Opioid-Sparing Analgesia

Panacea or Pipedream

Minimizing Pain and Opiate Use in the Perioperative Period

Lisa Kunze MD, PhD
Definitions

- **Panacea**: fantasy hope, remedy for all ills
- **Pipe Dream**: unattainable goal
Disclosures

- NONE
Goals

- Review *Multimodal Analgesic Medications*:
- Review benefits/risks of non-opioid medications
- Discuss some issues with peripheral nerve blocks
- Describe how to put together an opioid-sparing analgesia plan
These concepts are applicable to **EVERY** patient who will have pain after surgery.

- Cardiac and thoracic surgery
- Orthopedic surgery
- Gynecologic surgery
- Colorectal surgery
- Plastic surgery
- Urologic surgery
- Etc, etc, etc....
- Craniotomies are a little more challenging
Opiates: the Good, the Bad, and the Ugly

- **Good:**
  - Excellent pain relief
  - Decreases sympathetic response to painful stimuli
  - Inexpensive
  - Familiar

- **Bad:**
  - PONV
  - *Incomplete analgesia*
  - Respiratory depression and sedation
  - Bowel dysfunction

- **Ugly:**
  - *Hyperalgesia*
  - *Diversion and societal problems*
Opioid Induced Hyperalgesia

- **Definition:** Paradoxical increase in pain to noxious stimulus with increasing opioid use\(^2\).

- **Causes:** acute and chronic opioid use

- **Mechanism?**
  - Peroxynitrite-mediated oxidative stress in the spinal cord\(^1\) with activation of neuroinflammation in spinal cord
  - Other mechanisms proposed: genetic, descending facilitation, central glutaminergic, facilitation of intracellular protein kinase C, etc.

---


In a PACU not so long ago.....

- Nurse: Lisa, Can you come to the PACU for a pain evaluation?

- Me: Sure. This is what I discover:
  - Patient has a pink basin by his mouth
  - Claims to have 10/10 pain yet appears to be sleeping
  - Has been in PACU for over 2 hours
  - Has had a boatload of fentanyl because CMS says that pain is a vital sign that needs treatin’
  - Respiratory rate is 6 (that is actually a vital sign)
  - Is supposed to go home
  - The surgeon said No to NSAIDS
  - IV acetaminophen was still a pipedream
Pain

- **Neuroendocrine stress response**
  - Release cytokines (IL-6,10), TNFα, leukotrienes
  - May cause hypercoagulability $\rightarrow$ VTE
  - Increased platelet reactivity $\rightarrow$ MI

- **Increased sympathetic tone**
  - Increased catechol amines
  - Secretion of cortisol, ACTH, renin
  - Water and sodium retention
  - Increased O2 consumption
  - Hyperglycemia
Pain is painful

- PONV
- Sedation
- PACU LOS
- Patient satisfaction
- Development of chronic pain
Multimodal Analgesia

• “Total or optimal pain relief allowing for normal function cannot be achieved by a single drug without a major strain on equipment or without major side effects”

• Henrik Kehlet 1993
Goals of Multimodal Analgesia

- Improve analgesia
- Decrease opioid use
- Decrease side effects associated with opioid-based analgesia
- Decrease risks of hyperalgesia and allodynia
Pain Pathway 101

Gabapentinoids

- Opioids
- Alpha_2_ agonists

- Local anesthetics
- Opioids
- Alpha_2_ agonists

- Local anesthetics

- Local anesthetics
- Anti-inflammatory drugs

- Trauma

- Peripheral nociceptors

- Spinothalamic tract

- Ascending input

- Descending modulation

- Dorsal horn

- Dorsal root ganglion

- Peripheral nerve

© D. Klemm '01
Cardiac Surgery

- Moderate to severe pain 30-70%
- Persistent Poststernotomy pain 4%
- Inadequate analgesia
  - Increased morbidity
  - Increased LOS
  - Increased costs

- Multimodal analgesia (RCT 180)
  - Improved analgesia with lower average pain scores POD 0-3
  - Decreased MI
  - Decreased stroke
  - Decreased HD
  - Decreased PONV

Not statistically significant

Example of Multimodal Analgesia for Cardiac Surgery

<table>
<thead>
<tr>
<th>Table 1 Overview of administered analgesics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multimodal</strong></td>
</tr>
<tr>
<td>Extubation</td>
</tr>
<tr>
<td>- Inj ketorolac 30 mg iv</td>
</tr>
<tr>
<td>- Inj dexamethasone 8 mg iv</td>
</tr>
<tr>
<td>- Inj ondasterone 4 mg iv</td>
</tr>
<tr>
<td>- Rectal suppositorium paracetamol 1000 mg</td>
</tr>
<tr>
<td>Day 1</td>
</tr>
<tr>
<td>- Tbl Ibuprofen 400 mg x 4</td>
</tr>
<tr>
<td>- Tbl Gabapentin 300 mg x 2</td>
</tr>
<tr>
<td>- Tbl Paracetamol 1000 mg x 4</td>
</tr>
<tr>
<td>Day 2</td>
</tr>
<tr>
<td>- Tbl Ibuprofen 400 mg x 4</td>
</tr>
<tr>
<td>- Tbl Gabapentin 300 mg x 2</td>
</tr>
<tr>
<td>- Tbl Paracetamol 1000 mg x 4</td>
</tr>
<tr>
<td>Day 3</td>
</tr>
<tr>
<td>- Tbl Ibuprofen 400 mg x 4</td>
</tr>
<tr>
<td>- Tbl Gabapentin 300 mg x 2</td>
</tr>
<tr>
<td>- Tbl Paracetamol 1000 mg x 4</td>
</tr>
<tr>
<td>Day 4</td>
</tr>
<tr>
<td>- Tbl Ibuprofen 400 mg x 4</td>
</tr>
<tr>
<td>- Tbl Gabapentin 300 mg x 2</td>
</tr>
<tr>
<td>- Tbl Paracetamol 1000 mg x 4</td>
</tr>
</tbody>
</table>

Administrations are noted by times daily with (x), x2 equals twice daily and x4, four times daily. Inj = injection, iv = intravenous, tbl = tablet.

In addition 1 g Magnesium oxide/day

Cardiac and Thoracic Multimodal Techniques

- Multimodal Analgesia: Drugs alone or Drugs + blocks

- Nerve blocks
  - PVB ↓ hypotension, risk of epidural hematoma, N/V, urinary retention
  - Subserratus catheters
  - Pleural catheters
  - Bilateral sternal blocks
  - Wound catheter? NOT for cardiac

- Epidural
  - TEA for cardiac is controversial
  - 1460 pts - MI, stroke
  - Epidural hematoma 1/5500

Opioid-sparing in Cardiac Surgery

- **Ketorolac**: 488 pt retrospective study (many OPCABG)
  - NO difference GI bleed, reoperation, PRBC
  - Decreased LOS, stroke, TIA, MI, renal insufficiency!

- **Dexmedetomidine**
  - Decreased all cause mortality 30d and 1 year
  - Decreased delirium

- **Gabapentin or Pregabalin** (40 pts x 3 days PG)
  - Decreased pain after extubation
  - Tramadol use decreased 60%
  - ? If useful for decreasing risk of PSP
Drugs Useful in Multimodal Analgesia

- NMDA receptor antagonists
- \( \alpha 2 \) Agonists
- Glucocorticoids
- NSAIDS and Acetaminophen
- Gabapentin or Pregabalin

Other drugs

- Esmolol
- Lidocaine
- Naloxone
- Nicotine
- Magnesium
Acetaminophen

- Safe
- Inexpensive (oral)
- Long history of use
- **Side effects are trivial** (avoid in cirrhosis, severe liver dysfunction)
- Few drug interactions (isoniazid, phenytoin, warfarin)
- **Effective!**
- **Opioid-sparing!** (38 mg morphine used in 24 hr compared to 57 mg in placebo group for major orthopedic reconstruction)¹

Pregabalin vs Gabapentin

- **Mechanism:** binds to presynaptic voltage-gated Ca^{++} channels in spinal cord and DRG (reduces Ca-dependent release of NTs?) (affects pathways in brainstem?)

- **Onset:**
  - Pregabalin: 1 hour (crosses BBB more readily)
  - Gabapentin: 2-3 hours

- **Bioavailability:**
  - Pregabalin: 90%
  - Gabapentin: 30-60%

- **Side effects:** Similar
  - Sedation
  - Dizziness
  - Visual changes (pregabalin)
Pregabalin and Gabapentin: Analgesia

- Pregabalin in TJA patients is *morphine sparing*\(^1\).
- Both equally effective in spine surgery\(^2\)
- Both may *decrease chronic postsurgical pain*\(^3,4\)

Dexamethasone

- **Intravenous**¹
  - 0.1-0.2 mg/kg reduced pain at rest and activity
  - 1.25-20 mg reduced opioid consumption 10% in first 24 hr.
  - Studies looking at PONV showed no effect on pain
  - No studies as monotherapy for pain
  - Some increased risk GI bleeding and elevated Blood sugars³.
  - *No MIs, wound infections, AVN* when used in cardiac, spine, trauma, and other non-cardiac surgeries

- **Nerve Blocks**²
  - 801 pts meta-analysis (4-10 mg)
  - Increased sensory and motor block
  - No adverse events (? If enough power)
  - Only 1 study compared IV with nerve block: same effect

---

NMDA Receptor Antagonists

- **Ketamine**
  - Reduces average pain scores in patients with chronic pain without reducing opioid
  - Antihyperalgesic in rats
  - **Opioid-sparing after TJA**
  - Most effective in orthopedic, thoracic, upper abdominal procedures
  - Inhibits IL6, TNFα - down regulation of proinflammatory pathways
  - Decreases risk of PTSD in military trauma
  - Suggested doses: < 0.2 mg/kg/hr

- **Magnesium**
  - 30-50 mg/kg or 10 mg/kg/hr - direct analgesia

- **Nitrous Oxide** - *greenhouse gas*

- **Methadone**

Dexamethasone

- Decreased pain in TJA\(^1\)

- Reduces need for supplemental opioids (10% reduction/24 hr)\(^2\)

- No adverse effects for single dose use
  - Infection
  - Avascular necrosis

- Decreases PONV

α2 Agonists

- **Dexmedetomidine**¹:
  - Spares anesthesia agents
  - Useful to decrease hyperalgesia
  - Helpful in patients with high opioid tolerance
  - May prolong nerve blocks
  - Decreases opioid consumption
  - Bradycardia, hypotension, sedation
  - May not be opioid-sparing²

- **Clonidine**:
  - May prolong nerve blocks
  - Oral and transcutaneous formulations

Nonsteroidal Anti-inflammatory Agents

- Many studies support use of NSAIDS in the perioperative period
  - Opioid-sparing
  - No N/V
  - IV, PO, IM

- Few studies have demonstrated any difference in adverse side effects
  - Bleeding: increased if given prior to hemostasis. Give at end of surgery
  - Bone healing: No difference in pseudarthrosis of spine (short-term use)
  - Renal function: may increase with ketorolac > 5 days
  - Anastomtic leaks: increased risk in 1 study- never duplicated

- Non-selective NSAIDS or COX-2 inhibitors provide superior analgesia
- Some studies support COX-2s and other support Non-selectives: Not Clear
- May decrease recurrence of breast cancer!
- Increased risk of surgical site bleeding in high-risk procedures:
  - Tonsillectomy
  - Controversial in plastic surgery
- Recent meta-analysis is controversial: did not include many relevant studies.

Adverse Cardiac Effects?

- **Myocardial Infarction**
  - *Meta-analysis* 300K pts in 2013 (9% w/ atherosclerosis)
    - Major CV event risk 1.41 for diclofenac and coxibs
    - High dose Naproxen did not elevate risk
    - Increased risk of MI, Stroke, HF, AF, Death (1-2 events/1000 person-years)

- **Heart Failure**
  - All selective and nonselective can increase edema
  - Risk highest with diastolic dysfunction and hypertension
  - Risk small (1-2%) in low risk patients

- **Arrhythmias**
  - Small increased risk of atrial fibrillation

Bhala N. CNT collaboration 2013 Lancet 382:769-79
<table>
<thead>
<tr>
<th>Medication</th>
<th>Odds Ratio (Conf. Int.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen</td>
<td>0.98 (0.41 to 2.37)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>2.39 (0.69 to 8.64)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>3.98 (1.48 to 12.70)</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>2.07 (0.98 to 4.55)</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>4.07 (1.23 to 15.70)</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>1.58 (0.88 to 2.84)</td>
</tr>
<tr>
<td>Lumiracoxib</td>
<td>1.89 (0.64 to 7.09)</td>
</tr>
</tbody>
</table>

Favors NSAIDS vs Favors Placebo

NSAIDS: Adverse Effects

- **Use of Acetaminophen** for analgesia:
  - RR of acetaminophen vs non-users for major cardiac event is 1.4

- **Risk of Opioids vs NSAIDS:**
  - Opioid users 2.25 x more likely to have MI
  - All cause RR mortality is 2.25 for oxycodone users at 30 days.

- Is it the PAIN or is it the Therapy?
Esmolol

- Useful to decrease sympathetic stimulation
  - Can use less opioids intraoperatively
  - Less tachycardia during intubation and extubation
  - Be aware of bradycardia during insufflation

- Dosing:
  - Intubation: 10-30 mg (literature suggests 1 mg/kg...?)
  - Bolus 10-20 mg during procedures prn
  - During laproscopy: 5-15 mcg/kg/min

- Not directly analgesic
- Not helpful for procedures where pain is moderate to severe (Ortho)
- Not helpful to blunt hypertension
# Esmolol vs Remifentanil vs Control

## Laproscopic Cholecystectomy

<table>
<thead>
<tr>
<th>treatment</th>
<th>Fentanyl in pacu</th>
<th>PONV %</th>
<th>PACU LOS (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esmolol</td>
<td>91 +/- 42 mcg</td>
<td>30</td>
<td>120 +/- 20</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>237 +/- 54 mcg</td>
<td>68</td>
<td>160 +/- 50</td>
</tr>
<tr>
<td>Control</td>
<td>168 +/- 96 mcg</td>
<td>66</td>
<td>180 +/- 50</td>
</tr>
</tbody>
</table>

Other Options

- **Nicotine**\(^1\) systematic review 662 pts
  - Smokers have less N/V
  - Opioid consumption was decreased over 24 hours in NON-smokers
  - VAS scores not decreased
  - N/V was increased!!!

- **Naloxone**
  - Much too challenging to use!
  - Small doses give analgesia but larger doses cause hyperalgesia.

- **Lidocaine patch**\(^3\)
  - No decrease in LOS, pain intensity, opioid consumption
  - Perhaps useful for management of non-surgical site related pain?

---

Local to the Incision?

- Yes/maybe:
  - Orthopedics surgery
  - Laproscopy
  - Endoscopic sinus surgery

- No:
  - Not helpful in caesarean section patients

- Follow the pain
  - Visceral
  - Somatic
Can Local Last Longer?

- Nerve catheter techniques
- Wound catheters
  - Thoracotomy (subserratus) 60 pt\(^1\)
  - Other surgeries (except cardiac)

- Transdermal
  - Useful in chronic pain
  - Not useful in acute pain (251 pts)\(^2\)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Wound catheter</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6, 10, TNF(_\alpha)</td>
<td>decreased</td>
<td>---</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain with cough</td>
<td>decreased</td>
<td>----</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>morphine</td>
<td>14 mg</td>
<td>26 mg</td>
<td>0.01</td>
</tr>
<tr>
<td>FEV1, FCV</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
</tbody>
</table>

Local Can Last Longer

- **Liposomal formulation (EXPAREL™)¹,²**
  - 72 hours
  - Reduced opioid use 71% thru POD 3 s/p rhytidectomy
  - Not helpful in TKA?

- **Hydrogel formulation (very early studies)³**
  - Poly(lactic-co-glycolic acid) with chitosan coated with a thermoresponsive gel (pluronic F-127)
    - Prevented opsonization
    - Avoided the foreign-body inflammatory reaction
    - Not cytotoxic
    - **Releases bupivacaine up to 7 days**


Nerve Blocks

- Interscalene Nerve Block 1090 pt
  - Analgesia 6-8 hours
  - Decreases PONV 24 hours
  - Decreases opioid use up to 12 hours
  - Decreases PACU LOS
  - Patients satisfied with pain relief at 24 hours

- More pain at 24 hours compared to no block
  (Rebound pain vs hyperalgesia)

Can we Avoid rebound Pain?

- Use longer lasting techniques (catheters) OR
- Utilize multimodal medications for several days postoperatively
  - Gabapentin or pregabalin
  - Acetaminophen
  - NSAIDS or COX-2 inhibitors

- INSURANCE costs, Physician hassles, patient costs, side effects?

- Perhaps we can become more involved with postoperative pain management? $$$
Multimodal Analgesia Plan

- **Preoperative Medications**
  - Acetaminophen
  - Pregabalin or gabapentin
  - Nerve blocks +/- dexamethasone or dexmedetomidine/clonidine
  - Epidural
  - Consider Cox-2 inhibitor
  - Clonidine patch (selected patients)

- **Intraoperative Medications**
  - Local by surgeon
  - Neuraxial anesthesia: nothing
  - GA:
    - Opioids- if necessary, small doses
    - Esmolol in appropriate patients
    - Ketamine (NMDA Receptor antagonist)
    - NSAIDs
    - 2 agonist

- **Postoperative Medications**
  - PO opioids, IV if patient is unable to take PO
  - Continue
    - Acetaminophen
    - NSAIDS (short term or per surgeon)
    - Gabapentinoid if moderate to severe pain
    - Ketamine gtt for selected patients
    - Clonidine for selected patients
**Pain Pathway Plan**

1. **Patients who will have minimal pain** (cataracts, d&c, hysteroscopy, ercp)
   1. Minimize drugs, consider using nothing for pain
   2. Use acetaminophen +/- nsaids when appropriate

2. **Patients who have a complete nerve block** (some orthopedic, hand/foot)
   1. Utilize acetaminophen, NSAIDs when appropriate
   2. Consider what will happen when block wears off.
   3. Consider using long-acting bupivacaine or catheter technique

3. Patients who have an incomplete nerve block (ACL, hysterectomy, rectal)
4. Patients who can have local to the surgical site (sinus surgery)
5. Patients in whom local and nerve blocks are impractical

*May Need a more complex and comprehensive analgesia plan!*
Pain Pathway Plan

- Patients who have an **incomplete nerve block** (ACL, breast surgery, shoulder arthroplasty, open abdominal procedures)

- **Patients who can have local to the surgical site** (laparoscopy, knee scopes, thoracoscopy, total hip replacement, face lift)

- Patients in whom local and nerve blocks are **impractical** (spinal surgery, trauma patients with multiple long bone injuries +/- rib fractures, cardiac surgery*)

**Need comprehensive plan in addition to nerve blocks:**

- Preoperative acetaminophen, gabapentin/pregabalin, ? COX-2
- Intraoperative NSAID, dexamethasone, small dose opioids, low dose ketamine, consider esmolol for induction, esmolol gtt, lidocaine gtt, dexmedetomidine, etc
- Postoperative: Opioids - oral preferred, gabapentinoids, acetaminophen, NSAIDs, ketamine gtt, clonidine
<table>
<thead>
<tr>
<th>Pt</th>
<th>surgery</th>
<th>anesthesia</th>
<th>Preop opioids</th>
<th>Analgesics</th>
<th>Preop pain</th>
<th>POP (pacu)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE</td>
<td>THA</td>
<td>spinal</td>
<td>Yes</td>
<td>ketorolac</td>
<td>8</td>
<td>0-4 oxycodone 5 mg</td>
</tr>
<tr>
<td>CE-2</td>
<td>THA</td>
<td>GA</td>
<td>Yes</td>
<td>Dilaudid 2 mg</td>
<td>10</td>
<td>9 - 5 dilaudid 0.4 mg + PCA</td>
</tr>
<tr>
<td>CG</td>
<td>TKA</td>
<td>GA+ FNB</td>
<td>Yes</td>
<td>Ketamine 20 mg</td>
<td>6</td>
<td>0-10-3-sleeping 0.2 mg Dilaudid</td>
</tr>
<tr>
<td>CG 2</td>
<td>TKA</td>
<td>GA + FNB</td>
<td>Yes</td>
<td>Ketamine 20 mg</td>
<td>4</td>
<td>0-10-5 with 0.4 mg dilaudid</td>
</tr>
<tr>
<td>WN</td>
<td>TKA-complex</td>
<td>GA + FNB</td>
<td>No</td>
<td>Ketamine 30 mg, Ketorolac 0.5 mg</td>
<td>5</td>
<td>2 No meds given</td>
</tr>
<tr>
<td>MG</td>
<td>R lap colectomy</td>
<td>GA + Local by surg.</td>
<td>No</td>
<td>Ketamine 20 mg, Ketorolac</td>
<td>2</td>
<td>2-4</td>
</tr>
<tr>
<td>BR</td>
<td>Lap rectopexy</td>
<td>GA + Local by surg.</td>
<td>No</td>
<td>Ketamine 10 mg, Esmolol gtt</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

All patients had preop acetaminophen, pregabalin or gabapentin and intraop bupivacaine
It took me 3 years to get from here..........................to there

WHAT WE ARE

LEAP OF FAITH

WHAT WE WANT TO BE

MAKE THE JUMP.
Thank You!
lkunze@bidmc.harvard.edu