Ketamine: Old Drug, New Tricks (...for Pain)

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“The hazards and pitfalls of recreational use loom dramatically larger than with any other psychedelic...it seems unlikely that K's popularity will increase.”
Rameses Sputz
High Times, (1989)

OBJECTIVES
1. Describe the basic pharmacology of ketamine, its unique characteristics, and its effects on each distinguished body system.
2. Discuss the historic use of ketamine in contrast to its newer, off-label uses related to pain management.
3. Critique selected literature describing the off-label use of ketamine, both for adjunctive and for monotherapy, in acute and postoperative pain.
4. Develop evidence-based recommendations for the optimal use of ketamine as an analgesic agent.

Ketamine: Old Drug

TIMELINE OF EVENTS

1958
• Phencyclidine (PCP) introduced for clinical anesthesia

1960s-1969
• POP off market; ketamine trials initiated

1970
• Ketamine FDA approved, general anesthetic

2000s - present
• Increase in clinical use of ketamine

August 1999
• Ketamine becomes Schedule III

1970s-80s
• Ketamine popularized as drug of abuse

CLINICAL PHARMACOLOGY
• FDA-approved indications:
  — Induction and maintenance of general anesthesia
    • Procedures not requiring paralysis/skeletal muscle relaxation
  — Supplement to other sedative agents
• Sites of Action:
  • N-methyl-D-aspartate (NMDA) receptor
  • Mu/delta/kappa opioid receptors
  • Monoaminergic, muscarinic, nicotinic receptors
  • Neuronal sodium/potassium channels
**UNIQUE PROPERTIES OF KETAMINE**

- Dissociative Anesthesia
- Analgesia
- Amnesia
- Minimal Respiratory Depression
- Bronchodilation
- Sympathetic stimulation

**“DISSOCIATIVE” ANESTHESIA**

- Cataleptic state
  - Eyes remain open, nystagmus
  - Involuntary movements
- Increased lacrimation and salivation
- Increased cerebral blood flow
  - +/- increased ICP?
  - Neuroprotective?

**CLINICAL PHARMACOLOGY**

**Dosage/Administration**

- **Induction:**
  - IV: 1–4.5 mg/kg
  - IM: 6.5–13 mg/kg
- **Maintenance:**
  - ½ to full dose PRN or
  - Continuous infusion: 0.1–0.5 mg/minute, (1–6 mg/minute have also been used)

**Onset/Duration**

- **IV:**
  - Onset: rapid (30 seconds)
  - Duration: 5-10 minutes
- **IM:**
  - Onset: 3-4 minutes
  - Duration: 12-25 minutes

**ADVERSE DRUG EFFECTS**

**SYMPATHOMIMETIC EFFECTS**

- ICP ELEVATION
- IOP ELEVATION
- CNS STIMULATION
- OTHERS
- LONG-TERM USE

**EMERGENCE PHENOMENON**

When?

- ‘Emerging’ from dissociative state (transitional period)

What?

- Visual and auditory disturbances: mood, time, unreality, feelings of floating, hallucinations, anxiety, paranoia

Who?

- Anyone may experience; children, elderly, lower doses least common; premedication may prevent severity

May range from mild to extreme discomfort

**Ketamine: New Tricks**
BY THE NUMBERS

PubMed Articles Referencing "Ketamine,"
Total Number per Year

BY THE NUMBERS

DOSE-RESPONSE CURVE

BY THE NUMBERS

ADVERSE DRUG EVENTS, REVISITED

SYMPATHOMIMETIC EFFECTS

ICP ELEVATION

IOP ELEVATION

CNS STIMULATION

LONG-TERM USE

OFF-LABEL UTILITY

– Acute pain
– Chronic pain
– Procedural pain
– Adjunctive for pain
– Neuropathic pain
– Sickle-cell crisis
– Post-anesthetic shivering

– Affective disorders
– Status epilepticus
– Depression
– Asthma
– Agitation
– ... etc.

WHY LOW-DOSE KETAMINE FOR PAIN?

• Multimodal analgesia preferred
• Aging population
• Avoidance of opioid overuse
  – Dose-limiting side effects
• Rise of opioid misuse, abuse, overdose

...HCAHPS?

EVIDENCE GRADE ASSESSMENT

GRADE

Quality of Evidence

Methodology

A (high)

Randomized, controlled trial (RCT)/meta-analysis

B (moderate)

Downgraded RCTs or upgraded observational studies

C (low)

Well-done observational studies with control RCTs

D (very low)

Downgraded controlled studies or expert opinion based on other evidence

STRENGTH OF RECOMMENDATION

1 (strong)

2 (weak)
ACUTE PAIN

- Pain is the #1 complaint for emergency department (ED) visits
- Current 'standard of care':
  - Short-acting opioids
  - NSAIDs
  - Muscle relaxants
- Difficult balance of risk vs. benefit

LOW-DOSE KETAMINE (LDK): ADJUVANT AGENT FOR PAIN

KETAMINE UTILITY IN THE ED

- Unique NMDA-receptor-mediated effects:
  - Decreased central sensitization?
  - Decreased pain memory?
- Ketamine versus opioids:
  - May aid in opioid-refractory pain
  - Opioid-tolerant patients
  - Less associated adverse events
  - Possible opioid-sparing effect?

LOW-DOSE KETAMINE IN THE ED

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Inclusion Criteria</th>
<th>Intervention</th>
<th>Summed pain-intensity (P) differences</th>
<th>Reduced pain intensity during procedure (1.5 µg/kg IV vs. placebo and morphine, over 10 minutes and 0.3 mg/kg ketamine IV vs. morphine and 0.3 mg/kg ketamine IV)</th>
<th>Patient's pain intensity during procedure (1.5 µg/kg IV vs. placebo and morphine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bracht, et al. 2014</td>
<td>40</td>
<td>Ages 14-65; acute moderate/severe pain</td>
<td>Midazolam 0.1 mg/kg IV vs. 1.5 µg/kg IV over 10 minutes and 0.3 mg/kg ketamine IV vs. morphine and 0.3 mg/kg ketamine IV</td>
<td>NS</td>
<td>&lt;0.02</td>
<td>&lt;0.05 throughout 96 h; shorter duration of PCA (P&lt;0.05 during first 24 h; P&lt;0.05 during 72 h; P&lt;0.001 at 15, 30, and 60 min vs. control)</td>
</tr>
<tr>
<td>Messina, et al. 2009</td>
<td>60</td>
<td>Ages 14-65; procedural analgesia, orthopedic reduction or arthrotomy drainage</td>
<td>Ketamine 2.2 µg/kg IV vs. ketamine 0.3 mg/kg IV (in addition to bupivacaine)</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>Less respiratory adverse events with ketamine</td>
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<tr>
<td>Dailo, et al. 2007</td>
<td>210</td>
<td>Ages 55-80 years with acute, severe pain, without hemodynamic or neurologic compromise</td>
<td>Ketamine 2.2 µg/kg IV vs. placebo and morphine 0.1 mg/kg vs. placebo and morphine 0.1 mg/kg IV</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>100-point visual analog score Ketamine 34.1 (25.6 to 43.6) vs. placebo and morphine 39.3 (25.8 C.I. = 33.8 to 46.0); P&lt;0.05; Psych adverse effects were greater with ketamine</td>
</tr>
</tbody>
</table>

ADDICING LOW-DOSE KETAMINE TO MORPHINE (IV PCA)

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Surgical setting</th>
<th>Number of Patients</th>
<th>Ketamine regimen (IV) (mg/kg)</th>
<th>Duration of PCA in mg</th>
<th>Pain score (VAS)</th>
<th>Reduction in morphine consumption</th>
<th>Status PCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>领衔, et al. 1998</td>
<td>Laparoscopy</td>
<td>20</td>
<td>0.1 vs 0.15</td>
<td>Propofol 0.1 mg/kg/d</td>
<td>Significant difference (P&lt;0.05)</td>
<td>Opioid-sparing effect greater with ketamine</td>
<td>Significant difference (P&lt;0.05)</td>
</tr>
<tr>
<td>鍾, et al. 1998</td>
<td>Thoracoabdominal hysterectomy</td>
<td>30</td>
<td>1 vs 1</td>
<td>Significant difference (P&lt;0.05)</td>
<td>Significant difference (P&lt;0.05)</td>
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</tr>
<tr>
<td>范, et al. 1998</td>
<td>Total abdominal hysterectomy</td>
<td>20</td>
<td>1 vs 1 vs 2 vs 3</td>
<td>Significant difference (P&lt;0.05)</td>
<td>No significant difference (NS)</td>
<td>Significant difference (P&lt;0.05)</td>
<td>Significant difference (P&lt;0.05)</td>
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<tr>
<td>邓, et al. 1998</td>
<td>Total abdominal hysterectomy</td>
<td>20</td>
<td>1 vs 1 vs 2 vs 3</td>
<td>Propofol 0.1 mg/kg every 3 minutes until sedation</td>
<td>Significance difference (P&lt;0.05)</td>
<td>No</td>
<td>Significant difference (P&lt;0.05)</td>
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<tr>
<td>胡, et al. 1998</td>
<td>Side pain, breast, or pain</td>
<td>10</td>
<td>1 vs 1 vs 2 vs 3</td>
<td>No</td>
<td>No</td>
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<td>董, et al. 1998</td>
<td>Hip arthroplasty</td>
<td>50</td>
<td>1 vs 1 vs 2 vs 3</td>
<td>No</td>
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<td>刘, et al. 1998</td>
<td>Lower abdominal surgery</td>
<td>50</td>
<td>1 vs 1 vs 2 vs 3</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>李, et al. 1998</td>
<td>Thoracoabdominal surgery</td>
<td>40</td>
<td>1 vs 1 vs 2 vs 3</td>
<td>No</td>
<td>No</td>
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<td>郭, et al. 1998</td>
<td>Thoracoabdominal hysterectomy</td>
<td>30</td>
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<td>No</td>
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</table>

ACUTE POSTOPERATIVE PAIN

- Acute pain control in the perioperative phase is critically important!
  - Adequate pain control associated with:
    - Less hyperglycemia
    - Less immunosuppression
    - Better rehabilitation
    - Less progression to chronic pain
  - Multiple adverse effects with analgesics
SUMMARY: KETAMINE AS AN ADJUVANT AGENT FOR PAIN

- Multiple dosing protocols
- Management of breakthrough pain
- Multiple patient populations
- Primary outcomes
  - Subjective pain scales

What we know about low-dose ketamine:
1. Low-dose ketamine, in addition to opioids, is as effective as IV opioids alone for acute pain control (2B)
2. Low-dose ketamine, in addition to opioids, may reduce overall postoperative opioid requirements (2B)

MILLER, ET AL. LOW-DOSE KETAMINE VS MORPHINE FOR ACUTE PAIN IN THE ED: A RANDOMIZED CONTROLLED TRIAL.

- **Design:** Randomized, prospective, double-blind superiority trial
- **Population:** Patients with acute pain requiring IV opioids in ED
- **Methods:** 5-minute IV infusion of low-dose ketamine ([LDK] 0.3 mg/kg) or IV morphine (0.1 mg/kg)
  - Second dose at 20 minutes, if needed
  - If third dose requested, patient excluded

- **Primary Outcome:** maximum reduction in verbal numeric rating scale (NRS) from baseline
  - NRS collected at baseline, 5, 10, 20 and every 20 minutes up to 120 total

- **Secondary outcomes:** RASS, vitals, adverse events, need for repeat dosing, patient satisfaction
- **Data collected:** March to November 2012

- **Results:** n=45 (ketamine=24, morphine=21)
  - Maximum change in NRS pain score: 4.9 vs 5
    - Rapid reduction in pain at 20 minutes with ketamine
    - Pain reduction more gradual with morphine

- **Secondary Outcomes:**
  - Second dose given: 54% vs. 38% (P=.37)
  - Third dose, ketamine: 25% (6) vs. morphine: 14% (3) (P=.47)
    - Significant differences in SBP: T5, T10

- **Safety:** adverse events, 58% (14) vs. 57% (12)
  - Most common: nausea, vomiting, hallucinations

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- **Data collected:** March to November 2012
**Miller, et al. Low-dose ketamine vs morphine for acute pain in the ED: A randomized controlled trial.**

- **Conclusion:** Low-dose ketamine is not superior to morphine; comparable analgesia to opioids
  - LDK provides rapid, non-sustained pain relief
  - Increased rate of repeat dosing with ketamine
  - 25% of patients did not complete 120 minutes of study

- **Discussion:**
  - Ketamine provided at least 50% reduction in pain scores during all times measured
  - Small sample size, lack of control arm, repeat dosing permitted, strict inclusion criteria

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**Jouguelet-Lacoste, et al. The use of IV infusion or single dose of low-dose ketamine for postoperative analgesia: A review of the current literature.**

- **Design:** Systematic literature review (1966 to 2013)
- **Methods:** Any clinical trial using low-dose infusion of ketamine for acute, perioperative pain relief
  - Low-dose ketamine (LDK): infusion: ≤ 1.2 mg/kg/h or bolus: ≤ 1 mg/kg
  - n=39 trials, 5 meta-analyses
    - 26 trials: bolus dose followed by continuous infusion
    - 11 trials: single bolus doses
    - 2 trials: continuous infusion only
  - Evaluation according to type of surgery

- **Outcomes:** Efficacy according to primary endpoint
  - 24 studies: opioid consumption
  - 10 studies: pain scores
  - 5 meta-analyses assessed both endpoints

- **Results (meta-analyses):**
  - IV ketamine reduces opioid consumption (median 32%)
  - IV ketamine reduces pain scores at 24 hours postoperative (4 of 5 analyses):
    - 87.5%, 59%, 54.5%, and 35%, respectively

- **Results (trials):**
  - 40% mean reduction of opioid consumption (n=23 of 34)
  - Correlation between ketamine dose and magnitude of effect remains unclear
  - 8/34 studies: reduction of pain scores for at least 24 hours

- **Safety:**
  - Continuous infusion (CI) LDK is not associated with any severe side effects (n=940 patients)
  - No major differences between ketamine and control groups

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**Jouguelet-Lacoste, et al. The use of IV infusion or single dose of low-dose ketamine for postoperative analgesia: A review of the current literature.**

- **Administration techniques:**
  - Postoperative infusion for 48 hours
  - Intraoperative bolus, intraoperative infusion
  - Intraoperative bolus and 2-hour postoperative infusion
  - + 24-hour postoperative infusion
  - + 48-hour postoperative infusion
  - Repeat-bolus dosing

- **Results (trials):**
  - Efficacy of LDK: according to site of surgery
    - Decrease in opioid consumption: appendectomy, cervical, total hip, laparotomy, colorectal, heart, gastrectomy, ligament repair, renal, cholecystectomy, abdominal surgeries
    - Decrease in pain scores (for at least a few hours): appendectomy, cervical, gastrectomy, abdominal sites
    - Mixed results: abdominal, lumbar spine, hysterectomy
    - No benefit: ENT, prostatectomy
    - No conclusion can be made regarding site of surgery
Conclusion:
1. Benefits of ketamine driven by reduction of opioid burden more than a reduction of pain
2. Magnitude of reduction of opioid consumption appears to correlate with dose given
3. Optimal dose and regimen of administration remain unknown

SUMMARY: KETAMINE MONOTHERAPY FOR PAIN
- Multiple dosing protocols
- Multiple patient populations
  - Surgical site variability
- Multiple primary outcomes
  - Subjective pain scales
  - Opioid consumption

What we know about low-dose ketamine:
1. Low-dose ketamine may reduce postoperative opioid requirements (2B)
2. Low-dose ketamine appears safe for analgesia in postoperative patients (2B)

IS THIS DÉJÀ VU?
- Efficacy outcomes
  - Reduction in opioid-consumption?
  - Superior pain relief?
- Other outcomes
  - Reduction in length of stay?
  - Reduction in post-operative complications?
- Cost of therapy

PRACTICAL CONSIDERATIONS
- Schedule III, off-label use of an anesthetic
  - Nursing implications
  - Pharmacy implications
- Monitoring
  - Patient counseling
  - Other adverse events
- Administration techniques
  - IVP vs. intermittent infusion vs. PCA, etc.

LOW-DOSE KETAMINE FOR ANALGESIA
ADVANTAGES
- Hemodynamic stability
- Reduced opioid requirements
- Role in opioid-refractory pain
DISADVANTAGES
- May not be effective
- Current lack of data
- Practical considerations
RECOMMENDATIONS

- Low-dose ketamine for analgesia (2B):
  - Infusion: \( \leq 1.2 \text{ mg/kg/h} \) or bolus: \( \leq 1 \text{ mg/kg} \)
  - Slow administration of bolus doses
  - Monitoring not required
- Remember:
  - Higher doses required for dissociation/sedation
  - Pre-treatment with benzodiazepines, glycopyrrolate to augment adverse effects of ketamine
<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Surgical Setting</th>
<th>Number of Patients</th>
<th>Analgesia regimen in mg; (MOR vs. MOR:KET)</th>
<th>Pain scores (VAS)</th>
<th>Reduction in morphine consumption</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelet, et al.</td>
<td>Thoracotomy</td>
<td>50</td>
<td>1 vs 1:1</td>
<td>P&lt;0.05 at 48 and 60 h</td>
<td>P&lt;0.05 at 36-60 h</td>
<td>Desaturation P&lt;0.008; 1st and 2nd night</td>
</tr>
<tr>
<td>Burstal, et al.</td>
<td>Total abdominal hysterectomy</td>
<td>70</td>
<td>1 vs 1:2</td>
<td>Cough P&lt;0.03 day 1; allodynia P&lt;0.05; shorter duration of PCA P&lt;0.005</td>
<td>No significant difference (NS)</td>
<td>Dysphoria, nausea, pruritus P&lt;0.006 in the ketamine group</td>
</tr>
<tr>
<td>Nesher, et al.</td>
<td>Transthoracic lung and heart</td>
<td>57</td>
<td>1.5 vs 1:5</td>
<td>P&lt;0.05 during 72 h; shorter duration of PCA P&lt;0.01</td>
<td>P&lt;0.05 during first 24 h</td>
<td>Desaturation and respiratory frequency P&lt;0.005</td>
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<tr>
<td>Murdoch, et al.</td>
<td>Total abdominal hysterectomy</td>
<td>40</td>
<td>1 vs 1:0.75</td>
<td>NS</td>
<td>NS</td>
<td>Pruritus P&lt;0.05</td>
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<td>Kollender, et al.</td>
<td>Orthopedic-oncological</td>
<td>57</td>
<td>1.5 vs 1:5</td>
<td>P&lt;0.05 throughout 96 h; shorter duration of PCA P&lt;0.05</td>
<td>P&lt;0.05</td>
<td>Wakefulness P&lt;0.001; urinary catheter dependence &gt;24 h and performance score P&lt;0.05</td>
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<tr>
<td>Reeves, et al.</td>
<td>Upper/lower abdominal laparotomy</td>
<td>71</td>
<td>1 vs 1:1</td>
<td>NS</td>
<td>NS</td>
<td>Cognitive function test at 48h P&lt;0.05 in the ketamine group</td>
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<tr>
<td>Unlugunc, et al.</td>
<td>Major Abdominal</td>
<td>58</td>
<td>0.4 vs 0.4:1</td>
<td>P&lt;0.001 at 15, 30, and 60 min</td>
<td>P&lt;0.001 at 12 and 24 h</td>
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<tr>
<td>Javery, et al.</td>
<td>Lumbar microdiscectomy</td>
<td>42</td>
<td>1 vs 1:1</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>Nausea, pruritus, urinary retention P&lt;0.05</td>
</tr>
<tr>
<td>Sveticic, et al.</td>
<td>Major orthopedic</td>
<td>352</td>
<td>1.5 vs 1.5:1.5</td>
<td>NS</td>
<td>NS</td>
<td></td>
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<tr>
<td>Nesher, et al.</td>
<td>Thoracotomy for CABG/lung resection</td>
<td>41</td>
<td>1.5 vs 1:5</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001 during the 1st and 2nd hour, 4 h PCA activation rate P&lt;0.001</td>
<td>Desaturation P&lt;0.01</td>
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<td>Hercock, et al.</td>
<td>Total abdominal hysterectomy</td>
<td>49</td>
<td>1 vs 1:1</td>
<td>NS</td>
<td>NS</td>
<td>Less sleepiness P&lt;0.05; doses of antiemetic P&lt;0.05</td>
</tr>
</tbody>
</table>

VAS: Visual Analogue Score; PCA: Patient Controlled Analgesia, CABG: Coronary Artery Bypass Graft
Figure 1: KETAMINE AND POSTOPERATIVE OPIOID CONSUMPTION

<table>
<thead>
<tr>
<th>Study name</th>
<th>Comparison</th>
<th>Outcome</th>
<th>Std diff in means and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lefebvre et al, 2005</td>
<td>Preoxygen</td>
<td>Total opioid</td>
<td></td>
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<tr>
<td>Aubrun et al, 2008</td>
<td>Preoxygen + PCA</td>
<td>Total opioid</td>
<td></td>
</tr>
<tr>
<td>Sahin et al, 2004</td>
<td>Preoxygen</td>
<td>Total opioid</td>
<td></td>
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<tr>
<td>Engelhardt et al, 2008</td>
<td>Preoxygen + Intraop</td>
<td>Total opioid</td>
<td></td>
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<tr>
<td>Jakesch et al, 2002</td>
<td>Preoxygen + Intraop</td>
<td>Total opioid</td>
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<tr>
<td>Katz et al, 2004</td>
<td>Intraop</td>
<td>Total opioid</td>
<td></td>
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<tr>
<td>Murdoch et al, 2002</td>
<td>Intraop + Postop</td>
<td>Total opioid</td>
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<td>Henkel et al, 1999</td>
<td>Postop</td>
<td>Total opioid</td>
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<tr>
<td>Lebrun et al, 2005</td>
<td>Postop</td>
<td>Total opioid</td>
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<td>Reeves et al, 2001</td>
<td>PCA</td>
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<td>Jensen et al, 2008</td>
<td>Preoxygen + PCA</td>
<td>Total opioid</td>
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<td>Hercock et al, 1999</td>
<td>Preoxygen + PCA</td>
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<td>Henkel et al, 1999</td>
<td>Preoxygen + Intraop</td>
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<td>Deng et al, 2009(3)</td>
<td>Preoxygen + Intraop + Postop</td>
<td>Total opioid</td>
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<td>Van Elstraete et al, 2004</td>
<td>Preoxygen + Intraop</td>
<td>Total opioid</td>
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<tr>
<td>Gamme et al, 2005</td>
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<td>Total opioid</td>
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