SEEING KETAMINE IN A NEW LIGHT
BobbieJean Sweitzer, M.D., FACP
Professor of Anesthesiology
Director of Perioperative Medicine
Northwestern University
Bobbie.Sweitzer@northwestern.edu
I have no disclosures

LEARNING OBJECTIVES
At the conclusion of this activity, participants should be able to:
• Understand the role of ketamine as an anesthetic
• Understand the role of ketamine as a sedative
• Use ketamine as an adjunct for analgesia
• Incorporate ketamine into your practice

Off-Label Use
Ketamine FDA-Approved
• General anesthesia
• Procedural sedation
Ketamine NOT FDA-Approved
• Acute postoperative pain
• Psychiatric disease

KETAMINE
• Developed in search of an “ideal anesthetic”
• Introduced as a dissociative anesthetic in 1964
• Phencyclidine derivative
• Only “total anesthetic in a bottle”
• Hypnosis
• Analgesia
• Amnesia
• Immobility
• Inexpensive

KETAMINE AS A RECREATIONAL DRUG
• WAS the most common reason to burglarize veterinarian practices; now its tramadol
• “Special K” on the streets
• How bad can a drug be if it is used recreationally???

Pet Connection: Opioid Addicts Score Drugs From the Local Vet

KETAMINE
• Can be given IV, SC, IM, epidural, intrathecal, intraarticular, intranasal, oral and topically
• Attenuates sevoflurane induced emergence agitation in pediatric patients
• Anti-inflammatory effects
• May have anti-tumor effects
• Neuroprotective effects
• Prevents post-anesthesia shivering
• As co-induction agent: stable hemodynamics, reduced pain of propofol injection

Pet Connection: Opioid Addicts Score Drugs From the Local Vet

Pet Connection: Opioid Addicts Score Drugs From the Local Vet

Paediatr Anaesth. 2008;18:1114–5
MECHANISM OF ACTION
• Non-competitive NMDA receptor antagonist
• Partial opioid receptor agonist
• Short distribution and elimination (half-life 2 ½ hrs)
• LOW DOSE maximizes benefits; decreases side effects
• Adjunct to opioids, sedatives or local anesthetics
• Improves safety of sedation
• Modulates opioid tolerance
• Prevents development of increased pain sensitization

THE EFFECT OF KETAMINE VERSUS FENTANYL ON THE INCIDENCE OF EMERGENCE AGITATION AFTER SEVOFLURANE ANESTHESIA IN PEDIATRIC PATIENTS

Table 3: Incidence of emergence agitation

<table>
<thead>
<tr>
<th>Group</th>
<th>K (H28)</th>
<th>F (H28)</th>
<th>C (H28)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score 1</td>
<td>32 (8)</td>
<td>30 (7)</td>
<td>6 (15)</td>
<td></td>
</tr>
<tr>
<td>Score 2</td>
<td>1 (3)</td>
<td>3 (1-3)</td>
<td>17 (14-2)</td>
<td></td>
</tr>
<tr>
<td>Score 3</td>
<td>6 (15)</td>
<td>7 (12)</td>
<td>12 (3)</td>
<td></td>
</tr>
<tr>
<td>Score 4</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (12-3)</td>
<td></td>
</tr>
<tr>
<td>Emergence agitation</td>
<td>3 (1-3)</td>
<td>7 (12)</td>
<td>17 (12-3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Comparison between intranasal dexmedetomidine and intranasal ketamine as premedication for procedural sedation in children undergoing MRI: a double-blind, randomized, placebo-controlled trial

KETAMINE PREMEDICATION MORE EFFECTIVE THAN MIDAZOLAM TO PREVENT EMERGENCE AGITATION AFTER SEVO IN CHILDREN

INTRAOPERATIVE USE OF KETAMINE
• Maintenance of respiratory drive
• Airway patency
• Deep sedation without need for supplemental O2
• Advantages for facial, airway & OBA procedures
• Analgesia
• Amnesia
• Immobility
• Reduced opioid requirements/tolerance

Reduces secondary hyperalgesia
Prevents central sensitization from peripheral pain

Ketamine attenuates post-operative cognitive dysfunction after cardiac surgery.

METHODS:
• Placebo (0.9% NaCl: n=26) or iv bolus of ketamine (0.5 mg/kg; n=26) during induction
• A nonsurgical group (n=26) included as control
• Verbal & nonverbal memory and executive functions assessed before and 1 week after surgery (or 1 wk later for control group)
• C-reactive protein (CRP) determined before surgery and POD 1

CONCLUSIONS:
• Ketamine attenuates POCD 1 week after cardiac surgery
• CRP significantly (P<0.01) lower in the ketamine-treated
• Effect may be related to the anti-inflammatory action of ketamine
POSTOPERATIVE BENEFITS OF INTRAOPERATIVE KETAMINE

- Maintenance of respiratory drive
- Airway patency
- Analgesia
- Reduced opioid requirements
- Reduced postoperative pain
- Less PONV
- Euphoria

KETAMINE MODULATION OF PAIN

- NMDA receptor antagonism
- Interferes with pain transmission in the spinal cord
- Results in analgesia
- Prevents central sensitization in dorsal horn neurons
- Inhibits nitric oxide synthase (lowers the production of nitric oxide involved in pain perception)
- Further contributes to analgesia

PHYSIOLOGY OF PAIN

Ketamine

Inflammatory Mediators

Peripheral Sensitization

KETAMINE EFFECTS ON POSTOP PAIN

Suzuki, Anesth Analg 1999

PACU PAIN SCORES

Anesth Analg 2001;93:606

Intraoperative Small-Dose Ketamine Enhances Analgesia After Outpatient Knee Arthroscopy

Morphine + Ketamine
**Pain 30%**

**Side effects 80%**

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

**KETAMINE COMPARED TO OPIOIDS**

- No tolerance
- Less sedation
- Less N/V
- Less urinary retention
- No delayed gastric emptying
- No prolonged ileus or constipation
- Less respiratory depression

**Perioperative ketamine for acute postoperative pain (Review)**

Bull RE, Dahl JB, Moore RA, Kalow EA

http://www.thecochranelibrary.com

Postoperative hyperalgesia (cm²)

<table>
<thead>
<tr>
<th>Days after Surgery</th>
<th>Placebo (N=10)</th>
<th>Ketamine (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>40</td>
<td>160</td>
</tr>
<tr>
<td>Day 3</td>
<td>120</td>
<td>160</td>
</tr>
<tr>
<td>Day 7</td>
<td>200</td>
<td>200</td>
</tr>
</tbody>
</table>

* P<0.01

**HYPERALGESIA AND CHRONIC PAIN**

Area of Hyperalgesia at 60 N (cm²) vs Incidence of pain at 6 months

R=0.81 P < 0.001

**PSYCHOTROPIC EFFECTS**

- Euphoria
- Hyper-alert
- Vivid dreams
- Often colorful
- Often with religious overtones
- Talkative
- Wakefulness

**Eisenach, Reg Anesth Pain Med 2006**

**THE COCHRANE COLLABORATION™**
Wakefulness and Well-Being

**NON ANESTHETIC/ANALGESIC USES**

- Incidental antidepressant effect observed with chronic pain Rx
- Early study: Rapid antidepressant effect of ketamine within hours
  - Dose 0.5 mg/kg in 45 minutes
  - Saline vs ketamine infusions
- Later studies for both unipolar and bipolar depression
  - 24 hours after infusion: 25%-70% patients respond
  - 72 hours after infusion: 14%-50% patients respond
- Antidepressants take days-weeks to be effective
- ECT takes days to work

**Post-traumatic stress disorders**

- Near constant obsession responds to ketamine
  - Effect within 24 hours
  - lasts 7 days
- Refractory OCD responds immediately
  - lasts 24 hours
- 41 patients in randomized, double blind, crossover study
- Ketamine vs midazolam
- PTSD symptoms reduced in ketamine group at 24 hrs, lasting 7 days

**Obsessive compulsive disorders**

- Near constant obsession responds to ketamine
  - Effect within 24 hours
  - lasts 7 days
- Refractory OCD responds immediately
  - lasts 24 hours

**MAC/SEDATION CHALLENGES INCLUDE:**

- Safety
  - Hemodynamic stability
  - Airway maintenance
  - Adequate ventilation (normocarbia)
- Immobilized patient
- Expectations
  - Analgesia
  - Amnesia
  - Immobilized patient

**KETAMINE FOR MAC**

- Stimulates ventilation
- Enhances airway patency
- Analgesia
- Amnesia
- Immobility
- Enhances hemodynamics
  - Increases heart rate
  - Increases blood pressure
  - Increases cardiac output

**PROPOFOL FOR MAC**

- Respiratory depression
- Cardiovascular depression
  - Decreases cardiac output
- Decreases blood pressure
- Pain on injection
- disinhibited state
- Increased movement
- No analgesia

**MAC/SEDATION CHALLENGES INCLUDE:**

- Safety
  - Hemodynamic stability
  - Airway maintenance
  - Adequate ventilation (normocarbia)
- Immobilized patient
- Expectations
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**OBSESSIVE-COMPULSIVE DISORDERS**

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The Effects of Small-Dose Ketamine on Propofol Sedation: Respiration, Postoperative Mood, Perception, Cognition, and Pain

ETCO2 during MAC with Propofol vs Ketamine + Propofol

Figure 1. End-tidal \( \text{PCO}_2 \) (mean with 95% confidence intervals) during monitored anesthesia care in the Propofol (\( n = 20 \)) and Concomitant (\( n = 19 \)) groups. *P < 0.0001 between the groups.

Anesth Analg 2001;92:1465

Opioids vs Ketamine for MAC Breathing, Oxygenation

KETAMINE + PROPOFOL = KETAFOL

- Wide range of ketamine:propofol ratio reported in literature
- 1:10 or 2:10 ratio of ketamine and propofol combined
- Balancing of hemodynamic effects
- Propofol depresses cardiac function, lowers BP and HR
- Ketamine is a sympathomimetic and augments cardiac contractility, BP and HR
- Ease of a single infusion

IDEAL CANDIDATES FOR KETAMINE (OR KETAFOL)

- Sleep apnea
- Tolerance to opioids
- Chronic pain
- High-risk for chronic pain procedures
- Concern about awareness
- Inability to use oxygen (fire hazard)
- Difficult airway sedation cases
- High risk PONV
- Severe asthma

DOSING FOR SEDATION (OR ADJUNCT TO GENERAL ANESTHESIA)

- Ketamine
  - Bolus: 0.5 mg/kg (500 mcg/kg)
  - Infusion: 3-5 mcg/kg/min
- Ketofol
  - 1:10 ratio of Ketamine:Propofol
  - Bolus: 250-500 mcg/kg using propofol setting (25-50 mcg/kg of ketamine)
  - Infusion: 25-75 mcg/kg/min using propofol setting (2.5-7.5 mcg/kg/min of ketamine)
- *Ketofol is like doubling the concentration of propofol*
Multimodal Anesthesia
- Propofol
- Opioids
- Benzodiazepines
- Beta-blockers
- Inhalational agents
- Lidocaine infusions
- Ketamine (low-dose)

Multimodal Sedation
- Propofol
- Opioids
- Benzodiazepines
- Ketamine (low-dose)

Multimodal Analgesia
- Opioids
- NSAIDs
- COX-2 inhibitors
- Gabapentin
- Acetaminophen
- Steroids
- Peripheral nerve blockade
- Local anesthetic injection
- Ketamine (low-dose)

Summary - Ketamine
- Effective sedative when used in low doses
- Especially when combined with propofol
- Decreased PONV, sedation and hypoventilation
- Effective analgesic in low doses
- Significantly improves pain scores (acute & chronic)
- Reduces opioid requirements by 40%-60%
- Minimal psychomimetic effects

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