Multimodal Perioperative Analgesia
Mechanisms and Clinical Presentation of Pain
MSNBI0 2622
March 26, 2009

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Multimodal and Multi-Pharmacologic Perioperative Analgesia, with ACL Reconstruction used for Illustration

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**Perioperative Pain Assessment**

1. If you don’t know the Preop Pain Score, you set the table for unrealistic expectations for patients and families.

2. Trying to achieve a postop pain score of 3 or less (per JCAHO) when the preop pain score is 2 or higher is an invitation for significant potential complications (apnea / desaturation, etc.).

3. How to determine, interpret, and manage the “5th vital sign”:
   - Measure / elicit all pain scores with movement (not rest); both preop and postop.
   - If preop pain score =0, then aim for postop pain score of <5.
   - AIM for the “best” postop pain score to be only 3–4 units higher than preop pain score.
Prevent chronic pain by “pre-empting,” or at least managing appropriately, acute pain.
Multimodal Perioperative Analgesia and Influence on Chronic Pain

Preventing the Development of Complex Regional Pain Syndrome after Surgery
Scott S. Reichen, M.D.*

Estimates are 2.3–4% after arthroscopic knee surgery,9,10 2.1–5% after carpal tunnel surgery,11-13 13.6% after ankle surgery,10 0.8–13% after total knee arthroplasty,14-17 7–37% for wrist fractures,3,10,18,19 and 4.5–40% after fasciectomy for Dupuytren contracture.20-24

Although the consensus among physicians in the medical community is to wait for the signs and symptoms of CRPS to resolve before performing surgery, there is no evidence-based medical research to support this theory. Increased preoperative pain has been shown to play a significant role in the development of CRPS after total knee arthroplasty. More prospective studies are needed to determine whether this holds true for other surgical procedures and whether reducing preoperative pain can decrease the incidence of postsurgical CRPS.
1200 ACLR patients at Tufts - Baystate.

- n=500: Vioxx & Tylenol for 48 hr preop; perioperative Femoral NB, plus intra-articular Bupiv-Clonidine-morphine; and postop Vioxx, Tylenol, OxyContin, “CryoCuff”
- n=700: Nothing preop or peri-op; postop Tylenol, Ibuprofen, and prn Oxycodone-IR
Multimodal Perioperative Analgesia and Influence on Chronic Pain

1-year follow-up ("standard" vs. "multimodal"):
- Anterior knee pain - 14% vs. 4%
- Lysis of adhesions – 8% vs. 2%
- CRPS - 4% vs. 1%
P<0.001 (all complications)

Outline

1. Multi-pharmacologic techniques
   - Acetaminophen – NSAID – COX-2 – Corticosteroids – Gabapentin – Local anesthetics – Clonidine – Beta Blockers – Opioids
2. Multimodal techniques
   - Systemic, subcutaneous, neuraxial, perineural, intra-articular
   - Site-specific drug combinations (perineural, intra-articular)
**Our Clinical Sequence:**

1. Nerve Block Catheter  
   (citations later)
2. Acetaminophen
3. Steroids / NSAID / COX2
4. Opioids (Bolus Last!)
5. Gabapentin

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**Acetaminophen**

1. Use for Mild Pain Management around-the-clock  
   - And not just “prn fever”  
   - Uncouple from opioids  
   - to maximize possible dose
2. Mechanism of Action unknown (?)COX–3?)
3. Reduces production of prostaglandins
Acetaminophen (cont.)

4. Analgesic and Antipyretic but not a very effective anti-inflammatory
5. Works synergistically with NSAIDS to decrease total opioid use post-operatively
6. “Opioid sparing” effect
7. Dose should never exceed 4 grams per day in a healthy adult

Corticosteroids

CURRENT CONCEPTS REVIEW

EFFICACY AND SAFETY OF STEROID USE FOR POSTOPERATIVE PAIN RELIEF

UPDATE AND REVIEW OF THE MEDICAL LITERATURE

BY ANGELO SALOMO, DIP APP SC, GRAD DIP, MPHD (POD SURG), AND ROBERT HERMAN, DPS

- Despite the availability of various analgesic regimens, patient surveys have indicated that moderate-to-severe postoperative pain is still poorly managed.
- The use of corticosteroids for postoperative pain relief, although popular, has yet to gain wider acceptance because of concerns over side effects, in particular adrenal suppression, osteonecrosis, impaired woundhealing, and concerns about efficacy. The medical literature provides evidence that should substantially decrease these concerns with regard to low and short-dose applications.
- The results of randomized trials have shown low, short-dose corticosteroid regimens to be safe and effective for reducing postoperative pain.
- There is strong, grade-A evidence supporting the use of corticosteroids in multimodal analgesia protocols to contribute to the postoperative recovery of the patient by minimizing opioid doses and therefore side effects. However, the optimal mode, dose, and timing of administration remain unclear.
Corticosteroids

Methylprednisolone specifically inhibits C-fiber transmission

Johansson A, Hao J, Sjolund B.
Local corticosteroid application blocks transmission in normal nociceptive C–fibres.
Dexamethasone

Routinely used as antiemetic (4–8 mg);
Probable analgesic crossover

NSAID and COX–2

3 types:
- Salicylates
- Traditional NSAIDS (Ibuprofen)
- Selective Cox–2 Inhibitors (Celecoxib)

Mechanism of Action
- Inhibit cyclooxygenase isoenzyme(s)
- Prevent formation of thromboxanes and prostaglandin from arachidonic acid
- Analgesic, antipyretic, anti–inflammatory
- Opioid–sparing
NSAID/COX-2 Adverse Effects

Traditional NSAIDS (Ibuprofen)
- GI, Renal, HTN, edema, coags/platelets

Celecoxib (COX-2)
- Not GI, Not coags/platelets
- More renal, more HTN, more edema
- More allergic reactions (sulfa)
- MI and CVA are controversial after celebrex, but well documented after Vioxx and Bextra (and now Etoricoxib)

Renal Failure Triad
- Lasix
- ACE inhibitor
- NSAID or COX-2
NSAID/COX-2
“Pseudo–Adverse” Effects

Healing, Traditional NSAIDS / Celecoxib
- **No** prospective studies exist in humans verifying adverse healing outcomes (bone and/or ligament)
- Patients are the real losers in this no-win argument

Pregabalin / Gabapentin

Mechanism of Action – From Davis/Koerber lectures:
- Binds $\alpha_2\delta$ subunit of voltage dependent N-type calcium channels and blocks channel pore.
- By blocking Ca++ current, it decreases transmitter release

Clinically:
“Narrows the diameter” of incisional pain

Clinical Uses: Partial seizures, fibromyalgia, anxiety, post–herpetic neuralgia, migraine, Neuropathic pain, Post–op chronic pain

Synergistic with morphine, NSAID, celecoxib
Pregabalin / Gabapentin

Side Effects:
- Dizziness, somnolence, memory loss
- Peripheral edema
- Rare cases of hepatotoxicity (gabapentin)

My preference / recommendation is to use gabapentinoids for:
“pain relief when nerve block catheter and moderate PCA doses aren’t enough”
“for sleep” (better pain reliever than Restoril, Xanax, Ambien, etc.)
Pregabalin / Celecoxib

The Analgesic Efficacy of Celecoxib, Pregabalin, and Their Combination for Spinal Fusion Surgery

Scott S. Rouben, M.D.*
Asokumar Buranadran, M.D.*
Jeffrey S. Kroin, Ph.D.*
Karthik Raghunathan, M.D.*

BACKGROUND: Optimal pain relief after surgery is difficult to achieve with the use of just one drug. Many patients advocate the use of two or more classes of medication to reduce side effects from any one drug. In this trial, we evaluated the analgesic effect of administering pregabalin, celecoxib, pregabalin and celecoxib, or both, to patients undergoing posterior lumbar laminectomy.

METHODS: Eligible patients were randomized to receive double-blind, placebo-controlled, postoperative analgesia, with pregabalin, celecoxib, pregabalin and celecoxib, or both. The primary outcome measure was pain intensity during the first 24 hours after surgery. Analyses were performed on all randomized patients who received at least one dose of study medication.

RESULTS: The combination group had the least amount of patient-controlled analgesia use. The overall pain scores were comparable between the groups, but the combination group had the most improvement in pain relief both at rest and during activity. The most common side effects were drowsiness and nausea in both groups, with no statistically significant differences.

CONCLUSION: The postoperative administration of the combination of celecoxib and pregabalin improved analgesia and caused fewer side effects than either of the individual drugs alone.

Gabapentin / Nerve Block

A Single Preoperative Dose of Gabapentin (800 Milligrams) Does Not Augment Postoperative Analgesia in Patients Given Interscalene Brachial Plexus Blocks for Arthroscopic Shoulder Surgery

Frederic Adam, MD†
Christophe Ménalours, MD†
Daniel L. Seiler, MD‡
Marcel Chauvin, MD§

BACKGROUND: Gabapentin is commonly used as an adjuvant analgesic in patients undergoing shoulder arthroscopy. The effect of a single preoperative dose of gabapentin on postoperative analgesia in patients given interscalene brachial plexus blocks for arthroscopic shoulder surgery was evaluated.

METHODS: Patients were randomized to receive either gabapentin 800 mg orally or placebo 1 hour before surgery. An interscalene brachial plexus block was performed before surgery. Pain scores, analgesic requirements, and side effects were assessed in the recovery room and at home for 48 hours.

RESULTS: Postoperative pain scores and analgesic requirements were similar in both groups. There were no significant differences in pain scores, time to first analgesic requirement, or analgesic consumption. The incidence and severity of side effects were comparable in both groups, with no statistically significant differences.

CONCLUSION: A single preoperative dose of gabapentin (800 mg) does not augment postoperative analgesia in patients given interscalene brachial plexus blocks for arthroscopic shoulder surgery.
Local Anesthetics (systemic)

Lidocaine IV and Lap Chole

Intraoperative infusion of lidocaine reduces postoperative fentanyl requirements in patients undergoing laparoscopic cholecystectomy

Results: Most patients received fentanyl for pain relief in the PACU, but the cumulative mean dosage was lower in the lidocaine group compared to the control group (98 ± 54 µg, vs 154 ± 99 µg, respectively, P = 0.018). Lidocaine infusion reduced by 10% the amount of desflurane required (P = 0.012).


Beta Blockers (systemic)

Esmolol IV and Lap Chole

Intraoperative Esmolol Infusion in the Absence of Opioids Spares Postoperative Fentanyl in Patients Undergoing Ambulatory Laparoscopic Cholecystectomy

Vincent Calland, MD
Cecil訊 Chen, MD
Ali Teagl, MD
Juan Francisco Areano, MD
Eman O. Feldman, MD
Corin M. Scard, MD
Franco Card, MD, MPhD

RESULTS: The use of opioids during ambulatory surgery can delay hospital discharge or cause unplanned hospital admission. Preliminary studies using an incorporate continuous infusion of esmolol in place of an opioid have surprisingly reduced the need for postoperative opioid administration. In this study, we compared continuous infusion of esmolol with intermittent bolus of oral oxycodone to patient-controlled analgesia (PCA) with standardized boluses of oral oxycodone with intermittent bolus of oral oxycodone.

Methods: Twenty-five patients (mean age 41 years, mean BMI 27 kg/m²) were randomized to receive esmolol or oxycodone. Patients were monitored in the PACU and recovery room. In the PACU, heart rate and blood pressure were measured every 15 minutes. In the recovery room, patients were monitored every 30 minutes. Patients were discharged when they met the following criteria: no nausea or vomiting, no pain, and no need for additional medication.

Results: The amount of fentanyl used in the postoperative care unit was significantly less in the esmolol group (mean 0.42 µg/kg/min) compared to the oxycodone group (mean 0.85 µg/kg/min) (P < 0.001). The incidence of nausea and vomiting was also lower in the esmolol group (mean 2%, vs 20% in the oxycodone group) (P < 0.001). The esmolol group reached the discharge criteria (no pain at rest, no nausea or vomiting) faster than the oxycodone group (P < 0.001).

Conclusions: Intraoperative IV infusion of esmolol contributes to a significant decrease in postoperative administration of fentanyl and oxycodone and is associated with an earlier discharge.

(grade: B: clinical trial; level: 2b; 2008-08-01)
Opioids: IV / Oral

Converting from IV to Oral:

http://www.globalrph.com/narcotic.cgi

1 mg Dilaudid im $\rightarrow$ 13 mg Oxycodone po

But first, reduce equivalent dose of “new” opioid by 33 to 50%, to account for “incomplete cross-tolerance”

1 mg Dilaudid $\rightarrow$ start 5 mg oxycodone, then “inch up” as needed.

Nice idea, in theory. Works best in “multimodal” context

Nerve blocks and catheters

“Single-Shot” Nerve blocks:
- Ropivacaine – 12 hours
- With clonidine – 15–18 hours
- With clonidine and buprenorphine – 20–22 hours

Interscalene, axillary, paravertebral, lumbar plexus, femoral, and sciatic

Acetaminophen and NSAID/COX–2 while block is working; ADD oxycodone when block is starting to wear off.
Nerve blocks and catheters

Nerve block catheters:
- Time limit if indwelling – 72 hours
- If straightforward preop pain history: ropivacaine (0.2%) only (or 0.125% bupiv)
- If complicated preop pain history: I add clonidine and/or buprenorphine on occasion if ropivacaine is not sufficient by itself
- “Dose and Pull” when catheters are removed may include ropivacaine bolus +/- clonidine, +/- buprenorphine

Lower Extremity Amputation

Madabhushi L. Reuben SS. Steinberg RB. Adesioye J.

Infusion of Clon + Bupiv:
case report of adequate pain control without phantom limb pain
Clonidine–Buprenorphine "Temporizing Sensory Block"


2 patients for “PCL reconstruction.” Fem-sci catheters. Painful posterior knee procedure.
Surgeon worries about common peroneal nerve.
One patient dosed preop via sciatic with clon-bupre;
other patient had postop rescue analgesia via sciatic catheter with clon-bupre.
Analgesia without crude motor block. ~6–8h (anecdote)

Obturator Innervation at Knee

2006 © www.NYSORA.com
Lumbar plexus block

Parasacral plexus block
Nerve blocks and catheters

Lumbar plexus catheters (for hip surgery) won’t block all hip pain (i.e., pain from sacral plexus → sciatic nerve)
- Postop pain surges (commonly overnight) are from the sacral plexus single-shot block wearing off after 12–18 hours
- Quads weakness and partial pain relief is from lumbar plexus block and catheter.
- Treat sacral plexus pain with Tylenol, NSAID/COX–2, Opioids, Gabapentin

Chronic Pain Patients (BW observation)

Chronic pain patients preop have notable postop pain even when the best-possible nerve block catheters are in place
- “Opioid-induced hyperalgesia”
- “Chronic pain and CNS plasticity” Unfortunate association with opioid-seeking behavior.
- This is most commonly physical dependence, not as commonly psychological dependence
1995–1999
ACL Clinical Pathway

948 ACLs

1995–1997:
- GA with/without Fem NB
- Epidural
1997–1999 ACL Clinical Pathway: Modifications

If GA, then standard bupiv FNB
If GA, 3 antiemetics recommended
- Perphenazine 2 mg IV, plus
- Dexamethasone 4 mg IV, plus
- 5HT3–antagonist

Standard intra-articular (meperidine, neostigmine, and bupivacaine)
Pain, Unplanned Admission, Hospital Costs and Role of RA / Nerve Blocks and GA

Predictors of Pain and Unplanned Admissions after Outpatient Knee Surgery

**Pain:**
- Use of Volatile GA: -2.1 OR (P<0.001)
- Complex procedure: -2.5 Odds Ratio vs. simple procedure
- Fem-Sci Blocks: -0.4 Odds Ratio vs. no block (P<0.01)
- No other predictors
  - Age, Gender
  - ASA/PS

**Unplanned Admission:**
- Volatile GA: -3.3 OR (P=0.001)
- Complex procedure: -4.7 OR (P<0.001)
- Fem or Fem-Sci Blocks: -0.4 OR (P=0.009)
- No other predictors
  - Age, Gender, ASA/PS

*Anesthesiology 98: 1206, 2003*
Hospital Costs: ACLR 1995–1999

Base costs and significant predictors of hospital costs

ACL base procedural cost: $3500
Using allograft tissue: $260
Inflation: $75/3m (2.1% of $3500)
Hospital Admission: $385
PACU bypass: $-420

All P values < 0.003

Bypassing PACU and same day discharge = $800 hospital cost savings (versus PACU stay with hospital admission)

Anesthesiology 2004; 100:697–706

Role of PACU Bypass in Hospital Cost Savings: 3000 Orthopedic Outpatients per Year

Cost Savings $1.2M

Traditional: GAVA, All PACU, 17% admissions
RA-based: 82% PACU Bypass, 4% admissions

Anesthesiology 2004; 100:697–706
Outcomes after ACLR: Effect of FNB

Sample size: N=270 (moderate effect size), 3 groups

**Femoral Nerve Block Bolus and Infusion:**

*Group 1:* Saline bolus, saline infusion X 55 hours

*Group 2:* Levobupivacaine 0.25% bolus (30 cc), saline infusion

*Group 3:* Levobupivacaine 0.25% bolus and infusion (5 cc/hr)

All patients: propofol sedation, ketamine 0.2 mg/kg
Spinal: ipsilateral hyperbaric bupivacaine 9–12 mg
ACL Study – Methods (cont.)

Intra-articular injection:
meperidine / neostigmine / ketorolac

Antiemetics:
perphenazine / dexamethasone / ondansetron

Postoperative per-oral analgesia:
- CR oxycodone 10–30 mg q12h
- IR oxycodone 5–10 mg q4–6h prn
- Rofecoxib 50 mg qam X 6d

Justifying the Methodology
**Why Spinal?**

See earlier data when GA-volatile agents were used.

Also, for “Category 1” Knee Scopes (n=62, Finland):

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Spinal</th>
<th>Des-ETT</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraop opioids</td>
<td>10%</td>
<td>70%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PACU VAS</td>
<td>0</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postop opioids</td>
<td>10%</td>
<td>41%</td>
<td>0.008</td>
</tr>
<tr>
<td>PONV</td>
<td>0</td>
<td>*19%</td>
<td>0.024</td>
</tr>
<tr>
<td>Same anes next time</td>
<td>97%</td>
<td>81%</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Spinal: 4 mg bupiv, no fentanyl

*GA PONV despite prophylaxis for “high risk.”


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**Why Spinal? (cont.)**

Also, for Category 1 Knee Scopes (n=41, Mayo):

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Spinal</th>
<th>Prop–N20 LMA</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACU Bypass</td>
<td>100%</td>
<td>35%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postop VAS (30–120 min postop)</td>
<td>0.2 – 0.5</td>
<td>1.7 –2.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Postop opioids</td>
<td>14%</td>
<td>45%</td>
<td>0.08</td>
</tr>
<tr>
<td>Time to first opioid (min)</td>
<td>280</td>
<td>120</td>
<td>0.1</td>
</tr>
<tr>
<td>Complete Satisfaction with anesthetic and pain mgmt (10/10 satis)</td>
<td>95%</td>
<td>60%</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Spinal: 6 mg bupiv, 15 mcg fentanyl

Why spinal? (conc.)

For knee surgery (instead of GA):
- Less postoperative pain
- Less PONV
- More PACU bypass
- Headaches are a non-issue with small-gauge pencil-point needles
- Speaker’s preference: Ipsilateral Hyperbaric (every time)

Why Ketamine?

For ACL Reconstruction (n=45, France)
GA with LMA propofol/N20:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ketamine 0.15mg/kg</th>
<th>Placebo</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS – first 12h (rest)</td>
<td>3.5</td>
<td>3.5</td>
<td>NS</td>
</tr>
<tr>
<td>VAS at 24h (rest)</td>
<td>2.5</td>
<td>4.2</td>
<td>NS</td>
</tr>
<tr>
<td>VAS at 48h (rest)</td>
<td>1.5</td>
<td>2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Morphine use-PT (POD1)</td>
<td>1.3</td>
<td>3.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total 48h Morphine mg</td>
<td>34</td>
<td>67</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>POD#1 Knee Flexion</td>
<td>45°</td>
<td>37°</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Why Ketamine? (cont.)

For \( n=39 \), Louisville) MAC with propofol +/- ketamine (1 mg/mL propofol), all outpatients:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ketamine 0.25mg/kg</th>
<th>No ketamine</th>
<th>( P= )</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET CO2</td>
<td>30</td>
<td>45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RR</td>
<td>16</td>
<td>14</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PACU Bypass</td>
<td>79%</td>
<td>85%</td>
<td>NS</td>
</tr>
<tr>
<td>Postop Mood VAS (0–100)</td>
<td>91</td>
<td>64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days until zero pain</td>
<td>3</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mortero RF et al.: *Anesth Analg. 92(6):1465–9, 2001*

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Why Ketamine? (cont.)

For \( n=40 \), France) spinal with propofol (uro / ortho) +/- ketamine (1 mg/mL propofol), all outpatients:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ketamine ~37 mg</th>
<th>No ketamine</th>
<th>( P= )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total propofol dose</td>
<td>146</td>
<td>137</td>
<td>NS</td>
</tr>
<tr>
<td>MAP</td>
<td>91</td>
<td>75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SaO2 &lt; 95% postop</td>
<td>2/20</td>
<td>3/20</td>
<td>NS</td>
</tr>
<tr>
<td>Supplemental O2</td>
<td>2/20</td>
<td>4/20</td>
<td>NS</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>2/20</td>
<td>1/20</td>
<td>NS</td>
</tr>
<tr>
<td>VAS pain</td>
<td>38</td>
<td>35</td>
<td>NS</td>
</tr>
</tbody>
</table>

Why Low-Dose Ketamine? (conc.)

• Better postop physical therapy
• Less opioid requirement
• Better intraop respiration
• Better intraop BP
• No postop cognition issues, better postop mood with ketamine

Why IA Meperidine?

N=40, Sweden
IA meperidine (50, 100, or 200 mg) versus IA prilocaine as the surgical anesthetic for “Category 1” knee arthroscopy.

100 mg IA dose not associated with any PONV, and led to “optimal surgical/analgesic conditions” (compared with meperidine 50 mg and prilocaine) and fewer side effects (when compared with meperidine 200 mg)

## Why IA Neostigmine?

For (n=20, Taiwan) Category 1 knee scope under GA (Pent/sux/tube/isoflurane/fentanyl);
IA neostigmine (0.5 mg) vs. IA morphine (2 mg):

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Neostigmine</th>
<th>Morphine</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td>1h VAS (0–100)</td>
<td>28</td>
<td>47</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>48h PCA morphine</td>
<td>2 mg</td>
<td>5 mg</td>
<td>NS</td>
</tr>
<tr>
<td>Time to 1st PCA use</td>
<td>340 min</td>
<td>200 min</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>


## Why IA Ketorolac?

For (n=40, Tufts) Category 1 knee scope under GA (Pent/sux/tube/isoflurane/fentanyl)  


<table>
<thead>
<tr>
<th>Parameter</th>
<th>IA Bupiv / Ketorolac</th>
<th>IA Bupiv</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2h VAS (0–10)</td>
<td>2.0</td>
<td>2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to 1st analgesic</td>
<td>90 min</td>
<td>400 min</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total 24h Tylenol#3</td>
<td>4.2 tabs</td>
<td>2.9 tabs</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Pittsburgh 2001–2004
ACL Study Results:

Public Health Goal – Prevent Moderate–Severe Pain at Home
(pain scores 5+ / 10)

*Anesthesiology, 104(2): 315–327, 2006*
Interpretation

LbLi treatment pain outcome is clinically and statistically better than placebo group outcomes throughout the first 2 days after surgery.

Single-shot equivalent (LbSi) group assumes placebo group outcome on Day 2

*Anesthesiology, 104(2): 315–327, 2006*
To analyze days 3–7 (after the catheter is out)...

We combine the placebo group with the drug bolus and saline infusion group (i.e., SbSi/LbSi combined)...

Anesthesiology, 104(2): 315–327, 2006
Interpretation

LbLi treatment pain outcome is statistically better than placebo/single-shot outcomes 3–4 days after surgery. All treatment groups’ pain scores balance out by 7 days.

*Anesthesiology, 104(2): 315–327, 2006*

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One Other Predictor of Pain

Preoperative VAS (0–10) > 2 with movement predicted higher postop VAS pain scores with movement.

*Anesthesiology, 104(2): 315–327, 2006*
How did we compare with the world’s literature?

Figure 6.1. Pain Scores After ACL Reconstruction: UPMC-Montefiore 1998-1999 versus Existing Studies

ACL Pain Scores POD 1-3

UPMC CFNB 2005
UPMC SS-FNB 2005
UPMC placebo 2005
UPMC FNB, outpatient 1999
France - Ketamine, inpt PCA
France - Ktmn plcb, inpt PCA
Tufts - Oxycodone, outpt
Canada - ACL HS FNB, outpt
Canada - ACL HS placebo, outpt
Tufts - SR Oxycodone, outpt

Verbal Pain Scores

POD3
POD1

0 2 4 6 8
Other Multimodal and Multi-Pharm Options:
1. Systemic
2. Articular
3. Perineural

ACL – TIVA GA with no other analgesics
Acetaminophen < ibuprofen (VAS@rest)
No benefit of combination therapy (underpowered)

<table>
<thead>
<tr>
<th></th>
<th>Acetaminophen (n = 20)</th>
<th>Ibuprofen (n = 17)</th>
<th>Combined (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS (mm)</td>
<td>28.7 ± 18.5</td>
<td>19.1 ± 18.4*</td>
<td>18.5 ± 18.7*</td>
</tr>
<tr>
<td>Verbal score (0–4)</td>
<td>1.56 ± 0.9</td>
<td>1.02 ± 1.0*</td>
<td>0.98 ± 0.8*</td>
</tr>
</tbody>
</table>

*P < 0.05 compared with the acetaminophen group.

courtesy, Spring McCann, MD


Systematic qualitative review

NSAID > acetaminophen in dental surgery (analgesia efficacy)

NSAID > acetaminophen in major and orthopedic surgery (analgesia efficacy)

Combination therapy may confer additional analgesic efficacy

courtesy, Spring McCann, MD

"In conclusion, the existing direct comparative studies show that NSAIDs are more effective than paracetamol in some situations, e.g. dental surgery, but the differences are less obvious after other types of surgery. Paracetamol is definitely a viable alternative to the NSAIDs, especially because of the lower incidence of adverse effects, and should be the preferred choice in high-risk patients. In the absence of firm data, paracetamol should also be considered instead of NSAIDs for pain management after major or orthopaedic surgery, as few differences in efficacies were found in existing data. It may be appropriate to combine paracetamol with NSAIDs, but future studies are required...."


ORTHOPEDIC SURGERY – DOSE ON POD#1 AFTER PAIN IS ALREADY ESTABLISHED

Methylprednisolone 125mg
or ketorolac 30 mg;
Both > placebo
Lower pain score for 24h;
less opioid consumption for 72h
Methylprednisolone was more analgesic and opioid sparing
courtesy, Spring McCann, MD

Meta-analysis

PCA morphine + acetaminophen > PCA morphine alone (morphine-sparing effect = 20%);

But, no reduction in opioid-related side effects

courtesy, Spring McCann, MD


HYSTERECTOMY (movement pain): Gabapentin + acetaminophen < gabapentin < placebo

courtesy, Spring McCann, MD
Pregabalin / Celecoxib

The Analgesic Efficacy of Celecoxib, Pregabalin, and Their Combination for Spinal Fusion Surgery

UI: 17056968

Ketamine

**CLINICAL CONCEPTS AND COMMENTARY**

Richard B. Warfield, M.D., Editor

UI: 15618805

Ketamine for Perioperative Pain Management

Sabira Ummelhassan, M.D., Marcel E. Doniec, M.D., Ph.D.

Pain therapy can be improved using intraoperative and postoperative ketamine in a variety of surgical procedures and anesthetic techniques. In particular, the intraoperative use of intravenous subanesthetic ketamine in general anesthesia provides pain prevention in the postoperative period.
Other Multimodal and Multi–Pharm Options:

1. Systemic
2. Articular
3. Perineural

Intra–articular Analgesics

Efficacious:

- Local anesthetics
- NSAID (NOT COX–2)
- Opioids
- Dexamethasone (=morphine)
- Ketamine
- Neostigmine
- Clonidine
- Midazolam (only 4h)
- Tramadol (=morphine)
Other Multimodal and Multi-Pharm Options:
1. Systemic
2. Articular
3. Perineural
### Perineural adjuvants (to local anesthetics)

**Efficacious:**
- Clonidine
- Buprenorphine
- Dexamethasone
- Midazolam
- Tramadol

**Not so much:**
- Ketamine
- Neostigmine

**Unknown:**
- NSAID
- (Tramadol has EtOH as diluent)
Clonidine – Axillary Block


Clonidine + mepiv > mepiv alone
(both anesthesia and postop analgesia)

courtesy, John Hache, MD

Clonidine – Axillary Block


Clonidine + mepivacaine > duration

courtesy, John Hache, MD
Clonidine – Axillary Block


Clon + Bupiv = longer onset time (vs. bupiv alone)
Clon + Bupiv = longer motor block (vs. bupiv alone)
Clon + Mepiv = longer motor block (vs. mepiv alone)
No Increase Ropiv + Clon
– Clon + Ropiv = 712 ± 52 min. motor block (vs. ropiv alone 702 ± 82 min.)

courtesy, John Hache, MD

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**FIGURE** Duration of motor blockade with mepivacaine 1%, bupivacaine 0.5%, ropivacaine 0.75% with and without clonidine 0.150 mg. The duration of blockade (in minutes) is prolonged by the addition of clonidine in the mepivacaine and the bupivacaine groups. Block was not prolonged by clonidine in the ropivacaine group.
Perineural anti-inflammatory class-effect of clonidine and dexmedetomidine?

Grade Zero inflammation after saline, or dexmedetomidine monotherapy, or dexmedetomidine with bupivacaine

Grade 3 inflammation after bupivacaine monotherapy without dexmedetomidine
Buprenorphine in Combination with Local Anesthetics


Buprenorphine >> > duration of postoperative analgesia

Was added to “Chicago SuperCaine”
- mepivacaine, tetracaine, epinephrine
- ~17 vs 5 hrs

Study repeated (with a systemic control group), and confirmed in 2002 (22 v. 12 v. 7 hrs)
Table 3. Average Duration of Postoperative Analgesia and First Reported Pain Scores

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative analgesia (hr)</td>
<td>23.3 ± 3.4†</td>
<td>12.5 ± 5.9†</td>
<td>5.6 ± 1.0†</td>
</tr>
<tr>
<td>(range)</td>
<td>(11-48 hr)</td>
<td>(4-93 hr)</td>
<td>(5-10 hr)</td>
</tr>
<tr>
<td>Percentage of patients with “0” pain score up to 48 hr</td>
<td>26</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>First reported pain score (0-10)</td>
<td>3.5 ± 0.64♂</td>
<td>4.4 ± 0.64♂</td>
<td>5.2 ± 0.66♂</td>
</tr>
<tr>
<td>(range)</td>
<td>(0-7)</td>
<td>(2-10)</td>
<td>(2-9)</td>
</tr>
</tbody>
</table>

†P = .012 between groups I and II.
♂P < .01 between groups I and III and II and III.
♀Total analog score 0 = “no pain,” 10 = “worst possible pain.”
♂P < .05 between groups I and II and I and III.
♀P < .05 between groups II and III.
Axillary Block

Movafegh A. Razazian M. Hajimaohamadi F. Meysamie A. 
Dexamethasone added to lidocaine prolongs axillary 
brachial plexus blockade. Anesthesia & Analgesia. 

Dexamethasone + lidocaine 
> lidocaine alone 
(sensory and motor duration)

courtesy, John Hache, MD

Supraclavicular Block


Dexamethasone + Bupivacaine 
>> than Tramadol + Bupivacaine 
(analgesic duration)

courtesy, John Hache, MD
Midazolam in Combination with Local Anesthetics


Midaz + bupiv = faster onset, longer duration (vs. bupiv alone)

No reported side effects (50 pts).

courtesy, John Hache, MD
**Midazolam – Brachial Plexus Block**


Midaz + Bupiv =
- faster onset (clonidine slowed onset)
- longer duration
- no apparent side effects
(n=40)

courtesy, John Hache, MD

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**Tramadol in Combination with Local Anesthetics**
Axillary Block: Tramadol+Lido


Tramadol + lidocaine > lidocaine alone, for block duration, but limited value due to slow onset

courtesy, John Hache, MD

Axillary Block – Tramadol + Mepiv


Tramadol + mepivacaine > analgesia vs. mepiv alone

courtesy, John Hache, MD
Axillary Block – Tramadol+Mepiv


Tramadol + mepivacaine:
prolonged block;
no side effects

courtesy, John Hache, MD

Basic Science Lab (Williams et al.)

*Lidocaine*
- Toxic to neurons in culture:
  - first reported in 1998,
  - verified in 2008–09 Pittsburgh model
- Toxicity may explain cauda equina syndrome after lidocaine spinal, and possibly TNS/TRI after lidocaine spinal

*Ropivacaine*
- Non–toxic to neurons in culture

*Levobupivacaine*
- Duration longer than ropivacaine when prolonged with epinephrine
- When used in equal doses, provides less dense neural blockade than ropivacaine
**Basic Science Lab (cont.)**

**Clonidine**
- Not toxic to neurons in culture
- Focal perineural anti-inflammatory effects (Eisenach)
- Longer block duration (motor), but improves postoperative analgesia
- Longer duration offset by addition of bicarbonate
- Prolongs mepiv duration without increasing time to sensory block
- Prolongs bupiv duration but increases time to sensory block
- Does not increase duration of ropivacaine motor block
- Potential use for prevention of phantom limb pain

**Basic Science Lab, etc. (cont.)**

**Buprenorphine**
- Not toxic to neurons in culture
- Longer postoperative analgesia
- Basic science evidence of being both analgesic and anti-hyperalgesic

**Combined Clonidine – Buprenorphine**
(Williams)
- Not toxic to neurons in culture
- Sensory without motor block
- 22 hour duration with ropivacaine, versus 18 hours for ropiv-clon, for ISBs
- No complications in >1000 single-shot interscalene blocks since 2002
**Basic Science Lab, etc. (cont.)**

*Dexamethasone*
- Not toxic to neurons in culture
- Improves IVRA post operative analgesia, and perineural nerve block duration

*Midazolam*
- Non-toxic to neurons in culture
- In small studies presented, not associated with nerve toxicity
- Shortened onset time
- Improved analgesia

**Basic Science Lab, etc. (cont.)**

*Neostigmine*
- No perineural benefit, but yes benefit with intra-articular use

*Tramadol*
- No benefit with lidocaine
- Increases duration of perineural analgesia/anesthesia with mepivacaine
Acknowledgment

Williams lab cell culture data
to be submitted to
2009 ASA Annual Meeting

Co-investigators:
Gebhart, Gold, Hough

Funded by:
- NIH/NCRR 1UL1 RR024153
  through University of Pittsburgh
- NIH/NIDA 1K01 DA025146-01

Summary / Observations

Set realistic expectations.
Know the Preop Pain Score With Movement.
Nerve block, then Tylenol, then NSAID / COX-2,
then opioids, then pregabalin or gabapentin.
Nerve blocks are good, but “too much block”
isn’t always better (e.g., falls).
Chronic pain patients’ blocks often
don’t work to the patient’s satisfaction,
commonly due to unrealistic expectations
and chronic pain physiology.