96, df = 9 (P = 0.0008); I² = 72%
Test for overall effect: Z = 3.71 (P < 0.0002)

3 perioperative period

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>DEX group</th>
<th>Control group</th>
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<th>Odds ratio</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M.H.</td>
<td>Random, 95% CI</td>
</tr>
<tr>
<td>Deiner S 2017</td>
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<tr>
<td>LI X 2017</td>
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<td>143</td>
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<tr>
<td>Yang X 2015</td>
<td>2</td>
<td>39</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>370</td>
<td>384</td>
<td>21.5%</td>
<td>0.87 [0.56, 1.36]</td>
</tr>
</tbody>
</table>

Total events: 53
Heterogeneity: Tau² = 0.00, Ch² = 1.83, df = 2 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.80 (P = 0.50)

4 intraoperative period

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>DEX group</th>
<th>Control group</th>
<th>Odds ratio</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M.H.</td>
<td>Random, 95% CI</td>
</tr>
<tr>
<td>Chang J 2017</td>
<td>0</td>
<td>29</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>Liu Y 2016</td>
<td>15</td>
<td>99</td>
<td>43</td>
<td>98</td>
</tr>
<tr>
<td>Ma P-P 2013</td>
<td>2</td>
<td>30</td>
<td>11</td>
<td>30</td>
</tr>
<tr>
<td>Maldonado JR 2009</td>
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<td>60</td>
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<td>Park JS 2014</td>
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<td>Prye S 2015</td>
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<td>32</td>
<td>5</td>
<td>32</td>
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<tr>
<td>Shiahb 2009</td>
<td>13</td>
<td>152</td>
<td>22</td>
<td>147</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>514</td>
<td>543</td>
<td>43.2%</td>
<td>0.35 [0.24, 0.51]</td>
</tr>
</tbody>
</table>

Total events: 17
Heterogeneity: Tau² = 0.00, Ch² = 0.02, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 4.24 (P < 0.0001)

Test for subarous differences: Ch² = 1.54, df = 2 (P = 0.469); I² = 67.4%

DEK Other comparator

0.01 0.1 1 10 100
Dexmedetomidine

• When stratified for POD as primary outcome (9 studies) may be evidence to suggest
  • ± loading dose of 0.5 µg•kg⁻¹•hr⁻¹
  • maintenance infusion at 0.2 µg•kg⁻¹•hr⁻¹ may be optimal
  • But still unclear on timing/duration

• Further evidence needed to elucidate optimal dosing tailored to procedure
Novel Strategies – Paracetamol?

DEXACET RCT (2019)

• 120 patients ≥60yo undergoing on-pump CABG, or CABG + Valve Replacement

• Randomized to one of 4 groups
  • Dexmed + Paracetamol
  • Dexmed + Placebo
  • Propofol + Paracetamol
  • Propofol + Placebo

• Sedation started at chest closure, paracetamol given q6h x 48hrs
Novel Strategies – Paracetamol?

• Paracetamol group
  • Lower incidence of POD
  • Reduced opioid requirements
  • Shorter ICU length of stay

• Dexmedetomidine group
  • No difference in terms of incidence of POD or ICU length of stay
  • Reduced opioid requirements
Novel Strategies

- 282 patients going for elective primary hip/knee replacement under spinal anesthesia
- Anesthesiologist aspirates 5mL of CSF
  - sent for analysis of beta-amyloid, and tau proteins
- Independent association of CSF Beta-amyloid and tau proteins levels to be predictive of POD
- May be due to subclinical Alzheimer Dementia
- Potentially useful for follow up, early intervention?
Recommendations

• Identify patients at risk!
• Consult geriatrician or treat as geriatrician would
  • Adequate preop hydration, correction of electrolyte imbalance where possible
  • May be ideal role for PAC
• Consider haldol, dexamethasone
• May use BIS/Sedline, titrate inhalational to avoid burst suppression
• Prudent to keep MAP > 55mmHg
• Potential utility of dexmedetomodine
Recommendations

• We are perioperative physicians
• Include in anesthetic considerations for the at risk patient
Acknowledgements

- Dr Clinton Torok-Both
- Dr Michael Vargo
Additonal References