Low Dose Ketamine...Everything?

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How do you use ketamine in your practice of emergency medicine?

- Procedural sedation in children? Adults?
- Induction agent for RSI?
- Treatment of pain
- Control of the agitated patient

Is there more than anecdotal evidence to the use of low dose ketamine?

Objectives

- History and pharmacology of ketamine
- Anesthetic vs. sub-anesthetic doses of ketamine
- Clinical scenarios and evidence
The history of ketamine starts with PCP

- 1958: Phencyclidine (PCP) introduced into clinical anesthesia
- Anesthetic effects attributed to NMDA receptor antagonism
- Hallucinations, confusion, and delirium led to its discontinued use in humans

Ketamine History

- 1962: Ketamine synthesized by Stevens
- 1965: Ketamine trials in humans. Most promising of 200 different PCP derivatives
- 1970: Ketamine released for clinical use in U.S.
Mechanism of action

- Complex pharmacology
- Non-competitive NMDA receptor antagonist

NMDA Receptors

- Neurotransmitter glutamate
- Glutamate released with noxious peripheral stimuli
- Activation of NMDA receptors associated:
  - Hyperalgesia
  - Neuropathic pain
  - Reduced opioid sensitivity.

Dissociative Dosing

<table>
<thead>
<tr>
<th>Route</th>
<th>Dose</th>
<th>Onset</th>
<th>Time to peak effect</th>
<th>Duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>1.0 mg/kg</td>
<td>&lt; 1 min</td>
<td>3-5 min</td>
<td>5-10 min</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>2-4 mg/kg</td>
<td>2-5 min</td>
<td>20 min</td>
<td>30 min</td>
</tr>
<tr>
<td>Nasal</td>
<td>5 mg/kg</td>
<td>10 min</td>
<td>20 min</td>
<td>1 hour</td>
</tr>
</tbody>
</table>

What is low-dose Ketamine?

- “Poorly” defined as
  - 0.1 - 0.6 mg/kg IV
  - 0.5 - 1.0 mg/kg IM (reference below)
  - 0.5 mg/kg IN
- 70 kg male doses between 7 to 40 mg IV
Why even consider?

- May provide effective analgesia
- Can be given by a number of different routes
- Airway responses are protected
- Minimal cardiovascular effects
- Rapid onset, short duration of action, titratable

Clinical Scenario #1

- A 13-year-old female with no significant medical history presents to the ED with a left arm deformity after a skateboard accident. Exam is significant for an obvious deformity above the right elbow. The patient is neurovascular intact distal to the injury site. She is crying and reports 9/10 pain.

Ketamine for acute pain - Evidence

- Prospective cohort study in prehospital setting
- 27 patients
- Rx groups: Morphine vs. Morphine + ketamine
- Pain scores lower in morphine/ketamine group
- Blood pressure was high in morphine/ketamine group

Conclusion: Morphine + LDK provides adequate pain relief in patients with bone fractures


- 40 adults with acute musculoskeletal trauma
- SQ ketamine 0.1 mg/kg/hr vs IV Morphine 0.1 mg/kg
- Pain relief better with ketamine (VAS)
- Patients in ketamine group had less drowsiness and were easier to mobilize (traction/splinting)
- Nausea and vomiting in morphine group high
- No pts in ketamine groups required supplemental analgesia
Ketamine for acute pain - Evidence


Conclusion: Subcutaneous ketamine safe and effective analgesia in acute musculoskeletal trauma

Ketamine for acute pain - Evidence

Management of severe acute pain in emergency settings: ketamine reduces morphine consumption

Michel Gauvin M.***, François Bouchard MD, Daniel Benoit MS, Philippe Marier MD, François Tremblay MD, Jean Coté MD, MP, Frederic Laprade MD, Patrick Abreu MD, PhD

- 65 trauma patients with acute pain
- IV morphine injection of 0.1 mg/kg, followed by 3 mg every 5 hours
- Placebo (saline) or ketamine 0.2 mg/kg over 10 minutes
- Ketamine group required much less morphine
- Ketamine group higher incidence of neuropsych side effects

Intranasal ketamine for pain?

Case series of 40 patients with mod to severe pain
- IN ketamine 0.5 mg/kg initial bolus
- IN ketamine 0.25 mg/kg single repeat dose pm
- Objective pain measurements (VAS)
Intranasal ketamine for pain?

**Conclusion:** IN ketamine provides rapid, well-tolerated and clinically significant analgesia in ED patients.

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### Study protocol

**PICOFORM (Pain InChildren Fantany OR Ketamine) TRIAL comparing the efficacy of intranasal ketamine and fentanyl in the relief of moderate to severe pain in children with limb injuries:** study protocol for a randomized controlled trial.

- **Primary outcome:** Median change in pain scores
- **Secondary outcomes:** Incidence of adverse events

**Inclusion criteria:**
- Children aged 5-12 years with isolated musculoskeletal limb injury
- RX groups: IN ketamine (1 mg/kg) vs IN fentanyl (1.5 μg/kg)

**Awaiting results:**
Clinical Scenario #1

A 13 year-old female with no sig PMH presents to the ED with a left arm deformity after a skateboard accident. Exam is significant for an obvious deformity above the right elbow. The patient is neurovascular intact distal to the injury site. She is crying and reports 9/10 pain.

Clinical Scenario #1

- Several small studies suggest efficacy in this setting
- Intranasal route is compelling
- May obviate need for close respiratory monitoring
- More studies are needed

Clinical Scenario #2

- A 35 year old male with h/o IV heroin abuse presents with a left deltoid abscess. Exam sig for a 10 x 7 cm left lateral deltoid abscess. He complains of 10/10 pain and will barely allow you to touch his arm. He screams out in pain when the nurse attempts to place an IV. Home meds include methadone 120 mg daily. He is given a total of 4 mg of dilaudid without improvement in pain. How would you continue to manage of this patient?

Ketamine for acute pain - Evidence

- 2 year retrospective review of pts receiving ketamine in the ED
- LDK defined as < 0.6 mg/Kg for pain control
- 35 cases identified
- Most common use was abscess
- Chronic pain medication use described in 80% of cases
- Low dose ketamine improved pain in 54% of cases
Conclusion: ED physicians used low dose ketamine primarily in patient with high opiate tolerance

Evidence in opiate tolerant patients?

- Preemptive bolus dose of ketamine has opiate sparing effects in opioid abusers undergoing moderate sedation

**Ketamine for acute pain - Evidence**

**Low-dose ketamine for analgesia in the ED: a retrospective case series**

- Conclusions: Ketamine was used for analgesia in the ED, primarily in patients with high opiate tolerance.

**Evidence in opiate tolerant patients?**

- Randomized, double blind study design
- Rx groups: Ketamine 0.1 mg/kg vs Placebo
- Both groups received intermittent doses of remifentanyl during the procedure
- Ketamine group required lower doses of opiates and had improved pain scores.

**Opioid-Sparing Effect of Preemptive Bolus Low-Dose Ketamine for Moderate Sedation in Opioid Abusers Undergoing Extracorporeal Shock Wave Lithotripsy: A Randomized Clinical Trial**

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**Evidence in opiate tolerant patients?**

- Conclusion: Preemptive bolus dose of ketamine has opiate sparing effects in opioid abusers undergoing moderate sedation

- 31 yo male with SCC
  - Fentanyl PCA
  - Oxycodone
  - Ketorolac
  - Methadone
  - Venlafaxine
  - Gabapentin

- After 30 days of admission, placed on ketamine infusion with marked improvement in pain.

"Doctor it's a 12!!"
Evidence in opiate tolerant patients?

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Efficacy</th>
<th>Reduction of pain</th>
<th>Severity</th>
<th>Side effects</th>
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<tbody>
<tr>
<td>Tally et al.</td>
<td>CR (17)</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Joerg et al.</td>
<td>CR (14)</td>
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<tr>
<td>Walsh et al.</td>
<td>CR (11)</td>
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<td>None</td>
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<tr>
<td>Jordon et al.</td>
<td>CR (9)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Scenario 1</td>
<td>CR (1)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
</tr>
</tbody>
</table>

14/17 cases showed improvement in pain

Clinical Scenario #2

A 35 year old male with h/o IV heroin abuse presents with a left deltoid abscess. Exam sig for a 10 x 7 cm left lateral deltoid abscess. He complains of 10/10 pain and will barely allow you to touch his arm. He screams out in pain when the nurse attempts to place an IV. Home meds include methadone 120 mg daily. He is given a total of 4 mg of dilaudid without improvement in pain. How would you continue to manage of this patient?

Clinical Scenario #2

- Several small studies suggest a particular benefit of LDK in this patient population
- Likely reduces opiate consumption
- Needs to be studies in a controlled fashion in the emergency department setting.

Clinical Scenario #3

- A 35 year-old male with a history of alcohol abuse presents brought in by medics after he was found down on the sidewalk with a large hematoma to his parietal scalp. Upon arrival in the emergency department he is agitated, spitting and attempting to hit multiple staff members.
Ketamine for agitation?

Here using dissociative dosing 5 mg/kg IM

Ketamine for agitation?

Intramuscular Ketamine for the Rapid Tranquilization of the Uncontrollable, Violent, and Dangerous Adult Patient

Ketamine sedation for patients with acute agitation and psychiatric illness requiring aeromedical retrieval

Ketamine and agitation

- Case series of psychiatric patients undergoing aeromedical transport.
- Initial ketamine dosing range given was 0.5-1 mg/kg.
- If two doses required infusion started at initial rate of 1-1.5 mg/kg per hour.
- Amount given titrated to achieve a “calm, cooperative patient who could still respond to verbal commands.”

Ketamine and agitation

- 4/19 patients with tachycardia and hypertension
- 1/19 vomiting but no intervention required
- No cases in which psychiatric symptoms were deemed to have worsened.
- Authors conclude: ketamine sedation valid and safe strategy for managing the agitation of psychiatric patients.
What about ketamine and potential head injury?

- Evidence that ketamine elevates ICP is weak
- No evidence that ketamine causes harm in TBI
- Ketamine’s hemodynamic stability may be of benefit in TBI

Clinical Scenario #3

- A 35 year-old male with a history of alcohol abuse presents brought in by medics after he was found down on the sidewalk with a large hematoma to his parietal scalp. Upon arrival in the emergency department he is agitated, spitting and attempting to hit multiple staff members.

Clinical Scenario #3

- Intriguing data from case reports and case series
- Higher doses may be required
- Concern of administration in psychiatric patients may be overblown
- Need more ED based studies

Clinical Scenario #4

- A 16 year-old female with h/o severe asthma and prior intubations presents with acute onset of SOB and wheezing. Exam is significant for hypoxia with O2 sat 90%, tachypnea, and wheezes with diminished air movement bilaterally. She is initially treated with albuterol, atrovent, and steroids without significant improvement.
Low dose ketamine in the asthmatic

**Randomized, double blind, placebo controlled study design**
- 68 patients enrolled
- Rx groups: ketamine (0.2 mg/kg + infusion) vs placebo
- Outcome: validated asthma score
- Results: No difference between the two groups

**Conclusion:** Low dose ketamine had no incremental benefit compared with placebo

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Clinical Scenario #4

- A 16 year-old female with h/o severe asthma and prior intubations presents with acute onset of SOB and wheezing. Exam is significant for hypoxia with O2 sat 90%, tachypnea, and wheezes with diminished air movement bilaterally. She is initially treated with albuterol, atrovent, and steroids without significant improvement.

**No real indication for low dose ketamine here**
- Higher doses of ketamine may be beneficial
- Furthers studies needed
The bottom line...

• Multiple studies demonstrate LDK effective in the treatment of acute pain.
• LDK appears reduces opiate requirements
• LDK may be particularly effective in patient with high opioid tolerance
• Unclear utility of low dose ketamine in the agitated patient
• LDK does not appear to improve outcomes in nonintubated asthmatics

Thank You

Questions?

References

• Ghaeei N, et al. Gastric Ischemic Effect of Premeptive Bilious Low-Dose Ketamine for Moderate Severe Upper Gastointestinal Ulceration. Anesthesiology Shock Trauma. A Randomized Clinical Trial. Anesthesia and Analgesia Jan 2013; 116(1) 75-90
• Ubeda O, et al. Ketamine infusion for sickle cell pain crisis refractory to opioids: a case report and review of literature