Opioid-Sparing Anesthesia: What Can We Learn to Address The Opioid Crisis

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2018 University of Minnesota

Objectives

The learner will be able to:
• Describe the role of Opioid-Sparing Techniques in Anesthesia.
• Describe the outcomes achieved with opioid-sparing compared to traditional techniques.
• Differentiate the value of quality versus quantity of anesthesia through Opioid-Sparing Strategies

Opioids: Public Health Issue
Opioids: Public Health Issue

Opioid-Related Deaths, Especially From Synthetic Opioids Like Fentanyl, Are On The Rise In The U.S.

Drug overdose deaths involving opioids, by type, per 100,000 population

- Any opioid
- Synthetic opioids (fentanyl, carfentanil, and other synthetic opioids)
- Natural and semi-synthetic opioids

2010-2015

2016-2017

2018

Opioids: Public Health Issue

Fentanyl Overdoses Are Rising And Science Can't Keep Up

AMERICA'S HEROIN EPIDEMIC IS BEING OVERTAKEN BY ANOTHER DEADLY DRUG ADDICTION:
FENTANYL

What Is Fentanyl? The Facts About the Opioid That Caused Prince's Death

Opioids: Public Health Issue

To put this in perspective, wild African elephants—an animal that Carfentanil is used on—weigh between 5,600 and 5,900 lbs as reported by National Geographic, which is roughly 2,500-2,750 times the weight of your average adult male of 2.5 lbs.

3 Marylanders die from carfentanil overdoses

Updated: 4:47 PM EDT Apr 14, 2017
Opioids: Public Health Issue

This new street drug is 80,000 times more potent than morphine, and now it's showing up in Canada and the U.S.

W-18 Overdoses In Alberta May Not Be Curable With Naloxone Kits

It is Everywhere

Addiction Center
Social Security
Did anyone see the bushes?
Did anyone see the Dumpster?
You are Here!

Philosophically

Dr. Charles Darwin

Is this ... Natural Selection?
Ethics versus Economics

Opioids: Public Health Issue

- How did we get here?
  - Imbalance Serotonin Octopamine

Opioids: Public Health Issue

- **Addiction**: disrupting the positive feedback loop
  - Initial dose: exhilarating, but only with drug level threshold
  - Stopping:
    - Drug level drops
    - Toxins rise
    - Anxiety Centers: HYPER-RESPOND
    - Human Behavior …. Fixing problem is easy


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Opioids: Why Avoid?

1. Tolerance
2. Dependence
3. Addiction

- Headache
- Nausea
- Vomiting
- Sweating
- Heartburn

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What Can You Do?

- **BREATHE**
- **BEAT**
- **SECOND**
- **WE ARE THERE**
Goal: Opioid-Sparing

- Reduce Stress & Inflammation
  - Cortisol & Catecholamine release
- Optimize Immune Function
  - Natural Killer & T-Cell Function
- Spare Opioids maximally
- Reduce Symptom Burden
  - Rapid Rescue where prudent

The Evidence

Opioid-induced hyperalgesia: Cellular and molecular mechanisms

Laurie-Anne Reches, Glenn-Marie La Cuz, Claire Guevremont-Ruff and Frédéric Simonin
Neuromodulation, 2018-03-05, Volume 21, Pages 155-162, Copyright © 2018 BMJ

The Evidence

Opioid-induced hyperalgesia: Cellular and molecular mechanisms

The Mechanism of Hyperalgesia and Anxiety Induced by Remifentanil: Phosphorylation of GiαR1 Receptors in the Anterior Cingulate Cortex
by Je Zeng; Si Li; Chao Zhang; See more...
Journal of Molecular Neuroscience, 05/2018
The Evidence

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- Increased Hyperalgesia and Proinflammatory Cytokines in the Spinal Cord and Dorsal Root Ganglion After Surgery and/or Fentanyl... by Chang; Lu; Yi; Fang; Luo; Quehua: See more...

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Remifentanil-induced postoperative hyperalgesia: current perspectives on mechanisms and therapeutic strategies

Opioid-Sparing: Underlying Premise


Opioid-Sparing: Underlying Premise

Endogenous Chemicals Causing Pain

- 5-HT = 5-hydroxytryptamine
- 5-HT1AR = 5-HT1A receptor
- 5-HT2AR = 5-HT2A receptor
- CB1R = cannabinoid CB1 receptor
- CB2R = cannabinoid CB2 receptor
- COX-2 = cyclooxygenase-2
- CRF = corticotropin-releasing factor
- GABA = γ-aminobutyric acid
- GDNF = glial cell line-derived neurotrophic factor
- GFRα1 = GDNF family receptor α1
- IAM-1 = intracellular adhesion molecule-1

- IL-6 = interleukin-6
- IL-1β = interleukin-1β
- N/OFQ = nociceptin/orphanin FQ
- p38 MAPK = p38 mitogen-activated protein kinase
- PGES2 = prostaglandin E2 synthetase 2
- p-GluN1 = phosphorylated GluN1
- TRPV1 = transient receptor potential cation channel subfamily V member 1
- VIP = vasoactive intestinal polypeptide
Why Avoid Opioids?


Opioid-Sparing: Framework


Opioid-Sparing: Theory

- Regional Anesthesia
  - Controversy M & M
- Pre-emptive Analgesia
  - Prevent “pain” sensitization
    - Controversy
      • Regional Anesthesia
      • Agents?
      • Research: Poor!

Opioid-Sparing: Theory

- Pharmacological Agents
  - Receptor Model Theory
  - Ionic Channels
  - Opioid/mu
  - GABA
  - NMDA
  - Adrenergic
  - Muscarinic
- Modulation & Feedback
  - Agonist/Antagonists
  - Transporter Proteins
  - Synergism Theory

Opioid-Sparing: Innovation

**Liposomal Bupivacaine: Background**

**Medication Dosing**

- Liposomal Bupivacaine 266mg/20ml (13.3mg/ml)
- Dilute: up to 280ml sterile saline (300 ml Total)
  - With Free Bupivacaine: < 50% Liposomal Dose
  - Typical total volume 40ml to 60ml

“Bupivacaine HCl may be administered immediately before EXPAREL or admixed in the same syringe, as long as the ratio of the milligram dose of free bupivacaine HCl to EXPAREL does not exceed 1:2”

**Bupivacaine Comparison**

<table>
<thead>
<tr>
<th>Liposomal</th>
<th>Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset: 5 minutes</td>
<td>Onset: 5-10 minutes</td>
</tr>
<tr>
<td>Peak Onset: 30-120 minutes</td>
<td>Peak Onset: 30-45 minutes</td>
</tr>
<tr>
<td>Half-Life: 24-34 Hours</td>
<td>Half-Life: 3.5 Hours</td>
</tr>
<tr>
<td>Duration: 24 Hours (Local) &amp; 96 Hours (Systemic)</td>
<td>Duration: 6-8 Hours</td>
</tr>
</tbody>
</table>
Surgical Wound Infiltration

Opioid-Sparing: Innovation

- Lidocaine
- Gabapentinoids
- NSAIDS
- COX-2 Inhibitors
- Acetaminophen
- TCAs & SSRI
- Magnesium

Lidocaine Infusion

Infusion: 2mg/minute
Lidocaine Infusion

Infusion: 2mg/minute

Key points

- a potent anti-inflammatory, anti-hyperalgesic, and gastrointestinal pro-peristaltic drug.
- Level 1 evidence from gastrointestinal surgery demonstrates decreased pain scores, opioid analgesic consumption, and side-effects.
- Useful acute pain adjunct to achieve enhanced recovery after surgery outcomes.
- Patients may show particular benefit when they have acute hyperalgesia, when opioids are not effective in treating acute pain, or both.
- Lidocaine infusions may be safely continued for several days after operation.

Opioid-Sparing: Innovation

- Gabapentinoids

- NSAIDS
- COX-2 Inhibitors
Acetanilide Derivative (Acetaminophen)

1000mg IV Q4Hours

- Pharmacodynamic Profile
- IV is Superior: Why?
  - IV 70% Availability

Res ipsa loquitur

Opioid-Sparing: Innovation

- Acetaminophen
- Alpha-2 Agonists
- NMDA Antagonist
- GABA-type A
- Local Anesthetics
- Steroids
- Beta-Blockade
Opioid-Sparing: Innovation

- **Alpha-2 Agonists**
  - Clonidine, Dexmedetomidine
  - Infusion: 0.3 mcg/Kg/hr
  - **anti-hypertensive effect**
  - **sedative, anxiolytic, analgesic**
    - **Modulation Pain Pathway**
  - **side effects:**
    1. Bradycardia
    2. Hypotension
    3. Sedation
Opioid-Sparing: Innovation

- NMDA Antagonist


NMDA Receptor Antagonist (Ketamine)
Infusion: 10 mg/Hr

“survived the strong winds of time”

Wide variety of clinical applications & newly found effects:
1. Neuroprotective
2. Anti-inflammatory
3. Anti-tumor Effects

“ usefulness of low dose ketamine regimens have helped to widen the clinical application profile of ketamine. ”

NMDA Receptor Antagonist (Ketamine)
Infusion: 10 mg/Hr
Opioid-Sparing: Innovation

- GABA-type A

Sedative Hypnotic
(Propofol)

Infusion: 25-150 mcg/Kg/minute

Post-Operative Nausea & Vomiting (PONV) Prevention

- Caused by:
  1. Risk Factors (i.e. Female, Non-Smoker, PONV Hx, Postoperative Opioids)
  2. Liberal Opioid Administration
  3. Stress & Inflammatory Response
- Delayed Gut Function
- Decreases Ambulation
- Increases Metabolic Requirements
Opioid-Sparing: Rescue

Post-Operative Nausea & Vomiting (PONV)

- 15%-33% occurrence surgical outpatients
- Adjusted incremental cost $75 (95% CI - $67-$86) per patient
- Average Delayed Discharge by 60 minutes (234 min. versus 171 min.)
- Lasting Effects: up to 72 hours
- Quality of Life: lower for PONV – The Intangible!
  - Only 49% rate 1 for PONV versus 94% rated 1 for POD 1 to 3
  - Most Patients experiencing PONV at 72 hours
Post-Operative Nausea & Vomiting
• 33% occurrence surgical outpatients
• Adjusted incremental cost $75 in 2011
• 33 of 100 patients “Time Value Cost”
  o $87.12 per patient today
  o $2,874.96 per day
  o $14,374.80 per week
Post-Operative Nausea & Vomiting
- 33% occurrence surgical outpatients
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  - $87.12 per patient today
  - $2,874.96 per day
  - $14,374.80 per week
  - $57,499.20 per month

Post-operative Ileus (POI)
- Occurrence: 10-40% in patients undergoing Radical Cystectomy
  - Average Occurrence Rate: 15.6%
  - POI Contributes to 50-70% of all complications
  - Increases LOS: mean of 4 days (Range: 3-10 days)
    - Doubles the cost of Hospital Stay
    - Cause: Opioid binding to gastrointestinal mu-receptors
    - Additional Overall Cost due to POI: $10,246.00 per event
- Prevention: Alvimopan which binds to gastrointestinal mu-receptors
- Direct Cost: $700 per hospital stay
- Results: 50% Rate Reduction in POI to 7.8%
Respiratory Depression: ORAE

N = 37,031 Patients ***
Incidence: 4,955 (13.6% Overall)
Cost: $6,721 per patient (Overall)
LOS: 55% (4 Days)
30-Day Readmission: 36%
Mortality: 3.4 times
Most Common: Lower Abdominal Surg.
Risk Factors:
• Age & Male: 67%
• Obesity: 11%
• Pre-Surgical Opioid: 34% ***

Respiratory Depression:

N = 319,898
Incidence: 3.3% (12.2% Overall)
Cost: $155.33 per patient
LOS: 3.3 Days
30-Day Readmission: 6.4%
Post-Operative Urinary Retention (POUR)

- **Occurrence**: 2.1%, based on the Surgical Care Improvement Project
  - **Sample Size**: 415,409 surgical patients
  - **Study**: 43,030 developed POUR
    - POUR Contributed 9.2% of Urinary Tract Infections
  - **Increases LOS**: mean of 1.1 days
  - **CAUTI Literature**: $1357 per incidence

Incidence: Variable Cost Per Episode

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Cost Per Episode</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Depression</td>
<td>$568.00</td>
<td>3.30%</td>
</tr>
<tr>
<td>PONV</td>
<td>$87.12</td>
<td>15.00%</td>
</tr>
<tr>
<td>Post-Operative Ileus</td>
<td>$10,247.00</td>
<td>15.60%</td>
</tr>
<tr>
<td>Urinary Retention</td>
<td>$1,357.00</td>
<td>2.00%</td>
</tr>
<tr>
<td>Mental Status Change</td>
<td>$2,500.00</td>
<td>15.00%</td>
</tr>
<tr>
<td>DVT</td>
<td>$4,159.00</td>
<td>2.20%</td>
</tr>
<tr>
<td>30-Day Readmission</td>
<td>$11,200.00</td>
<td>5.40%</td>
</tr>
<tr>
<td>Length of Stay</td>
<td>$2,064.00/Day</td>
<td>10.0 Days</td>
</tr>
</tbody>
</table>
## Cost Benefit & Cost Effectiveness

### A Factor of 5.6

<table>
<thead>
<tr>
<th>Incidence</th>
<th>ERAS Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.00% Pruritus</td>
<td>0.00%</td>
</tr>
<tr>
<td>3.30% Respiratory Depression</td>
<td>0.00%</td>
</tr>
<tr>
<td>15.00% PONV</td>
<td>7.50%</td>
</tr>
<tr>
<td>15.00% Post-Operative Ileus</td>
<td>7.80%</td>
</tr>
<tr>
<td>2.00% Urinary Retention</td>
<td>0.00%</td>
</tr>
<tr>
<td>15.00% Mental Status Change</td>
<td>3.00%</td>
</tr>
<tr>
<td>2.20% DVT</td>
<td>1.00%</td>
</tr>
<tr>
<td>5.40% 30 Day Readmission</td>
<td>0.00%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10.0 Days Length of Stay</th>
<th>7.00 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1,379.38 Cost Per Episode (Probability)</td>
<td>$247.69</td>
</tr>
</tbody>
</table>

## Cost Benefit & Cost Effectiveness

### Cost

<table>
<thead>
<tr>
<th>Traditional Strategy</th>
<th>Cost ERAS Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>$297.94</td>
<td>Direct Cost $1,428.30</td>
</tr>
<tr>
<td>$1,379.38</td>
<td>Indirect Cost $247.69</td>
</tr>
<tr>
<td>$0.00</td>
<td>Early Discharge -$619.00</td>
</tr>
<tr>
<td>****</td>
<td>Intangible Cost **</td>
</tr>
</tbody>
</table>

| $1,677.32 Recovered Revenue | $4,516.01 |

## Summary

- Public Health: Opioid Pandemic
- Opioid Crisis
- Non-Opioid Framework
- Non-Opioid Premise
- Non-Opioid Theory
- Non-Opioid Techniques
- Opioid Rescue