Respiratory Depression and Considerations for Monitoring Following Ophthalmologic Surgery

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Disclosures

I have no financial relationships to disclose.

I will not discuss off label use or investigational use in my presentation.
Learning Objectives

1. To discuss the impact of sedation and General Anesthesia (GA) on postoperative respiration.

2. To review the efficacy of postoperative monitoring in capturing respiratory depression.
Postoperative Opioid-induced Respiratory Depression: A Closed Claims Analysis

- Temporary/Minor: 23%
- Permanent Brain Damage: 22%
- Death: 55%

n=92

Lee et al. Anesthesiology. 2015
Risk Factors

33% involved **multiple prescribers**

34% received concurrent **non-opioid sedatives**

31% received **inadequate assessment** or response
Additional Observations

Discovery within 2 hours: 42%  15 minutes: 16%

Somnolence was present in 62% of patients

2/3 of patients were obese

1/4 of patients had either diagnosed or suspected OSA based on Stop Bang criteria

Lee et al. Anesthesiology. 2015
1. **Snoring** Do you snore loudly (louder than talking or loud enough to be heard through closed doors)? Yes No
2. **Tired** Do you often feel tired, fatigued, or sleepy during daytime? Yes No
3. Observed Has anyone observed you stop breathing during your sleep? Yes No
4. **Blood pressure** Do you have or are you being treated for high blood pressure? Yes No
5. **BMI** BMI more than 35 kg/m²? Yes No
6. **Age** Age over 50 yr old? Yes No
7. **Neck circumference** Neck circumference greater than 40 cm? Yes No
8. **Gender** Gender male? Yes No High risk of OSA: answering yes to three or more items Low risk of OSA: answering yes to less than three items

Chung et al. Anesthesiology. 2008
88% of events occurred within first 24 hours of surgery
Why did 12% of events occur after POD1?

<table>
<thead>
<tr>
<th>AHI, events per hour</th>
<th>Preop</th>
<th>N1</th>
<th>N3</th>
<th>N5</th>
<th>N7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-OSA</td>
<td>20</td>
<td>2 (1, 4)</td>
<td>3 (1, 23)*</td>
<td>8 (2, 18)*</td>
<td>3 (1, 22)</td>
</tr>
<tr>
<td>OSA</td>
<td>38</td>
<td>18 (10, 33)†</td>
<td>20 (8, 43)</td>
<td>29 (14, 57)†</td>
<td>22 (10, 38) †</td>
</tr>
</tbody>
</table>
Fentanyl

![Graph showing the relationship between EEG dose (µg) and age](image)

- **EEG Dose (µg)**
- **Age**

Scott et al. J Pharmacol Exp Ther. 1987
Obesity rates have increased substantially over the past 20 years and are highest in the US.

1. Data are based on measurements rather than self-reported height and weight.
Source: OECD Health Data 2012.
Association between OSA and Ophthalmologic Disease

Sleep Breath (2016) 20:1145–1154

<table>
<thead>
<tr>
<th>Study name</th>
<th>MH odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-value</th>
<th>p-value</th>
<th>Glaucoma / Total</th>
<th>MH odds ratio and 95% CI</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin, 2013</td>
<td>1.753</td>
<td>1.408</td>
<td>2.183</td>
<td>5.021</td>
<td>0.000</td>
<td>114 / 1012</td>
<td>410 / 6072</td>
<td>1.43</td>
</tr>
<tr>
<td>Sergi, 2007</td>
<td>5.845</td>
<td>0.293</td>
<td>116.520</td>
<td>1.156</td>
<td>0.247</td>
<td>3 / 51</td>
<td>0 / 40</td>
<td>0.01</td>
</tr>
<tr>
<td>Boonyaklephan, 2008</td>
<td>2.053</td>
<td>0.479</td>
<td>8.804</td>
<td>0.968</td>
<td>0.333</td>
<td>6 / 44</td>
<td>3 / 42</td>
<td>0.04</td>
</tr>
<tr>
<td>Karakucuk, 2008</td>
<td>8.345</td>
<td>0.428</td>
<td>162.834</td>
<td>1.400</td>
<td>0.162</td>
<td>4 / 31</td>
<td>0 / 25</td>
<td>0.01</td>
</tr>
<tr>
<td>Kadyan, 2000</td>
<td>0.872</td>
<td>0.087</td>
<td>8.756</td>
<td>-0.116</td>
<td>0.907</td>
<td>3 / 68</td>
<td>1 / 20</td>
<td>0.02</td>
</tr>
<tr>
<td>Lin, 2011</td>
<td>4.873</td>
<td>0.283</td>
<td>84.058</td>
<td>1.690</td>
<td>0.276</td>
<td>12 / 209</td>
<td>0 / 38</td>
<td>0.01</td>
</tr>
<tr>
<td>Boyko-Walker, 2001</td>
<td>1.736</td>
<td>1.509</td>
<td>1.996</td>
<td>7.726</td>
<td>0.000</td>
<td>228 / 2725</td>
<td>3410 / 68235</td>
<td>3.29</td>
</tr>
<tr>
<td>Stain, 2008</td>
<td>1.214</td>
<td>1.177</td>
<td>1.252</td>
<td>12.357</td>
<td>0.000</td>
<td>4567 / 151633</td>
<td>50533 / 2000082</td>
<td>93.51</td>
</tr>
<tr>
<td>Minaksa, 2014</td>
<td>4.512</td>
<td>0.263</td>
<td>77.518</td>
<td>1.038</td>
<td>0.299</td>
<td>16 / 202</td>
<td>0 / 25</td>
<td>0.01</td>
</tr>
<tr>
<td>Aptel, 2014</td>
<td>1.133</td>
<td>0.880</td>
<td>1.451</td>
<td>0.990</td>
<td>0.322</td>
<td>240 / 6754</td>
<td>89 / 2826</td>
<td>1.66</td>
</tr>
<tr>
<td>Mohini, 2013</td>
<td>5.505</td>
<td>0.258</td>
<td>117.486</td>
<td>1.092</td>
<td>0.275</td>
<td>2 / 51</td>
<td>0 / 54</td>
<td>0.01</td>
</tr>
<tr>
<td>Nowak, 2009</td>
<td>2.846</td>
<td>0.130</td>
<td>62.522</td>
<td>0.684</td>
<td>0.507</td>
<td>2 / 34</td>
<td>0 / 18</td>
<td>0.01</td>
</tr>
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</table>

Fig. 2 Forest plots of meta-analysis of the included studies showing the odds ratios of glaucoma for subjects with and without OSA

Huon et al. Sleep Breath. 2016
Opioids induce respiratory depression.
Pulse oximetry reliably captures episodes of respiratory depression in patients recovering from ophthalmologic surgery.
Pretest

Respiratory depression increases measured End Tidal CO2.
End Tidal CO2 measurement provides reliable detection of opioid induced respiratory depression.
Myth

Patients do not experience intense pain following intracranial surgery.

Surgical manipulation of the brain parenchyma *per se* is not painful.

Dunbar et al., Anesth Analg. 1999
FACT: 2/3 patients report moderate to severe pain

Gottschalk et al., J. Neurosurgery. 2007
How was the pain treated?

<table>
<thead>
<tr>
<th>Postoperative Day</th>
<th>Percentage of Patients Treated With Opioids</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>1st Postoperative Day</td>
<td>50.4</td>
<td>0.002</td>
</tr>
<tr>
<td>2nd Postoperative Day</td>
<td>32.6</td>
<td>0.015</td>
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Gottschalk et al., J. Neurosurgery. 2007
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<td>32.6</td>
<td>0.015</td>
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Potentially toxic doses of acetaminophen were ordered:

**POD1: 42%  POD2: 33%**
Eligible Patients of Participating Surgeons Presenting for Supratentorial Craniotomy Under General Anesthesia (N=601)

Not Randomized (n=522)
- Personnel Not Available for Study or Case Not a First-Start (n=507)
  - Declined (n=5)
  - Excluded (n=10)

Randomized (N=79)

PRN Group (N=40)
- Completed OR Protocol (n=35)
  - Protocol violations (n=1)
  - Unanticipated Neurologic Outcomes (n=3)
  - Other (n=1)
  - Completed NCCCU Protocol (N=35)

PCA Group (N=39)
- Completed OR Protocol (n=29)
  - Protocol violations (n=2)
  - Unanticipated Neurologic Outcomes (n=6)
  - Other (n=2)
  - Completed NCCCU Protocol (N=29)
Supratentorial Craniotomy Pain

![Graph showing pain scores over time from Neurosurgical ICU admission.]

P = 0.026

But is it SAFE?
Major Safety Concerns Regarding Opioids

- Hypercarbia
- Hypoxia
- Sedation
Influence of Opioids on Sedation

Hammoud et al., Pain. 2009 modified
A Mechanism for Opioid Induced Sedation

μ receptor activation hyperpolarizes cholinergic neurons projecting from the basal forebrain to the prefrontal cortex.

Osman et al., Anesthesiology. 2005
Titration of Opioids to Sedation ≠ Sufficient Analgesia

Table 3. Self-Assessment Questionnaire Regarding Postoperative Pain and Discomfort Experienced in the PACU in the Early Postoperative Period, and 24 h Postoperatively in the Ward. The overall satisfaction of pain care was also recorded.

<table>
<thead>
<tr>
<th>Question</th>
<th>Control group (n = 52)</th>
<th>Sedated group in pain (n = 26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>How are you this morning? (good/badly)</td>
<td>96/4</td>
<td>54/46</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>How did you sleep last night? (well/moderately/badly)</td>
<td>48/42/10</td>
<td>23/23/54</td>
<td>0.001</td>
</tr>
<tr>
<td>How is your pain this morning? (severe/moderate/no pain)</td>
<td>6/44/50</td>
<td>50/42/8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yesterday, how was your pain when you arrived in your room? (severe/moderate/no pain)</td>
<td>18/25/57</td>
<td>58/16/26</td>
<td>0.0006</td>
</tr>
<tr>
<td>Are you satisfied with the pain care provided for the first 24 postoperative hours? (yes/moderately satisfied/no)</td>
<td>96/2/2</td>
<td>50/30/20</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
“No Patient Shall Be Harmed By Opioid-Induced Respiratory Depression”
Relation between CO2 and Intraocular Pressure
Carbon Dioxide Production

Glycolysis:

\[ \text{C}_6\text{H}_{12}\text{O}_6 + 2 \text{NAD} \rightarrow 2 \text{C}_3\text{H}_4\text{O}_3 + 2 \text{NADH} \]

\[ 2 \text{ATP} + 2 \text{ADP} + 2 \text{Pi} \rightarrow 4 \text{ATP} \]

Oxidative decarboxylation:

\[ \text{pyruvate} \xrightarrow{\text{CoA, NAD, NADH}} \text{acetyl CoA} + \text{CO}_2 \]

Krebs cycle:

\[ \text{acetyl CoA} \xrightarrow{3 \text{ NAD, FAD, ADP, Pi}} 2 \text{CO}_2 \]

Net reactions for glycolysis of glucose, oxidative decarboxylation of pyruvate, and Krebs cycle. 2015
Carbon Dioxide Signaling - Central Chemoreceptors

**Reaction:**

\[
\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^- 
\]

**Arterial Blood** → **CSF** → **Medullary Chemoreceptors** → **Arterial Blood**

- Decreased pH
- Carbonic Anhydrase

**Diagram Notes:**
- B B B (Arterial Blood)
- B B B (CSF)
- B B B (Medullary Chemoreceptors)
- B B B (Arterial Blood)

**Arterial Blood** contains CO2, which diffuses into CSF where it reacts with water to form H2CO3. This then dissociates into H+ and HCO3-. The decreased pH activates medullary chemoreceptors, leading to a decrease in CO2 in arterial blood.
Central Regulation of Breathing

pre-Bötzinger complex (rhythm)
Central Regulation of Breathing

pre-Bötzinger complex (rhythm)
Peripheral Regulation of Breathing

Glossopharyngeal Nerve (CN IX)

Vagus Nerve (CN X)

Respiratory centers of the brain. 2013
Effect of Opioids on Breathing

pre-Bötzinger complex (rhythm)

Glossopharyngeal Nerve (CN IX)

Vagus Nerve (CN X)
Influence of Oxygen on Respiratory Drive

Loeschke et al., Arch Ges Physiol. 1958
modified
Influence of PaCo2 on Ventilation

Pattinson et al., Br. J. Anaesth. 2008 modified
Influence of Opioids on Ventilation

Pattinson et al., Br. J. Anaesth. 2008 modified
Relation between PaCO2 and PAO2

\[ \text{PAO2} \approx \text{FiO2} \left( P_{\text{ATM}} - p\text{H2O} \right) - \text{PaCO2/RQ} \]

100 mmHg \approx 0.21 (760 mmHg - 47 mmHg) - 40 mmHg / 0.8

**PAO2 at CO2 40 mmHg \approx 150 - 50 = 100**

**PAO2 at CO2 of 60 mm Hg \approx 150 - 75 = 75**
SaO2 Monitoring

Changes in SpO2 (closed) and EtCO2 (open) during hypoventilation in patients receiving FiO2 of 21%, 25%, and 30%
Effect of Remifentanil on Ventilation during Normoxia and Hyperoxia

Niesters et al., Br. J. Anaesth, 2013
Previous Estimates of Respiratory Depression (Intermittent Assessment)

### Table 1: Reported incidence of respiratory depression as indicated by ventilatory frequency lower than predetermined value

<table>
<thead>
<tr>
<th>Analgesic technique</th>
<th>Number of study groups</th>
<th>Total number of patients</th>
<th>Respiratory depression Mean (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>116</td>
<td>29,607</td>
<td>1.1</td>
<td>0.7–1.7%</td>
</tr>
<tr>
<td>I.M.</td>
<td>10</td>
<td>1,590</td>
<td>0.8</td>
<td>0.2–2.5%</td>
</tr>
<tr>
<td>I.V.-PCA</td>
<td>35</td>
<td>6,922</td>
<td>1.2</td>
<td>0.7–1.9%</td>
</tr>
<tr>
<td>Epidural</td>
<td>71</td>
<td>21,035</td>
<td>1.1</td>
<td>0.6–1.9%</td>
</tr>
</tbody>
</table>

### Table 2: Reported incidence of respiratory depression as indicated by oxygen saturation below predetermined value

<table>
<thead>
<tr>
<th>Analgesic technique</th>
<th>Number of study groups</th>
<th>Total number of patients</th>
<th>Respiratory depression Mean (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>32</td>
<td>1,516</td>
<td>17.0</td>
<td>10.2–26.9%</td>
</tr>
<tr>
<td>I.M.</td>
<td>9</td>
<td>246</td>
<td>37.0</td>
<td>22.6–45.9%</td>
</tr>
<tr>
<td>I.V.-PCA</td>
<td>11</td>
<td>707</td>
<td>11.5</td>
<td>5.6–22.0%</td>
</tr>
<tr>
<td>Epidural</td>
<td>12</td>
<td>563</td>
<td>15.1</td>
<td>5.6–34.8%</td>
</tr>
</tbody>
</table>

Cashman et al. Br J Anaesth. 2004
Incidence of Respiratory Depression (Measured Continuously)

Incidence of bradypnea
Respiratory rate less than 10 br/min lasting for greater than 2 minutes: 58%

Incidence of hypoxia
Saturations below 90%: 21%

Overdyk et al., Anesth Analg. 2007
Incidence of Respiratory Depression (Measured Continuously)

Incidence of bradypnea
Respiratory rate less than 10 br/min
lasting for greater than 2 minutes: 58% (1.2%)

Incidence of hypoxia
Saturations below 90%: 21% (11.5%)

Overdyk et al., Anesth Analg. 2007
Hospital staff experiencing "Alarm Fatigue"

- Overwhelmed by information
- Desensitized to number of alarms
- Immune to alarm sounds

Improper responses

- Turn down volume
- Turn alarms off
- Adjust settings outside safe limits

Serious or fatal consequences

- Patient falls
- Delays in treatment
- Treatment errors

PCA-SAME Study: Post Craniotomy Analgesia-Safety Monitoring with EtCO2

Primary Objective:
To determine the safety of opioid analgesic therapy in male and female adult post-supratentorial craniotomy patients randomly assigned to receive either IVPCA or IV PRN opioids as defined by

Respiratory rate < 10 breaths per minute [bpm] for greater than 2 minutes measured non-invasively by side stream capnography.
PRN PATIENT

O2 Sat

HR

CO2

RR

Doses

Morad et al., American Society of Anesthesiologists. 2015
Morad et al., American Society of Anesthesiologists. 2015.
A)

Dilating forces

Extraluminal pressures

Collapsing forces

B)

Impaired Respiratory Arousal
PORC, Anesthetics, Opioids

Dilating forces

Extraluminal pressures

Collapsing forces

Increased respiratory effort
Inflammation

Sasaki et al., Anesthesiology. 2013
Effect of Opioids on Breathing

The Upper Respiratory System
Opioids can induce respiratory depression.
Pulse oximetry reliably captures episodes of respiratory depression in patients recovering from ophthalmologic surgery.
Post Test

Respiratory depression increases measured End Tidal CO2.
End Tidal CO2 measurement provides reliable detection of opioid induced respiratory depression.
Summary

1. Opioids, alone and in combination with other sedatives, induce respiratory depression by decreasing respiratory drive AND obstructing upper airway motor tone.
2. Continuous monitoring for respiratory depression is better than intermittent assessment.
3. Supplemental oxygen masks opioid induced respiratory depression.
4. End-tidal CO2 monitoring in non-intubated patients is inadequate in detecting opioid induced respiratory depression.
5. Preoperative patient screening and postop monitoring protocols are critically important.
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My research participants, our NCCU staff and…

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