Pain and analgesia in the postoperative patient with obstructive sleep apnea

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DISCLOSURE
I have no financial relationships with commercial support to disclose.
Learning objectives

At the conclusion of this activity, participants should be able to:

Identify hyperalgesic phenotypes in obstructive sleep apnea
Evaluate the risk for altered pain perception in patients with OSA
Determine the risk for opioid-induced respiratory depression
Select appropriate analgesic regimens in the context of OSA
Is obstructive sleep apnea hyperalgesic?

Nocturnal intermittent hypoxia

Sleep deprivation; sleep disruption

Excessive daytime sleepiness

Systemic inflammation

Comorbid insomnia
Intermittent hypoxia

Cleveland Family Study
• Family-based longitudinal cohort
• 634 OSA and controls
• 4 types of pain

A decrease in the minimum nocturnal SpO₂ from 92 to 75% almost doubled the odds for reporting pain

Doufas, Anesthesiology, 2013
Sleep deprivation and sleep disruption

Sleep deprivation promotes inflammation\(^1\) and spontaneous pain\(^2\) in healthy volunteers

Sleep disruption decreased central pain inhibition by 60% in healthy women\(^3\)

CPAP (6-8 weeks) reduced sensitivity to heat pain by 40-100% in patients with severe OSA\(^4\)

\(^1\)Haack, Pain, 2007  \(^2\)Haack, Pain, 2009  \(^3\)Smith, Sleep, 2007  \(^4\)Khalid, Sleep, 2011
Excessive daytime sleepiness

“Sleepy” (MSLT 4.8 vs 12.6 min) pain-free volunteers have 40% lower pain thresholds than the non-sleepy ones\(^1\)

In “sleepy” volunteers, an extended sleep opportunity increased pain thresholds by 25%\(^2\)

Physiological sleepiness diminished the acute anti-nociceptive effect of codeine in healthy volunteers\(^3\)

\(^1\)Chhangani, Sleep, 2009 \hspace{1cm} \(^2\)Roehrs, Sleep, 2012 \hspace{1cm} \(^3\)Steinmiller, Exp Clin Psychopharmacol, 2010
Systemic inflammation

OSA is a chronic inflammatory state

Both sleep fragmentation and intermittent hypoxia can trigger systemic inflammation via:

• Oxidative stress and sympathetic activation\(^1\)

Cleveland Family Study

• Soluble IL-6 receptor levels were positively associated with nocturnal hypoxemia and arousal index\(^2\)

\(^1\)Arnardottir, Sleep, 2009

\(^2\)Mehra, Arch Intern Med, 2006
Insomnia comorbid with OSA

OSA and insomnia co-occur to a high degree\(^1\):

- 58\% of OSA patients complain about insomnia
- 67\% of patients with insomnia are also diagnosed with OSA

Experimental pain models have demonstrated:

- Insomnia decreased central pain inhibition\(^2\)
- Insomnia and chronic pain synergistically increase pain\(^3\)

\(^1\)Luyster, J Clin Sleep Med, 2010  \quad ^2\)Haack, Eur J Pain, 2011  \quad ^3\)Sivertsen, Pain, 2015
Opioid analgesia in patients with OSA

Animal and ex vivo models

Pediatric populations

Adult populations
IH enhances opioid sensitivity in animals

Recurrent hypoxemia increased binding in the mu-opioid receptors (MOR) in rat’s brainstem\textsuperscript{1}

\begin{itemize}
\item Up-regulation of MOR?
\end{itemize}

Recurrent hypoxemia during development increased sensitivity to the respiratory effects of fentanyl in rats\textsuperscript{2}

\textsuperscript{1}Laferriere, Brain Res Bull, 2003  \hspace{2cm} \textsuperscript{2}Moss, Anesthesiology, 2006
Tonsillectomy in children for OSA treatment

Nocturnal hypoxemia reduced morphine requirement for postoperative analgesia\(^1\)
- Nadir nocturnal SpO\(_2\)< 85%, decreased the dose of morphine by half\(^2\)

Increased morphine requirement postoperatively in OSA\(^3\)
- Higher incidence of respiratory complications

Racial disparity in the postoperative pain in OSA\(^4\)
- Increased pain and morphine requirement in AA, compared with Caucasian children with OSA

\(^1\)Brown, Anesthesiology, 2004
\(^2\)Brown, Anesthesiology, 2006
\(^3\)Sanders, Anesth Analg, 2006
\(^4\)Sadhasivam, Pediatrics, 2012
Adults with OSA and nocturnal hypoxemia

Nocturnal hypoxemia (lower nadir SpO₂) was associated with higher analgesic potency of remifentanil in experimental pain¹

Nocturnal hypoxemia (fraction of sleep time with SpO₂ < 90%) was associated with decreased morphine requirement for postoperative analgesia in bariatric patients²

¹Doufas, PLoS ONE, 2013
²Turan, PLoS ONE, 2015
# Pain and opioid analgesic effect in OSA

<table>
<thead>
<tr>
<th>Trials</th>
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<td>Time SpO₂ &lt; 90%</td>
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Opioids and severe respiratory depression

ADULTS

Death (55%) or permanent brain damage (22%), among 92 claims in the context of opioid analgesia

- Established diagnosis or high risk for OSA (25%); obesity (66%); somnolence before the event (62%)

Congestive heart failure, postoperative ARF, OSA, and DM, prevalent among patients with life-threatening respiratory events

OSA and respiratory events in PACU predict delayed respiratory depression

- Chronic and postoperative use of benzodiazepines also predict respiratory depression

CHILDREN

Death or neurologic injury post-tonsillectomy: 57% were at risk for OSA, based on ASA criteria

- In at-risk-for-OSA children, adverse event was predominantly attributed to apnea than hemorrhage

1 Lee, Anesthesiology, 2015
2 Ramachandran, J Clin Anesth, 2011
3 Weingarten, Anest Analg, 2015
4 Ramachandran, Anest Analg, 2017
5 Coté, Anest Analg, 2014
Opioids worsen sleep-disordered breathing

Sleep-disordered breathing and oxygenation worsen after surgery in both OSA$^{1,2}$ and non-OSA$^{3}$ patients

- Large variation of effect$^{1}$
- For OSA patients, age, preoperative AHI, and opioid dose were major predictors$^{2}$

Among 833 patients recovering from non-cardiac surgery, hypoxemia is common and persistent$^{4}$

- 21% averaged at least 10 min per hour with SpO$_2$ < 90%
- No difference between the use of long- or short-acting opioids$^{5}$
- STOP-Bang questionnaire does not predict hypoxemia$^{6}$

$^1$Chung, Anesthesiology, 2014  
$^2$Chung, Anesthesiology, 2014  
$^3$Chung, Anesth Analg, 2015  
$^4$Sun, Anesth Analg, 2015  
$^5$Belcher, Anesth Analg, 2016  
$^6$Khanna, Anesth Analg, 2016
Respiratory effects of opioids in OSA patients

A 0.5 mcg/kg bolus of fentanyl in children under general anesthesia led to apnea in 46% of OSA vs 5% of controls\(^1\)

Remifentanil infusion (0.075 mcg/kg/min) during a sleep study resulted in dramatic increase of central apnea in 4 out of 10 adults with OSA\(^2\)

- “Opioid-emergent central sleep apnea”

Variable effects of opioids on respiration in the context of OSA

\(^1\)Waters, J Appl Physiol, 2002
\(^2\)Bernards, Anesthesiology, 2009
Variability in OSA pathogenic mechanisms

Jordan, Lancet, 2014
Mitigation of opioid side effects

- Neuraxial anesthesia
- Ketamine preserves dilators

Opioid-induced Ventilatory Impairment

Respiratory Depression

Analgesia

Sedation

Airway Collapsibility

Minimize opioids
- Selective reversal (ampakines, GAL021)\(^1,2\)
- Biased ligands of \(\mu\)-OR (TRV130)\(^3\)

Use of CPAP\(^4\)

Short-acting anesthetics

Multimodal analgesia

Acetylcholinesterase inhibitors\(^5,6\)

Dose / Effect Site Concentration of Opioids

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\(^1\)Oertel, Clin Pharmacol Ther, 2010
\(^2\)Roozekrans, Anesthesiology, 2014
\(^3\)Soergel, Pain, 2014
\(^4\)Liao, Anesthesiology, 2013
\(^5\)Meuret, Anesthesiology, 2000
\(^6\)Hedner, Am J Respir Crit Care Med, 2003
\(^7\)Eikermann, Anesthesiology, 2012
Neuraxial & regional anesthesia in OSA

Analysis of more than 1,000,000 cases of total hip and knee arthroplasties between 2006 and 2013\(^1\):

- Increase in the use of peripheral nerve block from 9 to 15%
- Decrease in the daily prescription of opioids by 17%

Among 30,024 patients with OSA undergoing total joint arthroplasty\(^2\):

- 11% neuraxial, 15% combined and 74% general anesthesia
- Less complications with neuraxial vs general anesthesia; OR: 0.83 (95% CI: 0.74 - 0.93)

\(^1\)Cozowicz, Anesth Analg, 2017

\(^2\)Memtsoudis, Reg Anesth Pain Med, 2013
Opioid-sparing post-tonsillectomy in OSA

Postoperative ibuprofen is effective analgesic\(^1\)
- Randomized to morphine (N=30, 0.1 - 0.35 mg/kg, Q 4h), or ibuprofen (N=26, 10 mg/kg, Q 6h)
- No difference in pain; decreased number of desaturations events with ibuprofen

Intraoperative dexmedetomidine (Dex) infusion\(^2\)
- Randomized to Dex (N=61, 2 mcg/kg bolus, 0.7 mcg/kg/min), or Fentanyl (N=61, a bolus of 1 mcg/kg)
- Decreased postoperative opioid analgesia and desaturation events in Dex vs Fentanyl groups
- Maximum pain was higher in the F than Dex groups (5 vs 3, OPS)

\(^1\)Kelly, Pediatrics, 2015
\(^2\)Patel, Anesth Analg, 2010
Support airway patency postoperatively

Postoperative positive airway pressure (PAP)\(^1\)
- 177 patients were randomized to receive Auto-titrated PAP or routine care for 5 postoperative nights
- APAP decreased AHI by 89% on 3\(^{rd}\) postoperative night

CPAP early after bariatric surgery\(^2\)
- Crossover randomization of 38 bariatric (BMI: 46 kg/m\(^2\)) patients to atmospheric pressure (AP), or CPAP in PACU
- CPAP treatment decreased AHI during opioid analgesia in the PACU by 69%
- Total morphine-equivalent dose administered 2.9 vs 2.5 mg

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\(^1\) Liao, Anesthesiology, 2013
\(^2\) Zaremba, Anesthesiology, 2016
Summary

Several OSA-related phenotypes might enhance pain perception

Nocturnal intermittent hypoxemia in OSA might be associated with reduced requirement for opioid analgesia

Postoperative opioids may aggravate sleep-disordered breathing

• A direct link with life-threatening respiratory events is yet to be demonstrated

Mitigating respiratory depression during postoperative analgesia

• Maintaining arousal responses, minimizing opioids, and/or supporting the airway via mechanical means