Low-Dose Ketamine and Perioperative Analgesia

Is it the Answer?

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Disclosures

- No financial relationships to disclose

- Will be referencing off-label usages(s) of pharmaceuticals or instrumentation within this presentation
Ketamine FDA-Approved
  • General anesthesia
  • Procedural sedation

Ketamine NOT FDA-Approved
  • Refractory cancer pain
  • Neuropathic pain
  • Acute postoperative pain
Learning Objectives

• Understand the analgesic mechanism of ketamine in the treatment of postoperative pain

• Discuss the potential treatment strategies and clinical benefits of low-dose ketamine

• Describe the use of low-dose ketamine as a rescue adjuvant in the postanesthesia care unit (PACU)
Postoperative Pain

Clinical Consequences

- Deep venous thrombosis
- Pulmonary embolism
- Coronary ischemia
- Pneumonia
- Poor wound healing
- Insomnia
- Postoperative delirium
- Chronic pain syndromes

- Delayed rehabilitation
- Prolonged Hospital LOS
- Decreased satisfaction

Pain = 5\textsuperscript{th} Vital Sign
Joint Commission Initiative

- Joint Commission
- Effective: 2001
- Declared PAIN as the 5\textsuperscript{th} Vital Sign
- Condition of Accreditation
  - Adequate assessment
  - Monitoring
- Pain management \textit{must} become part of all patient care activities
- \textbf{Speak-Up™ Campaign}

Joint Commission Pain Management Standards  
www.jointcommission.org
Postoperative Pain Experience: Results from a National Survey Suggest Postoperative Pain Continues to Be Undermanaged

Jeffrey L. Apfelbaum, MD*, Connie Chen, PharmD†, Shilpa S. Mehta, PharmD†, and Tong J. Gan, MD‡

*Department of Anesthesia and Critical Care, The University Chicago Hospitals, Chicago, Illinois; †Pharmacia Corp., Skokie, Illinois; and ‡Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina

Postoperative pain can have a significant effect on patient recovery. An understanding of patient attitudes and concerns about postoperative pain is important for identifying ways health care professionals can improve postoperative care. To assess patients’ postoperative pain experience and the status of acute pain management, we conducted a national study by using telephone questionnaires. A random sample of 250 adults who had undergone surgical procedures recently in the United States was obtained from National Family Opinion. Patients were asked about the severity of post-surgical pain, treatment, satisfaction with pain medication, patient education, and perceptions about postoperative pain and pain medications. Approximately 80% of patients experienced acute pain after surgery. Of these patients, 86% had moderate, severe, or extreme pain, with more patients experiencing pain after discharge than before discharge. Experiencing postoperative pain was the most common concern (59%) of patients. Almost 25% of patients who received pain medications experienced adverse effects; however, almost 90% of them were satisfied with their pain medications. Approximately two thirds of patients reported that a health care professional talked with them about their pain. Despite an increased focus on pain management programs and the development of new standards for pain management, many patients continue to experience intense pain after surgery. Additional efforts are required to improve patients’ postoperative pain experience.

(Anesth Analg 2003;97:534-40)
Postoperative Pain
1995 vs. 2003 vs. 2012

Patients with Postop Pain (%)

- Any Pain
  - Gan (2012): 86%
  - Apfelbaum (2003): 82%
  - Warfield (1995): 77%

- Slight
  - Gan (2012): 24%
  - Apfelbaum (2003): 13%
  - Warfield (1995): 19%

- Moderate
  - Gan (2012): 49%
  - Apfelbaum (2003): 47%
  - Warfield (1995): 45%

- Severe
  - Gan (2012): 23%
  - Apfelbaum (2003): 21%
  - Warfield (1995): 23%

- Extreme
  - Gan (2012): 8%
  - Apfelbaum (2003): 18%
  - Warfield (1995): 8%
Postoperative Analgesic THerapy Observational Study: Practice Patterns in Central and Southern Europe

- Prospective, cross-sectional, observational, multi-center
- Randomized hospitals in 7 countries (N=746 hospitals)
- No institutional training on pain management: 34%
- No postoperative pain protocols: 75%
- Pain not assessed: 34%
- Pain scores not documented: 56%
- Balanced analgesia: 71% (after major surgery)

Benhamou, Pain 2008

Patient Based National Survey on Postoperative Pain Management in France Reveals Significant Achievements and Persistent Challenges

- 76 surgical centers (N=1900 Adult patients)
- Postop pain protocols: 74%
- Pain assessed and documented: 94% (every 4 hrs)
- Severe pain: 51% (4% at rest)
- Regional anesthesia (Epidural or PNB): 7%

Fletcher, Pain 2008
Acute Pain Physiology

Major Contributors of Pain:

- **Phase I:**
  
  Afferent pain signals

- **Phase II:**
Major Contributors of Pain:

- **Phase I:**
  
  Afferent pain signals

- **Phase II:**
  
  Inflammatory response
Central Sensitization

CNS

Spinal Cord

Spinal Wind-up

Primary Hyperalgesia

Secondary Hyperalgesia

Surgical Trauma

Peripheral Sensitization

Inflammatory Mediators

Hydrogen Ions
Histamine
Norepinephrine
Potassium Ions
Bradykinin
Purines
Prostaglandins
5-HT
Leukotrienes
Cytokines
Nerve Growth Factor
Neuropeptides
Multimodal Perioperative Analgesia

- Opioids
  - Sole analgesic agent
    - Pain 30%
    - Side effects 80%
Opioids

- Respiratory depression
- Cardiovascular depression
- Nausea & vomiting
- Postoperative ileus
- Urinary retention
- Pruritus
- Sedation & dizziness
- Tolerance & dependence

NSAIDs

- Operative bleeding
- GI bleeding
- Renal dysfunction
- Allergic reactions
- Bronchospasm
- Hypertension
- Pedal edema
Multimodal Perioperative Analgesia

- Opioids
- Non-steroidal anti-inflammatories
- COX-II Inhibitors
- Gabapentin
- Acetaminophen
- Peripheral nerve blockade
- Periarticular local anesthetic injection
- Ketamine (low-dose)
- Cryotherapy
CNS

Gabapentin
Clonidine
Opioids

Dorsal Horn
(Interneuron Cells)

Dorsal Root
Ganglion

Local
Anesthetics
Cryotherapy

Spinal Cord

NSAIDs
Corticosteroids

Surgical
Trauma

Prostaglandins
Multimodal Perioperative Analgesia

- Opioids
- Non-steroidal anti-inflammatories
- COX-II Inhibitors
- Gabapentin
- Acetaminophen
- Peripheral nerve blockade
- Periarticular local anesthetic injection
- Ketamine (low-dose)
- Cryotherapy
Ketamine

- Phencyclidine derivative (1962)
- Commercial preparation
  - Racemic mixture $S$ (+) and $R$ (-)
- Short distribution and elimination half-lives ($t_{1/2} = 2.5$ hrs)
- Extensive hepatic cytochrome p450 metabolism
- Primary metabolite: Norketamine
  - 1/3 to 1/5 potency
- Renal and biliary excretion

Kohrs, Anesth Analg 1998
Ketamine

Pharmacodynamic Effect

- "Dissociative Anesthesia"
  - Thalamocortical - Limbic
- Cataleptic state
  - Open eyes
  - Slow nystagmus
  - Non-communicative
  - Increased skeletal muscle tone (hypertonus)
  - Purposeless movement
- Amnestic
- Intense analgesia
Pharmacodynamic Effect

- "Dissociative Anesthesia"
  - Thalamocortical - Limbic
- Cataleptic state
  - Open eyes
  - Slow nystagmus
  - Non-communicative
  - Increased skeletal muscle tone (hypertonus)
  - Purposeless movement

Reduces secondary hyperalgesia and prevents central sensitization from peripheral pain
1. Partial opioid receptor agonist
   • $\mu$ (analgesia)
   • $\sigma$ (dysphoria)

2. N-methyl-D-aspartate (NMDA) Antagonist
   • Readily crosses Blood-Brain Barrier
   • Antagonize glutamate & opioid activation of NMDA-r
A-delta and C-fiber Primary Pain Afferents
(Pre-synaptic)

Ketamine
(An antagonist)

NMDA
Activation

NK-1
Activation

Clonidine
Inhibition

GABA-r

Post-synaptic membrane

Interneuron
(Inhibitory signal modulation)

Opioids

Inhibit activation

GABA

ACh

Clonidine

Neostigmine

Released from descending inhibitory neurons

Norepinephrine

Peripheral activation

Glu

Sub P

Inhibit release

Clonidine

\( \alpha_2 \)

\( m-1 \)

\([\text{ACh}] \uparrow \)

\( \text{SST} \)

\( \text{GABA} \)
Analgesic Effect

1. Partial opioid receptor agonist
   - μ (analgesia)
   - σ (dysphoria)

2. N-methyl-D-aspartate (NMDA) Antagonist
   - Readily crosses Blood-Brain Barrier
   - Antagonize glutamate & opioid activation of NMDA-r

- Cortical and Spinal Effects

- **Analgesic Effect**: Somatic >> Visceral
Low-Dose Ketamine and Postoperative Analgesia
Low-Dose Ketamine: Dose-Response

- Prospective, Randomized, Double-blinded, Placebo-controlled
- N = 140
- Elective Outpatient Surgery (GA)
  - Hardware removal
  - Inguinal hernia
  - Breast or LN biopsy
  - CTR or Nerve decompression
- Randomized: Morphine (50 mcg/kg IV bolus)
  1. Placebo
  2. Ketamine (50 mcg/kg IV)
  3. Ketamine (75 mcg/kg IV)
  4. Ketamine (100 mcg/kg IV)

Suzuki, Anesth Analg 1999
Low-Dose Ketamine: Dose-Response

Morphine Use (mcg/kg)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Placebo</th>
<th>Ketamine 50 mcg/kg</th>
<th>Ketamine 75 mcg/kg</th>
<th>Ketamine 100 mcg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>150</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td><strong>P &lt; 0.05</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

40% reduction

* *
Low-Dose Ketamine: Dose-Response

VAS Pain Scores

- Placebo
- Ketamine 50
- Ketamine 75
- Ketamine 100

PACU Arrival
30 min
PACU Discharge

* P < 0.05

35%
Low-Dose Ketamine: Dose-Response

NO DIFFERENCES

• Sedation
• Nausea & Vomiting
• Time to Fluid Intake
• Phase I (PACU) Recovery

• Time to Discharge
• Cognitive Function
• Mood Disturbance
• Dissociative State (Perception)

Suzuki, Anesth Analg 1999
Low-Dose Ketamine: Timing of Administration

- Prospective, Randomized, Double-blind, Placebo-controlled
- N = 45
- ACL Reconstruction
- Standardized General Anesthetic (Sufentanil infusion)

<table>
<thead>
<tr>
<th></th>
<th>PRE-INCISION</th>
<th>PRE-CLOSURE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CONTROL</strong></td>
<td>Normal Saline</td>
<td>Normal Saline</td>
</tr>
<tr>
<td><strong>PRE-</strong></td>
<td>Ketamine (150mcg/kg)</td>
<td>Normal Saline</td>
</tr>
<tr>
<td><strong>POST-</strong></td>
<td>Normal Saline</td>
<td>Ketamine (150mcg/kg)</td>
</tr>
</tbody>
</table>

Menigaux, Anesth Analg 2000
**Low-Dose Ketamine: Timing of Administration**

- **Morphine Use (mg)**
  - **Control**
  - **Pre-**
  - **Post-**

<table>
<thead>
<tr>
<th>Time</th>
<th>Control</th>
<th>Pre-</th>
<th>Post-</th>
<th>P &lt; 0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
24 Hour Post-Op Rehabilitation

Degrees of Flexion

Morphine Use (mg)

* P < 0.05
<table>
<thead>
<tr>
<th>Side-Effect</th>
<th>Control</th>
<th>Pre-</th>
<th>Post-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Retention</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nausea &amp; Vomiting</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory Depression</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sedation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diplopia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NS between groups
Low-Dose Ketamine: Timing of Administration

Conclusions

- Delays first request for analgesics (3-fold)
- Produces a significant (50%) reduction in morphine use within the first 48 hrs
- Facilitates knee mobilization (24 hrs)
- Effects independent of the timing of intra-operative administration

Menigaux, Anesth Analg 2000
Low-Dose Ketamine: Monitored Anesthesia Care

- Prospective, randomized, double-blinded
- N = 40
- Elective ambulatory procedures (M.A.C.)
  - Tubal ligation
  - Cervical conization
  - Ventral hernias
  - Biopsies
  - Skin lesions
  - Wrist/hand

- Randomized:
  1. Propofol (30 - 50 mcg/kg/min)
  2. Propofol + Ketamine (3.0 - 5.0 mcg/kg/min)

Mortero, Anesth Analg 2001
Low-Dose Ketamine: Monitored Anesthesia Care

Perioperative Endpoints
- Intra-op ventilation
- Post-op sedation
- Pain intensity
- Perceptual changes
- Mood states
- Cognition
- Thought process

Discharge Follow-up (5 Days)
- Pain intensity
- Opioid requirements
- Physical activity
- Patient satisfaction

Mortero, Anesth Analg 2001
Intraoperative Ventilation

**End Tidal PCO₂**

- 60
- 50
- 40
- 30
- 20
- 10

**Propofol**

- 15 min
- 30 min
- 45 min
- 60 min

**Prop + Ket**

* P < 0.0001
Postoperative Mood States

<table>
<thead>
<tr>
<th>Mood VAS</th>
<th>Elation</th>
<th>Agreeable</th>
<th>Confidence</th>
<th>Energy</th>
<th>Clearheaded</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Propofol</strong></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td><strong>Prop + Ket</strong></td>
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</table>
Postoperative Analgesia

![Graph showing pain scores and days to normalization for Propofol and Propofol + Ketamine treatments.](image)

- **VAS Pain Score**: Higher scores indicate more pain.
- **No rest pain**: Lower scores for Propofol indicate less pain.
- **No pain with activity**: Similar scores for both treatments, indicating minimal impact on activity.
- **Resume normal activity**: Scores for both treatments show they can resume activity.

* P < 0.0001
Conclusions

• Provided adequate sedation
• Improved ventilation
• Enhanced mood state
• No perceptual changes
• Earlier recovery of cognition
• Superior Acute and Extended Pain Relief
• Faster return to normal activities

Mortero, Anesth Analg 2001
Low-Dose Ketamine: Knee Arthroscopy

• Prospective, Randomized, Double-blinded
• N = 50
• Outpatient knee arthroscopy
• Standardized General Anesthesia
  • Propofol Infusion
  • Alfentanil (20 mcg/kg)
  • 60% Nitrous
• Randomized: (Post-Induction Administration)
  • Control: Normal Saline
  • Ketamine: 150 mcg/kg IV
    • Bupivacaine 0.5% (20cc)
    • Morphine (5 mg)

Menigaux, Anesth Analg 2001
• **PACU** (Aldrete score of 9)

• **Ambulatory Unit** (6 hrs)
  - Oriented x 3
  - Stable Vitals
  - Pain Control
  - Absence of Nausea
  - Ability to Void
  - Ability to Ambulate

• **Analgesia**
  - PACU: **Morphine 3 mg prn (VAS ≤ 3)**
  - Ambulatory Unit: **Naproxen 550 mg p.o.**
  - Home: **Naproxen b.i.d. and Propoxyphene q 6 hrs prn**

• **Discharge**: Daily Questionnaire x 3 days
<table>
<thead>
<tr>
<th></th>
<th>Ketamine (n=25)</th>
<th>Control (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sedation Scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 0</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Time 15</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Time 30</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Aldrete (Score = 9)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 15</td>
<td>100%</td>
<td>96%</td>
</tr>
<tr>
<td>Time 30</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Home Readiness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 120</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Ambulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 15</td>
<td>88%</td>
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<tr>
<td><strong>Morphine (% require)</strong></td>
<td>12%</td>
<td>36% *</td>
</tr>
<tr>
<td><strong>Outpatient Propoxyphene (tabs)</strong></td>
<td>13</td>
<td>27 *</td>
</tr>
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<td>Control (n=25)</td>
</tr>
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PACU-Ambulatory Unit
VAS Pain Scores

Control Group
Ketamine Group

* P < 0.05
Rest VAS Pain Scores

* P < 0.01
Rehabilitation VAS Pain Scores

Control Group
Ketamine Group

* P < 0.01
Distribution of Ambulation
Post-Op Day 1

* P < 0.05
Low-Dose Ketamine: Knee Arthroscopy

No Differences

- Nausea
- Vomiting
- Dysphoria
- Hallucinations
- Diplopia
- Cognitive or Memory impairments
- Respiratory Depression

Menigaux, Anesth Analg 2001
Conclusions

- Ketamine + Multi-modal Analgesic regimen
- Less Postoperative Pain
  - VAS Pain Scores
  - Analgesic Requirements
- Extend 48 hours Post-op
- Provide Analgesia at Rest & with Movement
- Facilitates Early Rehabilitation

Menigaux, Anesth Analg 2001
Small-Dose Ketamine Infusion Improves Postoperative Analgesia and Rehabilitation After Total Knee Arthroplasty

Frédéric Adam, MD, Marcel Chauvin, MD, Bertrand Du Manoir, MD, Mathieu Langlois, MD, Daniel I. Sessler, MD, and Dominique Fletcher, MD

Departments of Anesthesia and INSERM E 332, Hôpital Ambroise Pare, Assistance Publique-Hôpitaux de Paris, 92100 Boulogne, France; Hôpital Raymond Poincaré, Assistance Publique Hôpitaux de Paris, 92428 Garches, France; and the Outcomes Research™ Institute and Departments of Anesthesiology and Pharmacology, University of Louisville, Louisville, Kentucky

We designed this study to evaluate the effect of small-dose IV ketamine in combination with continuous femoral nerve block on postoperative pain and rehabilitation after total knee arthroplasty. Continuous femoral nerve block was started with 0.3 mL/kg of 0.75% ropivacaine before surgery and continued in the surgical ward for 48 h with 0.2% ropivacaine at a rate of 0.1 mL · kg⁻¹ · h⁻¹. Patients were randomly assigned to receive an initial bolus of 0.5 mg/kg ketamine followed by a continuous infusion of 3 μg · kg⁻¹ · min⁻¹ during surgery and 1.5 μg · kg⁻¹ · min⁻¹ for 48 h (ketamine group) or an equal volume of saline (control group). Additional postoperative analgesia was provided by patient-controlled IV morphine. Pain scores and morphine consumption were recorded over 48 h. The maximal degree of active knee flexion tolerated was recorded daily until hospital discharge. Follow-up was performed 6 wk and 3 mo after surgery. The ketamine group required significantly less morphine than the control group (45 ± 20 mg versus 69 ± 30 mg; P < 0.02). Patients in the ketamine group reached 90° of active knee flexion more rapidly than those in the control group (at 7 [5–11] versus 12 [8–45] days, median [25%–75% interquartile range]; P < 0.03). Outcomes at 6 wk and 3 mo were similar in each group. These results confirm that ketamine is a useful analgesic adjuvant in perioperative multimodal analgesia with a positive impact on early knee mobilization. No patient in either group reported sedation, hallucinations, nightmares, or diplopia, and no differences were noted in the incidence of nausea and vomiting between the two groups.

(Anesth Analg 2005;100:475–80)
Ketamine and THA

Prospective, Randomized, Blinded
N=154
Total Hip Arthroplasty

Standardized GETA
- I.V. Acetaminophen
- I.V. Ketoprofen
- I.V. Morphine (PCA)

Randomized
1. Ketamine 0.5 mg/Kg (Pre-incision) Infusion (2 mcg/kg/min) x 24 hr
2. Saline bolus + infusion

Patients with Pain after THA (%)

* P = 0.008

Remerand, Anesth Analg 2009
**Postoperative Hyperalgesia**

- Prospective, Randomized, Double-blinded
- N=20
- Donor nephrectomy
- Standardized GETA
- Randomized
  1. **Ketamine** 0.5 mg/kg I.V.
     - Infusion 2 mcg/kg/min x 24 hrs
     - Infusion 1 mcg/kg/min x 24 hrs
  2. **Saline control**
- **Endpoints**: Punctate *mechanical hyperalgesia*
  - Mechanical stimuli causing “wind-up pain”

Wind-Up Pain

Day 1                    Day 3                     Day 7

Patients with Wind-up Pain

Placebo (N=-10)
Ketamine (N=10)

* P<0.01
Postoperative Hyperalgesia

Area of Hyperalgesia (cm²)

Days after Surgery

Day 1                    Day 3                     Day 7

* P<0.01
Von Frey Filament

Surgical Incision: Median length 26 cm

Area of Hyperalgesia

Hyperalgesia and Chronic Pain

Area of Hyperalgesia at 48 hr (cm²)

Incidence of pain at 6 months

R = 0.81
P < 0.001

Eisenach, Reg Anesth Pain Med 2006
Ketamine and Chronic Pain

- Prospective, randomized, double-blinded, placebo
- N=165
- Opiate-dependent patients
  - Chronic back pain x 3 months; Daily opiate use x 6 wks
- Major lumbar spine surgery
- Randomized:
  1. Ketamine (0.5 mg/kg I.V. bolus + 10 mcg/kg/min infusion)
     - Induction to Wound closure
  2. Saline
- Endpoints: Opioid requirements, VAS pain scores
  Adverse side-effects (6-wk follow-up)

Loftus, Anesthesiology 2010
Chronic Pain: Opioid Requirements

Morphine Equivalents (mg)

<table>
<thead>
<tr>
<th></th>
<th>PACU</th>
<th>24 hrs</th>
<th>48 hrs</th>
<th>6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>40</td>
<td>150</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>Ketamine</td>
<td>30</td>
<td>100</td>
<td>150</td>
<td>200</td>
</tr>
</tbody>
</table>

Morphine Equivalents (mg/hr)

<table>
<thead>
<tr>
<th></th>
<th>PACU</th>
<th>24 hrs</th>
<th>48 hrs</th>
<th>6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>0.5</td>
<td>2.0</td>
<td>3.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Ketamine</td>
<td>0.4</td>
<td>1.5</td>
<td>2.5</td>
<td>3.5</td>
</tr>
</tbody>
</table>

* P<0.05

Loftus, Anesthesiology 2010
Chronic Pain: VAS Pain Scores

<table>
<thead>
<tr>
<th></th>
<th>PACU</th>
<th>24 hrs</th>
<th>48 hrs</th>
<th>6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Ketamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* P<0.05

Loftus, Anesthesiology 2010
Low-Dose Ketamine: Pediatric Surgery

- Prospective, Randomized Clinical Trial
- N = 50
- Tonsillectomy (Standardized GA)
- Randomization Pre-med:
  - Ketamine 0.1 mg/kg I.M.
  - Placebo
  - 20-min before induction
- Rectal diclofenac (2 mg/kg)
- Fentanyl (1 mcg/kg IV)

Elhakim, Acta Anaesth Scand 2003
Table 2

Postoperative pain relief observation. Values are expressed as median (range), or number, n (%).

<table>
<thead>
<tr>
<th>Time to awakening (min)</th>
<th>Saline n = 25</th>
<th>Ketamine n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 (14–28)</td>
<td>21 (18–31)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time to first analgesic (min)</th>
<th>Saline n = 25</th>
<th>Ketamine n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>84 (28–108)</td>
<td>130* (53–211)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Morphine titration, n (%)</th>
<th>Saline n = 25</th>
<th>Ketamine n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9 (36)</td>
<td>3* (12)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain assessed by the nurse at 6 h: resting</th>
<th>Saline n = 25</th>
<th>Ketamine n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.5 (2–6)</td>
<td>1.5* (0–3)</td>
</tr>
<tr>
<td></td>
<td>5.5 (1–7)</td>
<td>3.5* (1–5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain assessed by the patient at 6 h: resting</th>
<th>Saline n = 25</th>
<th>Ketamine n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.5 (1–7)</td>
<td>1.5* (0–3)</td>
</tr>
<tr>
<td></td>
<td>5.0 (3–8)</td>
<td>3.5* (2–6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain assessed by the patient at 12 h: resting</th>
<th>Saline n = 25</th>
<th>Ketamine n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.0 (0–6)</td>
<td>1.0** (0–4)</td>
</tr>
<tr>
<td></td>
<td>3.5 (1–8)</td>
<td>1.5** (1–6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain assessed by the patient at 24 h: resting</th>
<th>Saline n = 25</th>
<th>Ketamine n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.7 (1–5)</td>
<td>0.5** (0–3)</td>
</tr>
<tr>
<td></td>
<td>2.5 (1–7)</td>
<td>1.0** (0.5–4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory rate at 6 h</th>
<th>Saline n = 25</th>
<th>Ketamine n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18 (14–22)</td>
<td>13* (10–18)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory rate at 12 h</th>
<th>Saline n = 25</th>
<th>Ketamine n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18 (14–20)</td>
<td>14* (10–18)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory rate at 24 h</th>
<th>Saline n = 25</th>
<th>Ketamine n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17 (14–19)</td>
<td>16 (14–20)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient cooperation: ability to use visual analogue toy, n (%)</th>
<th>Saline n = 25</th>
<th>Ketamine n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>at 1 h</td>
<td>4 (16)</td>
<td>6 (24)</td>
</tr>
<tr>
<td>at 6 h</td>
<td>18 (72)</td>
<td>23 (92)</td>
</tr>
<tr>
<td>at 12–24 h</td>
<td>25 (100)</td>
<td>25 (100)</td>
</tr>
</tbody>
</table>

*P < 0.05, **P < 0.01.
Low-Dose Ketamine: Pediatric Surgery

Side-Effects

• No differences in N/V
• No reports of adverse effects
  • Dysphoria
  • Hallucinations
  • Diplopia
  • Bad dreams
  • Psychological sequelae

Elhakim, Acta Anaesth Scand 2003
Low-Dose Ketamine: Rescue Analgesia

- Prospective, Randomized, Double-blinded
- N=245
- General surgical patients
- PACU with severe pain (VAS ≥ 6)
  - Despite >0.1 mg/kg morphine IV last 30 min
- Randomized: (Up to 3 boluses)
  1. Morphine 30 mcg/kg IV + Saline
  2. Morphine 15 mcg/kg IV + Ketamine 250 mcg/kg

Weinbroum, Anesth Analg 2003
PACU Pain Scores

![Graph showing pain scores over time for Morphine+Saline and Morphine+Ketamine treatments.](image)
Respirations and Sedation

Graph showing changes in breaths per minute and SpO₂ (%) over time for two conditions: Morphine+Saline and Morphine+Ketamine.
Wakefulness and Well-Being

![Graph showing changes in wakefulness and feeling over time after injection.](image-url)
Ketamine: Rescue Analgesia

Side-Effects

Morphine Group
• More nausea & vomiting (38% vs. 12%)
• More pharmacologic interventions (nausea + pain)

Ketamine Group
• Light-headed sensation x 1-2 min (7% vs. 0%)
• One (0.7%) patient experienced a “bad-dream”
  • Required 2-doses

Weinbroum, Anesth Analg 2003
Limitations of Ketamine

Perioperative Ketamine Does Not Prevent Chronic Pain After Thoracotomy

- Prospective, Randomized, Placebo-Controlled Trial assessing chronic neuropathic pain
- N = 86
- Randomized
  1. Ketamine 1 mg/kg at induction
  2. Ketamine 1 mg/kg/hr (surgery) + 1 mg/kg (over 24 hr.)
  3. Normal saline (Placebo)
- No difference in neuropathic pain at 6 wk and 4 mo follow-up

Dualé, European J Pain 2009
Limitations of Ketamine

Low-Dose Ketamine with Multimodal Postcesarean Delivery Analgesia: A Randomized Controlled Trial

• Prospective, Randomized, Placebo-Controlled Trial assessing pain after Cesarean Delivery
• N = 174
• Spinal anesthesia (Bupiv + Fentanyl + Morphine)
• Randomized
  1. Ketamine 10 mg I.V. after delivery
  2. Saline (Placebo)
• No analgesic benefits identified at 24, 48, or 72 hrs

Ketamine as Adjuvant Analgesic to Opioids: A Quantitative and Qualitative Systematic Review

Kathirvel Subramaniam, MD, Balachundhar Subramaniam, MD, and Richard A. Steinbrook, MD

From the Department of Anesthesiology, Critical Care & Pain Management, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

Animal studies on ketamine and opioid tolerance have shown promising results. Clinical trials have been contradictory. We performed a systematic review of randomized, double-blind clinical trials of ketamine added to opioid analgesia. Thirty-seven trials with 51 treatment arms and 2385 patients were included. Studies were divided into 5 subgroups: IV ketamine as single dose (n = 11), continuous infusion (n = 11), patient-controlled analgesia (PCA) (n = 6), epidural ketamine with opioids (n = 8), and studies in children (n = 4). Outcome measures included pain scores, time to first request for analgesia, supplemental analgesics, and adverse events. Efficacy was estimated by statistical significance (P < 0.05) of outcome measures as reported in studies and also by calculation of weighted mean difference for pain scores during the first 24 h after surgery. As compared to morphine alone, IV PCA with ketamine and morphine did not improve analgesia. Intravenous infusion of ketamine decreased IV and epidural opioid requirements in 6 of 11 studies. A single bolus dose of ketamine decreased opioid requirements in 7 of 11 studies. Five of 8 trials with epidural ketamine showed beneficial effects. Adverse effects were not increased with small dose ketamine. We conclude that small dose ketamine is a safe and useful adjuvant to standard practice opioid-analgesia.

(Anesth Analg 2004;99:482–95)

Perioperative Ketamine

1. Single-dose Ketamine
2. Continuous infusion
3. Patient-controlled analgesia (with morphine)
## Single-Dose Ketamine

<table>
<thead>
<tr>
<th>Study</th>
<th>WMD (random)</th>
<th>Weight %</th>
<th>WMD (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>Dahl et al-Post (49)</td>
<td></td>
<td>5.38</td>
<td>-0.90 [-1.84, 0.04]</td>
</tr>
<tr>
<td>Dahl et al-Pre (49)</td>
<td></td>
<td>5.61</td>
<td>0.00 [-0.87, 0.87]</td>
</tr>
<tr>
<td>Kudoh et al (51)</td>
<td></td>
<td>7.24</td>
<td>-0.90 [-1.24, -0.56]</td>
</tr>
<tr>
<td>Mathisen et al-Post (52)</td>
<td></td>
<td>6.69</td>
<td>-0.80 [-1.35, -0.25]</td>
</tr>
<tr>
<td>Mathisen et al-Pre (52)</td>
<td></td>
<td>6.83</td>
<td>0.20 [-0.30, 0.70]</td>
</tr>
<tr>
<td>Menigaux et al-Pre (47)</td>
<td></td>
<td>4.39</td>
<td>-0.50 [-1.75, 0.75]</td>
</tr>
<tr>
<td>Menigaux et al (46)</td>
<td></td>
<td>6.49</td>
<td>-1.10 [-1.71, -0.49]</td>
</tr>
<tr>
<td>Menigaux et al-Post (47)</td>
<td></td>
<td>4.39</td>
<td>-0.50 [-1.75, 0.75]</td>
</tr>
<tr>
<td>Roytblat et al (48)</td>
<td></td>
<td>6.01</td>
<td>-1.00 [-1.76, -0.24]</td>
</tr>
<tr>
<td>Suzuki et al-50ug (45)</td>
<td></td>
<td>7.10</td>
<td>-0.80 [-1.20, -0.40]</td>
</tr>
<tr>
<td>Suzuki et al-100ug (45)</td>
<td></td>
<td>7.10</td>
<td>-1.70 [-2.10, -1.30]</td>
</tr>
<tr>
<td>Suzuki et al-75ug (45)</td>
<td></td>
<td>7.20</td>
<td>-1.80 [-2.16, -1.44]</td>
</tr>
<tr>
<td>Weinbroum (50)</td>
<td></td>
<td>7.42</td>
<td>-2.20 [-2.45, -1.95]</td>
</tr>
<tr>
<td>Lehmann et al (53)</td>
<td></td>
<td>5.77</td>
<td>-0.22 [-1.05, 0.61]</td>
</tr>
<tr>
<td>Xie et al (54)</td>
<td></td>
<td>7.23</td>
<td>-0.77 [-1.12, -0.42]</td>
</tr>
<tr>
<td>Heinke and Grimm (39)</td>
<td></td>
<td>5.15</td>
<td>0.41 [-0.60, 1.42]</td>
</tr>
</tbody>
</table>

Favours treatment Favours control

**Significant Benefit**
Continuous Infusion Ketamine

Significant Benefit
Ketamine+Morphine PCA

No Beneficial Effect
Prospective, randomized, double-blinded studies

N = 11 studies (887 patients)

Combined Ketamine + Opioid PCA

Orthopedic or Abdominal Surgery = No Benefit

Thoracic Surgery = Benefit

Caution: Large heterogeneity + Small sample sizes
Cochrane Review

- Randomized Controlled Trials (Adult patients)
- Independent quality and validity assessments (2 Reviewers)
- **Endpoints:**
  1. VAS Pain scores
  2. Opioid requirements
  3. Adverse side-effects
- 37 trials
- 2240 patients
- Multiple surgical procedures
- 27 of 37 trials
- Perioperative sub-anesthetic doses of ketamine
- **Reduced** (1) Need for rescue analgesia;
  (2) VAS pain scores; or
  (3) Both
• Ketamine reduced **24-hr opioid requirements and PONV**

• **Adverse events: Mild-to-Absent**
Ketamine and Postop Analgesia: Summary

- Low-dose Ketamine effective analgesic agent (Adjuvant)
- **Single-Dose:** 0.15-0.4 mg/kg I.V.  **Infusion:** 0.1-0.3 mg/kg/hr
- Significantly improves VAS pain scores
- Reduces opioid requirements by 40-60%
- Decreased risk of PONV, Sedation, and Hypoventilation
- May provide earlier hospital discharge and improved rehabilitation
- Minimal psychomimetic effects