Decreasing Intraoperative Opioid Consumption In The Opioid Epidemic Era

MSQC/ASPIRE COLLABORATIVE MEETING
APRIL 28TH 2017

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Disclosure

Funded Research

• Hemosonics
• Merck
Outline

• Opioid Epidemic in Numbers
• Epidemiology of Misuse, Abuse and Diversion
• The Perioperative Period—Priming Patients for Misuse, Abuse and Dependence?
• Perioperative Strategies:
  – Intravenous Lidocaine
  – Ketamine
  – Dexmedetomidine
  – Enhanced Recovery Programs
• Future Research
• Conclusion
Economic Impact of the Opioid Epidemic:

- **$55 billion** in health and social costs related to prescription opioid abuse each year.
- **$20 billion** in emergency department and inpatient care for opioid poisonings.

2013;14(10):1534-47.²

On an average day in the U.S.:

- More than **650,000 opioid prescriptions** dispensed.¹
- **3,900 people** initiate nonmedical use of prescription opioids.²
- **580 people** initiate heroin use.²
- **78 people** die from an opioid-related overdose.³

*Opioid-related overdoses include those involving prescription opioids and illicit opioids such as heroin.

Source: IMS Health National Prescription Audit¹ / SAMHSA National Survey on Drug Use and Health² / CDC National Vital Statistics System³
Shifting Patterns of Prescription Opioid and Heroin Abuse in the United States

Fentanyl
Carfentanil

NEJM 373;18, October 29, 2015
Deaths Involving Fentanyl Rise As Curbing Illicit Supply Proves Tough

November 18, 2016 · 3:27 PM ET
Heard on All Things Considered

MARTHA BEBINGER

AROUND THE NATION

Fentanyl Contributes To Record Drug Overdoses In New York City

December 21, 2016 · 5:06 AM ET
Heard on Morning Edition

MARY HARRIS
Heroin Epidemic Is Yielding to a Deadlier Cousin: Fentanyl

Two Pa. overdoses linked to use of elephant sedative; state issues warning

DEA Issues Carfentanil Warning to Police and Public

Dangerous opioid 10,000 times more potent than morphine and 100 times more potent than fentanyl
The New York Times

2 of a Farmer’s 3 Children Overdosed. What of the Third — and the Land?

By JACK HEALY    MARCH 12, 2017
Surgery and Opioid Use

- Preoperative
- Intraoperative
- Postoperative
- Long Term
Impact of Surgery On Chronic Opioid Dependence

- Increasing evidence that surgery can predispose to chronic opioid use
- This phenomena noted in opioid-naïve patients
- Patient and surgery-specific risk factors
- Approximately 3.1% of opioid-naïve patients continue to use opioids 90 days after major surgery

Sun et al. JAMA Intern Med. 2016;176(9):1286-1293
Clark et al. BMJ 2014;348:g1251
Impact of Surgery On Chronic Opioid Dependence

• Retrospective administrative health claims analysis
• January 1, 2001 to December 31, 2013
• 11 surgical procedures
• Multivariable logistic regression analysis to control for possible confounders
• Chronic opioid use: filled 10 or more prescriptions or more than 120 days’ supply of an opioid in the first year after surgery, excluding the first 90 postoperative days
• Nonsurgical cohort: filled 10 or more prescriptions or more than 120 days’ supply following a randomly assigned “surgery date.”

641 941 opioid-naive surgical patients
18 011 137 opioid-naive nonsurgical patients

## Impact of Surgery On Chronic Opioid Dependence In Opioid-Naïve Patients

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (SE)ᵃ</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.34 (0.0648)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age &gt;50 y</td>
<td>1.74 (0.0942)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Preoperative drug use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>1.82 (0.1049)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>1.65 (0.0928)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>1.14 (0.1330)</td>
<td>.28</td>
</tr>
<tr>
<td><strong>Medical comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>1.15 (0.0717)</td>
<td>.03</td>
</tr>
<tr>
<td>Psychosis</td>
<td>1.03 (0.2094)</td>
<td>.89</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>1.83 (0.2834)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>3.15 (0.5385)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Impact of Surgery On Chronic Opioid Dependence In Opioid-Naïve Patients

- Simple mastectomy
- Transurethral prostate resection
- Cataract
- Functional endoscopic sinus surgery
- Cesarean delivery
- Open appendectomy
- Laparoscopic appendectomy
- Open cholecystectomy
- Laparoscopic cholecystectomy
- Total hip arthroplasty
- Total knee arthroplasty
- Nonsurgical patients

Impact of Surgery On Chronic Opioid Dependence

• Population based retrospective cohort study
• 1 April 2003 and 31 March 2010
• 39,140 opioid naïve patients aged 66 years or older who had major elective surgery, including cardiac, intrathoracic, intra-abdominal, and pelvic procedures
• Prolonged opioid use after discharge: ongoing outpatient prescriptions for opioids for more than 90 days after surgery

Clark et al. BMJ 2014; 348:g1251.
## Impact of Surgery On Chronic Opioid Dependence In Opioid-Naïve Patients

<table>
<thead>
<tr>
<th>Factors</th>
<th>Odd ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Group (66-75 years)</td>
<td>1.63 (1.08 to 2.46)</td>
<td>0.03</td>
</tr>
<tr>
<td>Open lung resection</td>
<td>2.58 (2.03 to 3.28)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Minimally invasive lung resection</td>
<td>1.95 (1.36 to 2.78)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Benzodiazepines (Preoperatively)</td>
<td>1.26 (1.07 to 1.48)</td>
<td>0.005</td>
</tr>
<tr>
<td>SSRIs (Preoperatively)</td>
<td>1.41 (1.10 to 1.80)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Clark et al. BMJ 2014; 348:g1251.
Impact of Surgery On Chronic Opioid Dependence In Opioid-Naïve Patients Undergoing Spine Surgery

• Major spine surgery between 2011-2016
• Perioperative opioid/non-opioid use
• Determined opioid use 1, 6 and 12 months after surgery
• 1, 478 patients reviewed
  – 27.6% opioid-naïve preoperatively
  – 72.4 % required opioids preoperatively
Impact of Surgery On Chronic Opioid Dependence In Opioid-Naïve Patients Undergoing Spine Surgery

- Mean preoperative opioid dose: 32.8 ± 46.3 mg
- Opioid naïve group
  - 21% of patients had a prescription for opioids 12 months after surgery
- Non opioid-naïve group
  - 39% of patients had NO prescription for opioids 12 months after surgery
- Odds of being a chronic opioid user is higher for non-opioid naive patients than opioid-naive patients \( \chi^2(1) = 164.01, p < 0.001 \)
Impact of Surgery On Chronic Opioid Dependence In Opioid-Naïve Patients Undergoing Spine Surgery

Armaghani et al. Spine 2014;39:E1524–E1530
Opioid-Prescribing Patterns of Emergency Physicians and Risk of Long-Term Use

Michael L. Barnett, M.D., Andrew R. Olenski, B.S., and Anupam B. Jena, M.D., Ph.D.

A

Percent of Emergency Department Visits with an Opioid Prescription

Prescriber Quartile

B

Odds Ratio for Long-Term Opioid Use

Prescriber Quartile

(N1 low intensity, reference)

(N4 high intensity)
UVA Intraoperative Opioid Use and PACU Pain Scores

Average Morphine Equivalents - March 2011 thru November 2015

- 14.2 mg [13.5-15.0 mg]
- 9 mg (CI, 8.3-9.8 mg)
- 5.5 (CI, 5.2-5.6)
- 3.8 (CI, 3.6-4.0)

3/2011 to 11/2015
Non-Opioid Analgesic Use
Intraoperative Opioid Use and Stratified PACU Pain Scores
Opioids Only Group

N=3,076

15 mg (13.5-16.5)

7.5 mg (6.0-9.0)

3.6 (3.2-4.0)

1.3 (0.9-1.7)
Perioperative Non-opioid Therapy

- Intravenous Lidocaine
- Ketamine
- Dexmedetomidine
- Enhanced Recovery Programs
Perioperative Lidocaine

• Anti-inflammatory
• Analgesic
• Anti-hyperalgesic properties
• Proposed mechanisms:
  – Na⁺ channel blockade
  – G-protein coupled receptors
  – NMDA receptor blockade

Mol Pharmacol. 2001 Feb;59(2):294-301
J Pain. 2006 May;7(5 Suppl 3):S1-29
Perioperative Use of Intravenous Lidocaine

Lauren K. Dunn, M.D., Ph.D., Marcel E. Durieux, M.D., Ph.D.
Perioperative Lidocaine

- PONV – PACU
- PONV – late time points (0 to 72h)

- Pain – open abdominal surgery
- Pain – laparoscopic abdominal surgery

- Ileus
- Time to first flatus
- Time to first defecation

Level of evidence (Kranke et al., 2015)
- Moderate
- Low
Perioperative Lidocaine

**Induction**
- 1 mg/kg bolus with induction of anesthesia

**Intraoperative**
- 40 mcg/kg/min infusion during surgery
- Rate decreased to 0.5-1 mg/min at end surgery and continued to PACU

**PACU**
- Infusion continued (0.5-1 mg/min)
- Oral analgesics (celecoxib, oxycodone) initiated when patient tolerating oral medications

**POD 1**
- Infusion continued (0.5-1 mg/min)
- Patients monitored for toxicity (tinnitus, perioral numbness, cardiac dysrhythmias) by surgical and APS services
- Patients transitioned to oral analgesic regimen

**POD 2**
- Lidocaine Infusion discontinued
Lidocaine and Spine Surgery

51 adults for one-level laminectomy and discectomy randomized to control or lidocaine groups

Lidocaine group: 1.5-mg/kg bolus followed by 2-mg/kg/h infusion during procedure

Primary outcome: visual analog score (VAS) 0 – 100mm at 4 hrs postop

Secondary outcomes: VAS and Fentanyl consumption up to 48 hours, PCA, patient satisfaction, PONV, length of stay
Lidocaine and Spine Surgery

![Graph showing VAS scores over time for two groups, Group C and Group L.](image)

*K.-T. Kim et al. / The Spine Journal (2013)*
Lidocaine and Spine Surgery

![Graph showing fentanyl levels over time]

- **Time**:
  - 2hr
  - 4hr
  - 8hr
  - 12hr
  - 24hr
  - 48hr

- **Fentanyl (ug/hr)**

- **Legend**:
  - Black: Group C
  - Gray: Group L

*Significant difference indicated by asterisk.*

*K.-T. Kim et al. / The Spine Journal (2013)*
Lidocaine and Spine Surgery

Effect of Perioperative Intravenous Lidocaine Administration on Pain, Opioid Consumption, and Quality of Life after Complex Spine Surgery

- 115 patients for multi-level spine surgery randomized to lidocaine or placebo
- Lidocaine group - 2mg/kg/hr infusion continued postoperatively for maximum 8 hours
- Primary outcomes: pain scores and opioid requirements in the first 48 hours postoperatively
- Secondary outcomes: 30 day postop complications, postop 24 hr PONV incidence, hospitalization duration, and postop quality of life.

Farag et al. Anesthesiology 2013
Effect of Perioperative Intravenous Lidocaine Administration on Pain, Opioid Consumption, and Quality of Life after Complex Spine Surgery

VRS Pain Score

Placebo
Lidocaine

Recovery

0-2h 2-4h 4-6h 6-8h Overnight POD1 POD2

Farag et al. Anesthesiology 2013
• Lidocaine group had significantly lower pain scores

• Morphine consumption was less in the lidocaine group

• Lidocaine group had significantly higher physical composite scores at 1 and 3 months

• No difference in PONV incidences or duration of hospital stay

• Lidocaine group had slightly fewer 30 day complication rates

Farag et al. Anesthesiology 2013
\( \alpha_2 \) Agonists

- Possible mechanisms for analgesia:
  - Peripheral nerve blockade, especially in conjunction with local anesthetics
  - Interdependence between \( \alpha_2 \) receptors and mu receptors
  - Acts centrally on dorsal horn
  - Potentially acts supra-spinal on locus ceruleus and nucleus raphe magnus.

- Clonidine: \( \alpha_2:\alpha_1 \) selectivity of 200: 1

- Dexmedetomidine: \( \alpha_2:\alpha_1 \) selectivity of 1620:1
Effect of Perioperative Systemic α2 Agonists on Postoperative Morphine Consumption and Pain Intensity

Systematic Review and Meta-analysis of Randomized Controlled Trials

Clonidine

- 2 h: WMD [95% CI] -0.6 [-1.8, 0.5]
- 12 h: -9.8 [-16.2, -3.4]
- 24 h: -4.1 [-6.0, -2.2]

Favors Clonidine

Dexmedetomidine

- 2 h: WMD [95% CI] -6.3 [-8.3, -4.2]
- 12 h: -6.0 [-8.9, 3.0]
- 24 h: -14.5 [-22.1, -6.8]

Favors Control

Morphine equivalent (mg)

Anesthesiology 2012; 116:1312-22
Effect of Perioperative Systemic $\alpha_2$ Agonists on Postoperative Morphine Consumption and Pain Intensity

Systematic Review and Meta-analysis of Randomized Controlled Trials

- **Clonidine**
  - 1 h: WMD [95% CI] = -0.2 [-0.6, 0.2]
  - 2 h: -0.2 [-1.2, 0.8]
  - 4 h: -0.5 [-1.5, 0.5]
  - 12 h: -1.5 [-2.1, -1.0]
  - 24 h: -0.7 [-1.2, -0.1]
  - 48 h: 0.1 [-0.4, 0.7]

- **Dexmedetomidine**
  - 1 h: WMD [95% CI] = -1.4 [-2.7, -0.2]
  - 2 h: -0.3 [-0.8, 0.1]
  - 4 h: -0.6 [-0.9, -0.2]
  - 12 h: -0.6 [-1.2, 0.1]

*Anesthesiology* 2012; 116:1312–22
The Effect of Dexmedetomidine on Postoperative Opioid Consumption and Pain After Major Spine Surgery

Bhiken I. Naik, MBCh,*† Edward C. Nemergut, MD,*† Ali Kazemi, MD,* Lucas Fernández, MD, DSc,* Sarah K. Cederholm, MD,* Timothy L. McMurry, PhD,‡ and Marcel E. Durieux, MD, PhD*†

• Prospective Double Blind Study
• Evaluating intraoperative dexmedetomidine vs. placebo
• Major spine surgery
• N = 131
  – Dexmedetomidine = 63 patients
  – Placebo = 68 patients
• Primary outcome
  – Postoperative opioid consumption
  – Postoperative pain scores

Anesth Analg. 2016 May;122(5):1646-53
The Effect of Dexmedetomidine on Postoperative Opioid Consumption and Pain After Major Spine Surgery

Bhiken I. Naik, MBBCh,*† Edward C. Nemergut, MD,*† Ali Kazemi, MD,* Lucas Fernández, MD, DSc,* Sarah K. Cederholm, MD,* Timothy L. McMurry, PhD,‡ and Marcel E. Durieux, MD, PhD*†

Anesth Analg. 2016 May;122(5):1646-53
Ketamine and Spine Surgery

• Intraoperative Ketamine Reduces Perioperative Opiate Consumption in Opiate-dependent Patients with Chronic Back Pain Undergoing Back Surgery
  – Loftus et al. Anesthesiology 2010

• Continuous Low-Dose Ketamine Improves the Analgesic Effects of Fentanyl Patient-Controlled Analgesia After Cervical Spine Surgery

• Intra- and Postoperative Very Low Dose Intravenous Ketamine Infusion Does Not Increase Pain Relief after Major Spine Surgery in Patients with Preoperative Narcotic Analgesic Intake
• 101 adult patients with daily opiate use > 6 weeks for lumbar back surgery randomized to ketamine or control
• Ketamine group: 0.5mg/kg of ketamine at induction; 10ug.kg\(^{-1}\cdot\)min\(^{-1}\) infusion during case
• Primary outcomes: 48 hour morphine consumption
• Secondary outcomes: postop complications, side effects related to opioid and ketamine, PACU stay, hospital stay, pain scores up to 6 weeks, opiate consumption up to 6 weeks

Loftus et al. Anesthesiology 2010
<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ketamine</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hr total ME</td>
<td>202 ± 176</td>
<td>142 ± 82</td>
<td>0.03</td>
</tr>
<tr>
<td>48-hr total ME</td>
<td>309 ± 341</td>
<td>195 ± 111</td>
<td>0.03</td>
</tr>
<tr>
<td>6 week ME (mg/h)</td>
<td>2.8 ± 6.9</td>
<td>0.8 ± 1</td>
<td>0.04</td>
</tr>
<tr>
<td>6-week VAS</td>
<td>4.2 ± 2.4</td>
<td>3.1 ± 2.4</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Intraoperative Ketamine Reduces Perioperative Opiate Consumption in Opiate-dependent Patients with Chronic Back Pain Undergoing Back Surgery

<table>
<thead>
<tr>
<th>Ketamine Effect Stratified According to Preoperative Morphine Use</th>
<th>Treatment</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean (mg)</td>
<td>SD</td>
<td>N</td>
</tr>
<tr>
<td>≥0.556 mg/hr intravenously</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hr ME</td>
<td>17</td>
<td>168.8</td>
<td>94.4</td>
</tr>
<tr>
<td>48-hr ME</td>
<td>16</td>
<td>241.3</td>
<td>145.7</td>
</tr>
<tr>
<td>&lt;0.556 mg/hr intravenously</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hr ME</td>
<td>34</td>
<td>129.3</td>
<td>73.8</td>
</tr>
<tr>
<td>48-hr ME</td>
<td>33</td>
<td>172.7</td>
<td>83.2</td>
</tr>
</tbody>
</table>
Continuous Low-Dose Ketamine Improves the Analgesic Effects of Fentanyl Patient-Controlled Analgesia After Cervical Spine Surgery

200 patients

Ketamine 1mg/kg bolus

Ketamine 1
1mg/kg/24hrs

Ketamine 2
2mg/kg/24hrs

control

Cervical (n=23)

Lumbar (n=44)

Cervical (n=23)

Lumbar (n=46)

Cervical (n=22)

Lumbar (n=42)
Continuous Low-Dose Ketamine Improves the Analgesic Effects of Fentanyl Patient-Controlled Analgesia After Cervical Spine Surgery

* P < 0.05 versus control
τ P < 0.05 versus ket-1

Anesth Analg 2008;107:1041-4
Continuous Low-Dose Ketamine Improves the Analgesic Effects of Fentanyl Patient-Controlled Analgesia After Cervical Spine Surgery

* P < 0.05 versus control
\( \tau \) P < 0.05 versus ket-1

Anesth Analg 2008;107:1041-4
Multimodal approach to control postoperative pathophysiology and rehabilitation

H. Kehlet
## ERAS Colorectal Surgery

### Day before operation
- Regular diet until 6 pm; bowel preparation (mechanical and oral antibiotics); chlorohexidine shower night before and morning of surgery

### Day of operation, preoperative holding area
- Identify enhanced recovery patients and initiate protocol; allow patients to have clears up until 2 hours before operation; Gatorade 20 oz, must be completed 2 hours before operation
- Medications:
  - Acetaminophen 6/9 mg po

### Intraoperative
- Duramorph (100 µg) spinal preinduction; no intraoperative opioids without attending approval
- Induction: propofol, ketamine 0.5 mg/kg, magnesium 30 mg/kg (over 10 min), dexamethasone 4 mg
- IV analgesia: lidocaine 40 µg/kg/min (continued into PACU), ketamine 0.6 mg/kg/h (10 µg/kg/min, stop approximately 45 minutes before waking in laparoscopic, drop to 5 µg/kg/min for open cases)
- “Goal-directed” fluids guided by Pleth Variability Index; tidal volumes 6–8 mL/kg using 100% FiO₂

### PACU
- Diet: Clears begins night of surgery, solid food postoperative day 1
- Pain:
  - 1 g IV acetaminophen 6 hours after initial dose and every 6 hours
  - Lidocaine infusion (0.5–1 mg/min) until postoperative day 2
  - Oxycodone 5 mg po q4h prn mild pain, 10 mg q4h prn moderate pain, oxycodone 15 mg po q4h prn severe pain
  - Celecoxib 100 mg po bid in patients without coronary artery disease
- Activity: Ambulation begins night of surgery, head of bed at 30 degrees at all times
- Medications:
  - Alvimopan 12 mg bid for 7 days
  - Magnesium oxide 400 mg po daily
- Fluids:
  - LR at 40 mL/h for 24 h

### Discharge
- Medications: acetaminophen 1 g q8h for 1 week, oxycodone 5 mg q4h prn
- Arrange for early follow-up in high-risk patients with surgeon or primary care; follow-up phone call within 48 hours of discharge

---

# ERAS Colorectal Surgery

<table>
<thead>
<tr>
<th>Protocol elements</th>
<th>Before ER protocol (n = 98)</th>
<th>After ER protocol (n = 109)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative morphine equivalents, mg, mean ± SD</td>
<td>21.7 ± 10.7</td>
<td>0.5 ± 1.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total morphine equivalents, mg, mean ± SD</td>
<td>280.9 ± 395.7</td>
<td>63.7 ± 130.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Intraoperative net fluid balance, mL, mean ± SD</td>
<td>2,733 ± 1,464</td>
<td>848 ± 953</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total net fluid balance, mL, mean ± SD</td>
<td>4,409 ± 5,496</td>
<td>−182 ± 3,933</td>
<td>0.0001</td>
</tr>
<tr>
<td>Gatorade, n (%)</td>
<td>—</td>
<td>90 (83)</td>
<td>NA</td>
</tr>
<tr>
<td>Ambulate DOS, n (%)</td>
<td>0</td>
<td>84 (77)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ambulate by POD 1, n (%)</td>
<td>79 (81)</td>
<td>96 (88)</td>
<td>0.178</td>
</tr>
</tbody>
</table>

ERAS Pain Scores-Open Procedures

How Effective Are ERAS Programs Without Epidurals?

Surgery and Opioid Use

Preoperative → Intraoperative → Postoperative → Long Term

ERAS → ?
Enhanced Observational Study

Postoperative Pain Profiles, Analgesic Use, and Transition to Chronic Pain and Excessive and Prolonged Opioid Use Patterns
Outline

• Opioid Epidemic in Numbers
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