The Perioperative Management of Opioids

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Learning objectives

• Be able to describe the prevalence of chronic opioid use before surgery.
• Be able to describe the perioperative risks and challenges posed by preoperative opioid use.
• Be able to outline an approach to the perioperative management of opioids for chronic opioid consumers.

Trends in Opioid Use
(2014 Data)

World Consumption

US vs. Europe

University of Wisconsin
Pain and Policy Studies Group
Trends in Opioid Abuse
(2014 Data)

- 4% of US patients take opioids for pain.
- 4.3 Million Americans engaged in non-medical use of prescription painkillers in the last month.
- 1.9 Million Americans met criteria for prescription painkillers use disorder based on their use of prescription painkillers in the past year.
- 1.4 Million people used prescription painkillers non-medically for the first time in the past year.

SAMSHA/CDC

Chronic Preoperative Opioid Use
Surgery type and prevalence

- >70,000 Surgical patients at VA hospitals
- Chronic = Opioid use >90 out of previous 180 days
- An additional 25% of patients use opioids intermittently

Mudumbai et al., 2015
Pre- and Peri-Operative Opioid Use

Relevance?

- Perioperative pain management
  - Is it more difficult or hazardous?
- Functional and pain-related outcomes
  - Are they poorer?
- Persistent postsurgical opioid use
  - Is it more likely?

Chronic Opioid Consumption and Postoperative Opioid Requirements

**de Leon-Casasola et al. (1993)**
- Epidural morphine requirement 3 times a control population
- Breakthrough morphine requirement 4 times higher
- High potency opioids recommended

**Rapp et al., (1995)**
- Average Daily PCA Morphine
  - Control 42.8 mg  Chronic Opioid 135.8 mg
- Worse pain, worse side effects (incl. respiratory depression).

**Armaghani et al., (2014)**
- Preoperative opioid use predicted near- and long-term opioid consumption after spine surgery

**Hina et al., (2015)**
- Low dose opioids prior to surgery
- Increased mechanical pain wind-up
- Lower heat pain tolerance
Tolerance vs. OIH: Dual Causes of Elevated Opioid Requirements

- The laboratory definitions of tolerance and OIH are precise.
- Diagnosing tolerance and OIH clinically can be difficult.
  - Increased opioid requirements: Tolerance versus OIH
  - Aggravated pain: Progression of underlying disease versus OIH

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Trajectory of Postoperative Pain Resolution

Chapman et al., 2011
Opioids, Overdose and Respiratory Depression

- Hagle et al., J. Orthopedic Nursing, 2004
  - >18,000 patients in 8 studies
  - Risk factors for respiratory depression while on PCA:
    - Age, major organ system disease, obesity, sleep apnea, PCA dose and Continuous Infusion
- Bohnert et al., JAMA, 2011
  - 154,684 patients
  - Deaths attributed to prescription opioids
    - 1-20mg/day vs. ≥100mg/day
    - HR = 7.18

Predictors of In-hospital Postoperative Opioid Overdose

- A retrospective multi-institutional cohort study, 2002-2011
- 11,317,958 patients, 9458 (0.1%) had a postoperative OD
- Major risk factors:
  - Substance abuse OR 14.8
  - Renal dis. OR 2.89
  - Advancing age OR 1.72
  - Chronic pain OR 1.52
  - Pulmonary dis. OR 1.45
  - Mood disorder OR 1.35

Cauley et al., Ann. Surg., 2017
Chronic Postoperative Pain: Risk Factors (Opioids)

- Anterior cervical arthrodesis
- TKA
- Gynecological procedures
- Thoracoscopic splanchnicectomy
- Gastric electrical stimulation (GES)
- Shoulder arthroplasty
- Mixed spine surgeries
- Mesh removal
- Lumbar fusion
- Surgeon’s global impression
- Pain, Function, Range of motion
- Pain
- Pain, Opioid use
- Weight, Symptoms, Opioid use
- Function, Range of motion
- Functional outcomes
- Pain
- Return to work

Lawrence et al., 2008, Spine
Morris et al., 2015, J. Shoulder Elbow Surg.
Zwaans et al., 2015, World J. Surgery
Anderson et al., 2015, Spine

Outcome of Total Knee Arthroplasty

- 98 Patients undergoing knee arthroplasty
- 49 Opioid consuming, 49 naïve
- Very closely matched demographics, functional levels, surgical indications, insurance, smoking
- *Greater anxiolytic/antidepressant use in opioid group*

<table>
<thead>
<tr>
<th></th>
<th>Opioid Group</th>
<th>Non-Opioid Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of days to discharge (range)</td>
<td>4.3 (2 to 8)</td>
<td>3.4 (2 to 6)</td>
<td>0.013</td>
</tr>
<tr>
<td>Number of arthroscopic evaluations for unexplained pain (95% CI)</td>
<td>5 (2 to 11)</td>
<td>0 (0 to 4)</td>
<td>0.066</td>
</tr>
<tr>
<td>Number of revisions for recalcitrant pain and/or stiffness (95% CI)</td>
<td>0 (0 to 4)</td>
<td>0 (0 to 4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of patients referred for pain management (95% CI)</td>
<td>58 (4 to 77)</td>
<td>1 (0 to 6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Knee Society score at the time of final follow-up (range [95% CI])</td>
<td>76 (45 to 100 [76 to 93])</td>
<td>92 (91 to 100 [89 to 95])</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean range of motion at the time of final follow-up (range [95% CI])</td>
<td>107 (80 to 130 [102 to 112])</td>
<td>111 (75 to 130 [102 to 114])</td>
<td>0.223</td>
</tr>
</tbody>
</table>

Zywiel et al., 2011
Surgery Initiates Chronic Opioid Use

Surgery is associated with elevated rates of opioid use one year after procedures

Sun et al., 2016

Chronic Opioid Consumption and Duration of Postoperative Opioid Use

- 109 Consecutive patients undergoing surgery followed daily for pain and analgesic use.
- Preoperative demographic, psychological, pain and medication use information was collected.

Carroll et al., 2012
Postoperative Considerations
Sub-acute Management

Opioid Use Cessation after Surgery
N>65,000

Mudumbai et al., 2015

Priorities for the Management of Chronically Opioid Consuming Patients

- Manage opioids comprehensively
  - Preoperative
  - Intraoperative
  - Postoperative
  - Transitional Period
- Maximize the use of adjuvants
- Incorporate regional techniques whenever possible
Prevention and Treatment of CPSP
Continuum of Care

Perioperative Surgical Home

Presurgery Clinic  Core Anesthesiology  Acute Pain Mgt.  Chronic Pain Mgt.

Decision  Incision  Closure  Discharge

Optimization  Preventive Analgesia  Long Term Mgt.

Perioperative Management of the Chronic Opioid Consuming Patient

- Preoperative Considerations
  - Identification and discussion of
    - Precise opioid use: Standardize, consider conversion to long-acting drugs, **instruct to take the day of surgery**
    - Fears and expectations related to pain management
    - Previously effective strategies
    - Postoperative management options including regional techniques
  - Initiation of preemptive/adjuvant strategies
    - Gabapentin
    - Dextromethorphan
    - COX-2 Inhibitors
  - Taper from opioids?
  - Buprenorphine (Suboxone®, Subutex®, Butrans®, others)?
Perioperative Management of Buprenorphine

- Buprenorphine is a partial mu-opioid receptor agonist and kappa-opioid receptor antagonist.
- Used to treat addiction and as a pain reliever

- Overall use of buprenorphine is growing rapidly in the US

- Management options:
  - Continue and supplement buprenorphine
    - Adequate analgesia?
  - Continue and use high-potency opioids
    - Can antagonist effect be overcome safely?
  - Discontinue 3-5 days ahead of surgery and use conventional opioids
    - Return of abuse, efficacy of strategy

Perioperative Management of the Chronic Opioid Consuming Patient

- Intraoperative considerations:
  - Build base to cover daily requirement and part of postoperative requirement
  - Use short acting as component of anesthetic
  - Initiate adjuvant therapy

- Total required opioid is the sum of:
  - Chronic requirement
  - Anesthetic requirement
  - Anticipated postoperative requirement

- Considerations for choice of opioid:
  - Remifentanil (other short-acting): Forgiving in large doses
  - Methadone (other longer acting): Titrate against respiratory rate
Postoperative Considerations
Opioid management

- Typical requirement is for 2-3 times the pre-surgical opioid levels, but the range is extremely wide.
- Avoid withdrawal
  - 50% normal daily dose normally prevents this
  - Can occur when neuraxial techniques are not supplemented with systemic opioid
- Therapeutic index may be narrowed.

Postoperative Considerations
Opioid management

- Systemic opioids (Conservative)
  - Sustained acting
    - Basal opioid requirement given as sustained acting opioid
    - Consider time to steady state of long-acting drugs
  - Remainder as PCA (no basal infusion) or PRN opioid
    - 1-3x standard doses (based on total pre-op use, response of patient in OR/PACU, disease states)
- Epidural opioids
  - High potency possibly more effective than morphine
  - High end of normal concentration range (combined with LA)
- Use caution
  - Supplemental monitoring, pulse oximetry, nursing checks etc.
  - Cautions with additional sedating medications like sleep medications or anxiolytics
Therapeutically Accessible Receptor Systems

- Beta-2-Adrenergic – Epinephrine
  - Propranolol
- 5HT3 – Serotonin
  - Ondansetron, other -trons
- Alpha-2-Adrenergic – Norepinephrine
  - Clonidine, Dexmedetomidine
- NMDA – EAAs, Glutamate/Aspartate
  - Ketamine, Dextromethorphan, Methadone, Mg, Amantadine, Memantine
  - Opioid consuming patients:
    - Reduced pain scores 6 weeks post spine surgery (Loftus et al., 2010).
    - Greater improvement in pain 6 months post spine surgery (Nielsen et al., 2017)

Perioperative Ketamine

- Mechanism(s) of action:
  - NMDA antagonist (channel and allostERIC binding sites)
  - Regulates activity of: HCN1, AMPA, Opioid, Ca²⁺ channels, NOS, mChR, nAChR, NT reuptake inhibitor, etc.
- Pharmacokinetics:
  - T1/2 (α) ~10min, (β) 2-4 hours
  - Extensive hepatic metabolism, renal elimination of metabolites
- Key toxicities:
  - CNS: Hallucinations, memory defects, panic attacks, somnolence
  - Hepatotoxicity: Elevated enzymes particularly upon repeated exposure
  - Uropathy: Ureter and bladder toxicity in ketamine abusers
- Infusion guidelines:
  - Contraindications: Allergy, Unstable BP/HR, Elev. IOP, Unstable psych.
  - Loading dose: ~1mg/kg
  - Infusion: 0.1-0.4mg/min or 0.1-0.3mg/kg/ hr
  - Monitoring: Similar to PCA
Next Generation Opioids

- **Biased Agonists**
  - Selectively activate GTPase over β-arrestin signaling.
  - *TRV130, PZM21*

- **Orphanin F/Q Agonists**
  - Orphahin F/Q functionally antagonizes respiratory depression.
  - Cebranopadol

- **Low pKa Agonists**
  - Only binds μ-OR in acidic, peripheral wound-area environments.
  - NFEPP

Biased Opioid Agonists

- **Classical pharmacology**
  - Agonist, antagonist, partial agonist
  - The receptor is activated or not

- **Biased agonism**
  - Preferential activation of second messenger systems
  - Characteristic of G-protein coupled and other receptors
Biased Opioid Agonists
(Less β-Arrestin Activation)

- **β-Arrestin and opioid signaling (μ-OR)**
  - Reduces efficacy
  - Linked to side effects: Tolerance, respiratory depression, constipation
  - Addiction-related: Place preference (KO mice show enhanced reinforcement), Physical dependence (+/-)
- **TRV-130**
  - In rats: ED50 10x lower than morphine in hotplate assay
  - Less reduction in colonic motility and much less respiratory depression compared with morphine at equi-analgesic doses
- **PZM21**
  - Analgesia (affective), little respiratory depression and little reinforcement in CPP assay

TRV130 and Analgesia for Acute Pain

- **Bunionectomy patients**
  - N=195 (blinded, randomized, controlled Phase II trial)
  - Primary endpoint: Time-weighted 48hr pain

Viscusi et al., 2016
Soergel et al., 2014
Postoperative Considerations
Sub-acute Management

- Preparation for discharge
  - Requirements are for higher than normal doses for longer than normal time periods
  - Long acting drugs need time to reach steady state
  - Guideline:
    - Taper to pre-surgical levels over 2-4 weeks
    - Resolution of pain
    - Resolution of increased dependence
  - Prescribing
    - Tablet size to allow taper
    - Follow-up with normal prescriber in 1 month

Opioid Management in the Chronically Opioid Consuming Patient
(Summary)

- Commonly encountered
- Best recognized and planned for preoperatively
- Both pain and opioid requirements are likely to be elevated
- Enhanced monitoring may be required
- Adjuvants and regional anesthesia have special priority
- Careful transition planning is required
Thank You