Low-Dose Ketamine and Postoperative Analgesia

Is it the Answer?

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Ketamine FDA-Approved

- General anesthesia
- Procedural sedation

Ketamine NOT FDA-Approved

- Refractory cancer pain
- Neuropathic pain
- Acute postoperative pain
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

Breivik, Eur J Anaesthesiol 1998
Pain = 5\textsuperscript{th} Vital Sign

Joint Commission Initiative

- Joint Commission
- Effective: 2001
- Declared \textbf{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
Acute Pain Physiology

Major Contributors of Pain:

• Phase I: Afferent pain signals

• Phase II: Inflammatory response
Cerebral cortex

A-δ and C-fibers

Spinal cord

Traumatic injury
Multimodal Perioperative Analgesia

- Opioids
- Sole analgesic agent
  - Pain 30%
  - Side effects 80%
<table>
<thead>
<tr>
<th><strong>Opioids</strong></th>
<th><strong>NSAIDs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory depression</td>
<td>Operative bleeding</td>
</tr>
<tr>
<td>Cardiovascular depression</td>
<td>GI bleeding</td>
</tr>
<tr>
<td>Nausea &amp; vomiting</td>
<td>Renal dysfunction</td>
</tr>
<tr>
<td>Postoperative ileus</td>
<td>Allergic reactions</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Sedation &amp; dizziness</td>
<td>Pedal edema</td>
</tr>
<tr>
<td>Tolerance &amp; dependence</td>
<td></td>
</tr>
</tbody>
</table>
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 ($t_{\frac{1}{2}} = 2.5\ hrs$)

Kohrs, Anesth Analg 1998
Ketamine

- Phencyclidine derivative (1962)
- Commercial preparation
  - Racemic mixture S (+) and R (-)
- Short distribution and elimination half-lives \( t_{1/2} = 2.5 \text{ hrs} \)
- 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
Ketamine

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
Analgesic Effect

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

• 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)

- Placebo
- Ketamine 50 mcg/kg
- Ketamine 75 mcg/kg
- Ketamine 100 mcg/kg

* P < 0.05

40%
Low-Dose Ketamine: Dose-Response

- Placebo
- Ketamine 50
- Ketamine 75
- Ketamine 100

* 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>CONTROL</td>
<td>Normal Saline</td>
<td>Normal Saline</td>
</tr>
<tr>
<td>PRE-</td>
<td>Ketamine (150mcg/kg)</td>
<td>Normal Saline</td>
</tr>
<tr>
<td>POST-</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) vs. Time

- **Control**
- **Pre-**
- **Post-**

- **24 hrs**
- **48 hrs**

* P < 0.01
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
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: 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</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=25)</td>
<td>(n=25)</td>
</tr>
<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>
<td>68%</td>
</tr>
<tr>
<td>Time 30</td>
<td>100%</td>
<td>96%</td>
</tr>
<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>
<tr>
<td></td>
<td>Ketamine (n=25)</td>
<td>Control (n=25)</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------</td>
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</tr>
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</tbody>
</table>
PACU-Ambulatory Unit

VAS Pain Scores

Control Group
Ketamine Group

* P < 0.05
Rest VAS Pain Scores

Control Group
Ketamine Group

* P < 0.01
Rehabilitation VAS Pain Scores

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group</td>
<td>Ketamine Group</td>
<td></td>
</tr>
</tbody>
</table>

* 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
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

* P = 0.008
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

Days after Surgery

- Day 1
- Day 3
- Day 7

Patients with Wind-up Pain

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

* P<0.01
Postoperative Hyperalgesia

Days after Surgery

Area of Hyperalgesia (cm²)

Day 1                    Day 3                     Day 7

* P<0.01
Surgical Incision: Median length 26 cm

Area of Hyperalgesia

Von Frey Filament

Hyperalgesia and Chronic Pain

![Graph showing the relationship between Incidence of pain at 6 months and Area of Hyperalgesia at 48 hr (cm²).](image)

\[ R = 0.81 \]
\[ P < 0.001 \]

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) vs Morphine Equivalents (mg/hr)**

- **Saline**
- **Ketamine**

<table>
<thead>
<tr>
<th>Time</th>
<th>Saline</th>
<th>Ketamine</th>
<th>P&lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hrs</td>
<td></td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>48 hrs</td>
<td></td>
<td></td>
<td>37%</td>
</tr>
<tr>
<td>6 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* P<0.05

Loftus, Anesthesiology 2010
Chronic Pain: VAS Pain Scores

Loftus, Anesthesiology 2010

* P<0.05
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
Postoperative Pain Scores

**VAS Pain Scores**

12-hour

- Ketamine
- Placebo

1-hour

* P < 0.05
Table 2

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

<table>
<thead>
<tr>
<th></th>
<th>Saline n = 25</th>
<th>Ketamine n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to awakening (min)</td>
<td>20 (14–28)</td>
<td>21 (18–31)</td>
</tr>
<tr>
<td>Time to first analgesic (min)</td>
<td>84 (28–108)</td>
<td>130* (53–211)</td>
</tr>
<tr>
<td>Morphine titration, n (%)</td>
<td>9 (36)</td>
<td>3* (12)</td>
</tr>
<tr>
<td>Pain assessed by the nurse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 6 h: resting</td>
<td>2.5 (2–6)</td>
<td>1.5* (0–3)</td>
</tr>
<tr>
<td>at 6 h: drinking</td>
<td>5.5 (1–7)</td>
<td>3.5* (1–5)</td>
</tr>
<tr>
<td>Pain assessed by the patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 6 h: resting</td>
<td>2.5 (1–7)</td>
<td>1.5* (0–3)</td>
</tr>
<tr>
<td>at 6 h: drinking</td>
<td>5.0 (3–8)</td>
<td>3.5* (2–6)</td>
</tr>
<tr>
<td>at 12 h: resting</td>
<td>2.0 (0–6)</td>
<td>1.0** (0–4)</td>
</tr>
<tr>
<td>at 12 h: drinking</td>
<td>3.5 (1–8)</td>
<td>1.5** (1–6)</td>
</tr>
<tr>
<td>at 24 h: resting</td>
<td>1.7 (1–5)</td>
<td>0.5** (0–3)</td>
</tr>
<tr>
<td>at 24 h: drinking</td>
<td>2.5 (1–7)</td>
<td>1.0** (0.5–4)</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 6 h</td>
<td>18 (14–22)</td>
<td>13* (10–18)</td>
</tr>
<tr>
<td>at 12 h</td>
<td>18 (14–20)</td>
<td>14* (10–18)</td>
</tr>
<tr>
<td>at 24 h</td>
<td>17 (14–19)</td>
<td>16 (14–20)</td>
</tr>
<tr>
<td>Patient cooperation: ability to use visual analogue toy, n (%)</td>
<td></td>
<td></td>
</tr>
<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
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 PACU Pain Scores over time for Morphine + Saline and Morphine + Ketamine treatments.](image)
Respirations and Sedation

![Graph showing Respirations and Sedation](image-url)
Wakefulness and Well-Being

![Graph showing the change in wakefulness and feeling over time after injection of Morphine+Saline and Morphine+Ketamine.](Image)
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
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

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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

**Significant Benefit**

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

Favours treatment | Favours control
Continuous Infusion Ketamine

**Significant Benefit**
### Ketamine+Morphine PCA

<table>
<thead>
<tr>
<th>Study</th>
<th>WMD (random) 95% CI</th>
<th>Weight %</th>
<th>WMD (random) 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Bursta et al (31)</td>
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<td>17.11</td>
<td>-0.70 [-1.80, 0.40]</td>
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<td>Hercock et al (29)</td>
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<td>21.66</td>
<td>0.10 [-0.66, 0.86]</td>
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<tr>
<td>Javery et al (33)</td>
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<td>18.79</td>
<td>-2.20 [-3.17, -1.23]</td>
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<tr>
<td>Reeves et al (28)</td>
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<td>15.10</td>
<td>0.49 [-0.78, 1.76]</td>
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<tr>
<td>Unlugenc et al (32)</td>
<td></td>
<td>27.34</td>
<td>-0.38 [-0.65, -0.11]</td>
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<tr>
<td></td>
<td></td>
<td>100.00</td>
<td>-0.54 [-1.26, 0.18]</td>
</tr>
</tbody>
</table>

**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

Acute & Chronic