Low-Dose Ketamine for Pain Management in the Emergency Department: Can it tame the pain?

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Learning Objectives

1. Discuss current available pharmacotherapy approaches and limitations for acute pain
2. Identify the pharmacologic properties of ketamine
3. Develop an evidence-based recommendation for low-dose ketamine (LDK) as an analgesic agent in the emergency department (ED)
Pain in the Emergency Department

I. Background and epidemiology
   a. Pain is the most common presenting complaint to the ED
   b. Up to 78% of patients present to the ED with acute pain
   c. From 1996 to 2015, ED visits have risen over 46% from 90.3 million to 136 million
   d. Roughly 45% of ED visits involve either moderate or severe pain

II. Studies showing a lack of satisfactory pain management
   a. Todd KH et al.
      i. Of patients presenting to ED with pain complaint, 2/3 of patients never had
         assessment of pain documented
      ii. 1/3 of patients never had a pain reassessment
      iii. Upon discharge, 43% of patients were still in moderate to severe pain
   b. Wilson JE et al.
      i. 33% of patients received suboptimal analgesia
      ii. 69% of patients waited more than 1 hour to receive analgesics
      iii. 42% of patients waited more than 2 hours to receive analgesics

III. Barriers to Effective Pain Management
   a. Provider Barriers
      i. Lack of basic knowledge and formal education on pain management
      ii. Concerns about addiction
   b. Patient Barriers
      i. Underreporting pain
      ii. Fears of addiction
   c. Emergency Department Barriers
      i. Fast paced environment
      ii. Lack of established patient-provider relationship

Pain

I. Definition of pain
   a. Unpleasant sensory and emotional experience associated with actual or potential
      tissue damage

II. Pathophysiology of Pain
   a. Pain receptors (nociceptors) in the skin are activated by tissue damage
   b. Signals travel up the peripheral nerves to the spinal cord
   c. Within the spinal cord, neurotransmitters are released that activate other nerves
      that pass signals to the brain
   d. Thalamus in the brain relays signals to the somatosensory cortex (responsible for
      sensation), to the frontal cortex (responsible for thinking) and the limbic system
      (emotional response)
   e. End result is sensation of pain and an emotional reaction such as feeling irritated or
      annoyed
III. Types of Pain

a. Anatomical location
   i. Somatic
      1. Peripheral tissue injury
      2. Sharp, stabbing or dull pain; can be localized
   ii. Visceral
      1. Organ injury
      2. Vague characteristics (i.e. cramping); difficult to localize

b. Underlying etiology
   i. Nociceptive
      1. Result of direct tissue injury from a noxious stimulus
   ii. Neuropathic
      1. Result of direct injury to nerves leading to an alteration in sensory transmission
      2. Caused by central nervous system (CNS) and peripheral nervous system (PNS) disorders
   iii. Inflammatory
      1. Pain caused by inflammation
      2. Result of released inflammatory mediators that control nociceptive input
   iv. Psychogenic
      1. Somatic manifestation of psychiatric illness or exacerbation of pain severity due to previous experience, poor coping mechanisms, or social history

c. Temporal nature
   i. Acute
      1. Pain related to acute injury, harm, or repair and often shorter duration (typically less than 30 days)
      2. Examples: bone fractures, appendicitis
   ii. Chronic/persistent
      1. Pain that lasts longer than the expected time of healing
      2. Examples: diabetic neuropathy, low back pain
   iii. Acute-on-chronic
      1. Acute exacerbation of a chronic pain syndrome
      2. Examples: sickle cell pain episodes

d. Pain Intensity
   i. Mild
   ii. Moderate
   iii. Severe

e. Screening and assessment tool
   i. Numeric Rating Scale (NRS) (Figure 1)
      1. Most commonly used pain scale
      2. Patient reported pain on a scale from 0-10
Figure 1. NRS Rating Scale

Consensus Guidelines

   a. Goals
      i. Treatments should be: Patient-specific, pain syndrome-targeted, and based on appropriate non-pharmacological and pharmacological approaches
      ii. ED clinicians are in a unique position to provide optimal analgesia, educate patients and combat the opioid epidemic

II. Treatments
   a. Non-pharmacologic approaches
      i. Heat or cold therapies
      ii. Consider osteopathic manipulation techniques for patients presenting with pain syndromes of skeletal, arthrodial and myofascial origins
   b. Multimodal approach
      i. Using two or more different classes of drugs simultaneously to interrupt the pain pathway at various points
   c. Pharmacologic Management
      i. Non-Opioid analgesics
         1. Non-steroidal anti-inflammatory drugs (NSAIDs)
            a. Administer at their lowest effective analgesic dose in the ED and upon discharge
            b. Give for the shortest appropriate treatment course
            c. Use with caution in patients at risk for renal insufficiency, heart failure, gastrointestinal adverse effects
            d. Consider topical preparations if systemic use is contraindicated
         2. Acetaminophen (APAP)
            a. Oral and rectal forms of acetaminophen (APAP) either alone or in combination provide similar efficacy to IV APAP but with slower onset of action
b. Use oral or rectal dosage forms unless contraindicated

3. Regional Anesthesia
   a. Consider regional and local nerve blocks alone or in combination with other modalities

4. Lidocaine
   a. Limited data suggests may alleviate specific painful conditions (renal colic, herpetic/post-herpetic neuralgia)

5. Ketamine
   a. Low-dose ketamine administered alone or as part of a multimodal analgesic approach may be considered in the ED

### III. Table 1. Commonly used Non-Opioid Analgesics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial Dosing</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>650 mg – 1000 mg PO/rectal suppository/IV</td>
<td>Limited efficacy as monotherapy in moderate to severe pain</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Ibuprofen 400-800 mg PO</td>
<td>Limited efficacy as monotherapy in moderate to severe pain, potentially serious adverse effects, requires caution in multiple disease states</td>
</tr>
<tr>
<td></td>
<td>Naproxen 250-500 mg PO</td>
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<tr>
<td></td>
<td>Ketorolac 15-60 mg IV/IM</td>
<td></td>
</tr>
<tr>
<td>Muscle relaxants</td>
<td>Cyclobenzaprine 5-10 mg PO</td>
<td>Primarily used for musculoskeletal pain only</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Gabapentin 100-300 mg PO</td>
<td>Primarily used for neuropathic pain only</td>
</tr>
<tr>
<td></td>
<td>Pregabalin 75-150 mg PO</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline 5-10 mg PO</td>
<td>Primarily used for neuropathic pain only</td>
</tr>
</tbody>
</table>

IV: intravenous, PO: by mouth, IM: intramuscular

i. Opioid Analgesics
   1. Emergency medicine clinicians are uniquely positioned to combat the opioid epidemic by:
      a. Thoughtful prescribing of parenteral and oral opioids in the ED and upon discharge
      b. Engagement with opioid addicted patients in the ED
   2. Parenteral opioids when used in titratable fashion are effective, safe and easily reversible analgesics that quickly relieve pain
   3. Consider opioids when benefit is greater than risks
   4. Oral opioid administration is effective for most patients in the ED and immediate release morphine sulfate is associated with less euphoria
Table 2. Commonly used opioid analgesics\textsuperscript{12,15-16}

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial Dosing</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>0.1 mg/kg IV</td>
<td>• Constipation*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sedation*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Respiratory depression*</td>
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<tr>
<td></td>
<td></td>
<td>• Hypotension*</td>
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<tr>
<td></td>
<td></td>
<td>• Opioid-induced hyperalgesia*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Histamine-release</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.015 mg/kg IV</td>
<td>• Seizures (dose-dependent)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1-1.5 mcg/kg IV</td>
<td>• Serotonin syndrome</td>
</tr>
<tr>
<td>Tramadol</td>
<td>50 mg PO</td>
<td>• Serotonin syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Increase seizure risk</td>
</tr>
<tr>
<td>Hydrocodone/APAP</td>
<td>5/325 mg- 10/325 mg PO</td>
<td>• Increase liver toxicity</td>
</tr>
</tbody>
</table>

*Indicated side effect common amongst all opioids; IV: intravenous, PO: by mouth

IV. Limitations to Opioids

a. Adverse effects
   i. Listed in table 2

b. Opioid-induced hyperalgesia\textsuperscript{17}
   i. Defined as state of nociceptive sensitization caused by exposure to opioids
   ii. Characterized by a paradoxical response whereby a patient receiving opioids for the treatment of pain could become more sensitive to certain painful stimuli
   iii. Treatment options include:
       1. Discontinuing the offending opioid, adding a COX-2 inhibitor may be beneficial
       2. Antagonizing the NMDA receptor with ketamine may also be a reasonable strategy

V. Opioid Crisis

a. History and epidemiology\textsuperscript{18-21}
   i. In the late 1990s, pharmaceutical companies reassured the medical community that patients would not become addicted to prescription opioid pain relievers
   ii. Healthcare providers began to prescribe opioids at greater rates
   iii. This lead to widespread diversion and the misuse of opioids
   iv. In 2017, more than 47,000 Americans died due to an opioid overdose
   v. An estimated 1.7 million people suffered from a substance use disorder related to prescription opioid pain relievers in 2017
   vi. On average, 130 Americans die every day from an opioid overdose

b. Economic Burden\textsuperscript{22}
   i. CDC estimates that the total economic burden of prescription opioid misuse alone in the US is $78.5 billion a year

c. What do we know about the opioid crisis?
i. Roughly 21 to 29% of patients prescribed opioids for chronic pain misuse them

ii. Between 8 and 12% of patients develop an opioid use disorder

d. Role of ED in opioid crisis
id. ED may foster a role in the development of opioid addiction and dependence

ii. ED sees many patients for various pain-related problems

iii. Many patients frequently receive their first opioid treatment in the ED

iv. Patients with moderate to severe pain are often sent home with an opioid prescription if successfully treated with an opioid in the ED

Ketamine

I. Background

a. History of ketamine
   i. Developed in 1960s as a PCP derivative
   ii. Classified as a schedule III controlled substance in 1999

b. Negative stigma
   i. “Club drug”
   ii. Date rape drug
   iii. Hallucinogenic effects

II. Indications

a. Approved in 1970 by the Food and Drug Administration (FDA)
   i. Induction and maintenance of anesthesia

b. Potential indications
   i. Depression
   ii. Rapid sequence intubation
   iii. Asthma
   iv. Agitation
   v. Alcohol withdrawal
   vi. Acute pain
   vii. Chronic pain
   viii. Status epilepticus

III. Dosing and dosage forms

a. Routes include IV, Sub-Q, IM, oral, rectal, topical, intranasal, and sublingual

| Table 3. Ketamine Dosing Ranges |
|-------------------|----------------|
| Dose              | Effect          |
| 0.1-0.3 mg/kg     | Analgesia       |
| 0.2-0.5 mg/kg     | Recreational    |
| 0.4-0.8 mg/kg     | Partially dissociated |
| >0.8 mg/kg        | Fully dissociated |
IV. Mechanism of Action$^{25,28}$
   a. Non-competitive antagonist of CNS N-methyl-D-aspartate (NMDA) receptor
   b. Agonist at alpha and beta adrenergic receptor
   c. Antagonist at muscarinic receptor
   d. Blocks reuptake of catecholamines
   e. Agonist at opioid receptors

V. Pharmacologic effects
   a. Central nervous system (CNS)
      i. Sedation
         1. Produces a catatonic state
      ii. Analgesia
         1. Inhibits binding of excitatory amino acids (glutamate and aspartate) to the NMDA receptor in the CNS, blocking the transmission of painful stimuli
         2. NMDA antagonism produces analgesia and limits the development of opioid tolerance and hyperalgesia
      iii. Cardiovascular
         1. Elevates circulating epinephrine and norepinephrine leading to increased heart rate, blood pressure, cardiac output, and vascular resistance
   iv. Respiratory
      1. No respiratory depressant effects when given in low doses

VI. Pharmacokinetics$^{25}$

<table>
<thead>
<tr>
<th>Table 4. Ketamine Pharmacokinetics</th>
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<tbody>
<tr>
<td><strong>Onset of Action</strong></td>
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<tr>
<td><strong>Duration of Action</strong></td>
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<tr>
<td><strong>Distribution</strong></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
</tr>
</tbody>
</table>

VII. Adverse Effects$^{25}$
   a. Dizziness
   b. Psychomimetic effects such as feelings of unreality
   c. Nausea and vomiting
   d. Tachycardia
   e. Hypertension
   f. Emergence reactions

VIII. Emergence reactions$^{25,29}$
   a. Visual and auditory disturbances such as feelings of unreality, hallucinations, anxiety, paranoia
   b. May range from mild to extreme discomfort
   c. Occurs when “emerging” from dissociative state
d. No emergence reaction with subdissociative doses because the patient wasn’t ever in a true dissociative state

e. Rescue medications
   i. Benzodiazepines

f. Anticipation of emergence reactions are the number-one reason physicians fear the use of LDK in the emergency department

IX. Contraindications

a. Absolute
   i. Allergy to ketamine
   ii. Acute psychosis
      1. Ketamine may exacerbate psychosis
   iii. Age <3 months
      1. Reported cases of airway obstruction, laryngospasm and apnea; represents infant-specific differences in airway anatomy

b. Relative
   i. Pregnancy ketamine is a C drug (as are all opioids)
      1. Recommend not to use in first trimester but can consider use in second and third trimester after having discussion of risk/benefit with patient
   ii. Altered mental status
   iii. Acute thyrotoxicosis
   iv. Elevated intraocular pressure
   v. Cardiovascular disease, specifically acute decompensated heart failure and acute coronary syndrome

X. Monitoring

a. Prior to administration, baseline vital signs (VS) should be obtained and documented
b. During and after administration, frequent VS monitoring and documentation should be conducted

Literature Review

I. Clinical Question: Is low-dose ketamine SAFE and EFFECTIVE for use in acute pain management in the emergency department?

<table>
<thead>
<tr>
<th>Objective</th>
<th>Assess and compare the analgesic efficacy and safety of LDK with morphine in ED patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Prospective, randomized, double-blind controlled trial</td>
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Patient Population

<table>
<thead>
<tr>
<th>Inclusion</th>
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<tr>
<td>• Age 18 to 55 years old</td>
<td>• Pregnancy/breast-feeding</td>
</tr>
<tr>
<td>• Acute abdominal, flank, back or musculoskeletal pain</td>
<td>• Altered mental status</td>
</tr>
<tr>
<td>• Numeric rating scale (NRS) score of equal to or greater than 5 of 10</td>
<td>• Allergy to morphine or ketamine</td>
</tr>
<tr>
<td>• Deemed by the treating ER physician to require opioid analgesia</td>
<td>• Weight ≤ 46 kg or &gt;115 kg</td>
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<td>• Unstable vital signs</td>
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<tr>
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<td>• Medical history of acute head or eye injury, seizure, intracranial hypertension, chronic pain, renal or hepatic insufficiency, alcohol or drug abuse, psychiatric illness or recent opioid use (4 hours before)</td>
</tr>
</tbody>
</table>

Intervention

| Ketamine 0.3 mg/kg IV push over 3-5 minutes | Morphine 0.1 mg/kg IV push over 3-5 minutes |
| If patients reported a pain numeric scale score of 5 or greater and requested additional pain relief, fentanyl 1 mcg/kg was administered as a rescue analgesic |

Outcomes

| Primary Outcomes: | Secondary Outcomes: |
| Comparative reduction of numeric rating scale pain scores between recipients of ketamine and morphine at 30 minutes | Need for rescue analgesia at either 30 or 60 minutes |
| | Changes to vital signs |
| | Adverse effects |

Statistics

| Frequency distributions, paired t test and independent-sample t test |

Baseline Characteristics

| N= 90 (ketamine n=45, morphine n=45) |
| Baseline characteristics similar (i.e. age, gender, blood pressure, source of pain) |
| At the start, baseline pain scores for ketamine and morphine were 8.6 and 8.5 |

Results

Primary Outcome

| The primary change in mean pain scores was not significantly different in the ketamine and morphine groups |
| Mean difference in pain score of 4.1 versus 3.9 at 30 minutes |

Secondary Outcomes

| Adverse Effects: Ketamine vs Morphine |
| Dizziness: |
| 15 minutes: 53% vs 31% |
| 30 minutes: 8% vs 6% |
- Disorientation:
  - 15 minutes: 11% vs 0%
  - 30 minutes: 1% vs 0%
- Mood Changes:
  - 15 minutes: 11% vs 0%
  - 30 minutes: 1% vs 0%
- Nausea:
  - 15 minutes: 18% vs 11%
  - 30 minutes: 6% vs 9%
- The ketamine group experienced statistically more significant adverse effects in the first 15 minutes
- Most side effects dissipated by 30 minutes
- No changes in vital signs that were clinically concerning or required intervention

**Fentanyl Rescue Incidence:**
Ketamine vs Morphine
- 15 minutes: 0% vs 0%
- 30 minutes: 4% vs 1%
- 60 minutes: 4% vs 6%
- No statistically significant difference in the use of rescue fentanyl analgesia at 30 or 60 minutes

**Conclusion**
Ketamine administered at 0.3 mg/kg provides analgesic effectiveness and apparent safety comparable to that of IV morphine for short-term treatment of acute pain in the ED.

**Critique**

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
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</thead>
<tbody>
<tr>
<td>Randomized, double-blind trial</td>
<td>Single center</td>
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</table>


<table>
<thead>
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<tr>
<td>Assess and compare the analgesic efficacy and safety of low-dose ketamine compared to placebo, as an adjunctive treatment to opioids</td>
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</table>

<table>
<thead>
<tr>
<th>Methods</th>
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<tbody>
<tr>
<td>Prospective, randomized, double-blind controlled trial at a single academic emergency department</td>
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<th>Patient Population</th>
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<td>Inclusion</td>
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<tr>
<td>Age 18 to 70 years old</td>
</tr>
<tr>
<td>Numeric rating scale (NRS) score of equal to or greater than 6 of 10</td>
</tr>
<tr>
<td>Deemed by the treating ER physician to require opioid analgesia</td>
</tr>
<tr>
<td>Exclusion</td>
</tr>
<tr>
<td>Respiratory, hemodynamic, or neurologic compromise</td>
</tr>
<tr>
<td>History of chronic ventilation or dialysis or with previously diagnosed cirrhosis or hepatitis by history</td>
</tr>
<tr>
<td>Active psychosis</td>
</tr>
</tbody>
</table>
Intervention

- Patients received initial provider-determined treatment
- Patients reassessed after 15 minutes and if, after initial dose patient reported pain ≥ 6/10 then randomized to:
  - Ketamine 0.1 mg/kg IV push over 1 minute OR
  - Equivalent volume of normal saline (placebo)

Repeat doses of pain medication were given as 0.05 mg/kg morphine or equivalent dose of opioid analgesic when requested by the participant.

Outcomes

Primary
- Level of pain control
- Satisfaction with pain control

Secondary
- Total amount of opioids given
- Adverse effects

Statistics

Wilson rank sum tests, chi-squared tests, and Fischer’s exact test, t tests

Baseline Characteristics

- N=116
- Mean age: ~42 years
- Female: 44%
- Prior opioid use: 25.9%
- Chief complaint: Mostly abdominal pain 37.9%

Results

Primary Outcome:
Patients receiving ketamine reported lower pain scores over 120 minutes than patients receiving placebo
- P=0.015

Patient satisfaction (mean ± SD)
- Ketamine: mean ± SD = 2.66 ± 0.67
- Placebo: mean ± SD = 2.52 ± 0.50
- Not a statistically significant difference

Secondary Outcome:
Total opioid dose
- Ketamine: mean ± SD = 9.95 ± 4.83 mg
- Placebo: mean ± SD = 12.81 ± 6.81 mg
- Statistically significant difference in total opioid dose between the two treatments (p=0.02)
- Fewer repeat doses of analgesia in the ketamine group
Adverse Effects:
Ketamine versus Placebo
• Nausea: 4 (7.6%) vs 3 (4.8%)
• Light-headedness or dizziness: 16 (30.2%) vs 5 (7.9%)
• Dry mouth: 0 vs 2 (3.2%)
• Disorientation: 0 vs 1 (1.6%)
• Euphoria: 1 (1.9%) vs 1 (1.6%)
• Nystagmus: 2 (3.8%) vs 0
• 12 patients in placebo group and 27 in ketamine group reported side effects
• No patient had side effects lasting longer than 6 minutes

Conclusion
Ketamine, as an adjunct to opioid therapy, was more effective at reducing pain over 120 minutes and resulted in a lower total opioid dose as well as fewer repeat doses of analgesia.

Critique
Strengths
• Randomized, double-blind
• Assess side effects immediately after medication administration
• Included patients with chronic pain

Limitations
• Single center
• Small patient size
• Some patients received procedural analgesia and/or non-opioid rescue medications
• Initial provider dose was not consistent


Objective
Evaluate LDK as an adjunct for acute pain in the ED

Methods
Single center, prospective, randomized, double-blind controlled, placebo controlled trial

Patient Population

Inclusion
• Age 18 or older
• English speaking
• Chief complaint of acute pain with a numeric rating scale (NRS) score of equal to or greater than 3 of 10
• Acute pain was defined as onset of less than or equal to 15 days

Exclusion
• Hemodynamic instability
• Altered mental status
• Weight >166 kg
• Pregnancy/breastfeeding
• Allergy to study drugs
• Opioid use <=4 hours of presentation to ED
• Medical history of schizophrenia, depression, or substance abuse
• Traumatic head injury, headache, migraine, or increased intracranial or intraocular pressure

Intervention
• All patients received morphine 0.1 mg/kg IV push (max 10 mg) then randomized to:
  o Ketamine 0.3 mg/kg in 50 mL normal saline IVPB over 15 minutes or
  o Normal saline 50 mL infused over 15 minutes (placebo)
Outcomes

Primary Outcomes:
- NRS score after 15 minutes

Secondary Outcomes:
- Incidence of adverse effects
- Mean consumption of rescue analgesia
- Patient’s length of stay in the ED
- Patient satisfaction

Statistics

Kolmogorov Smirnov tests, Mann-Whitney U tests, t tests

Baseline Characteristics

- N=60 (30 in ketamine group and 30 in placebo group)
- Average age ~48 years
- Most patients presented with abdominal or musculoskeletal pain
- Mean baseline numeric rating scale >8 in both groups

Results

Study Outcomes

Primary Outcome
- Pain scores were significantly lower in the ketamine group than the placebo group at 15 minutes and 30 minutes after administration
- Median pain score at 15 minutes: ketamine 3.5 vs placebo 6.0
- P= 0.018

Secondary Outcomes
- No significant difference in the amount of rescue opioids used between the groups
- Statistically significant difference in patient satisfaction, favoring ketamine (8.57 vs 6.05, p=0.01)
- No difference in length of stay in ED

Adverse Events
- No statistically significant difference in adverse effects between groups
- Dizziness (53%) and disorientation (29%) were frequently reported immediately after ketamine injection

Conclusion

When used as an adjunct, LDK administered at 0.3 mg/kg over 15 minutes resulted in safe and effective analgesia for at least 30 minutes in patients who presented with acute pain in the ED

Critique

Strengths
- Randomized, double-blind
- Used short infusion of ketamine instead of IV push

Limitations
- Single center
- Small patient size
- Clinical diagnosis not evenly distributed


Objective

Compare adverse effects and analgesic efficacy of low-dose ketamine for acute pain in the ED administered either by single intravenous push (IVP) or short infusion (SI)

Methods

Prospective, randomized, double-blind, double-dummy trial
### Patient Population

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<thead>
<tr>
<th>Inclusion</th>
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<tbody>
<tr>
<td>- Age 18 to 65 years old</td>
<td>- Pregnancy/breast-feeding</td>
</tr>
<tr>
<td>- Primary complaint of acute abdominal flank, or musculoskeletal pain with initial pain score ≥ 5 on the numeric pain rating scale (NRS)</td>
<td>- Altered mental status</td>
</tr>
<tr>
<td>- Awake, alert and oriented to person, place and time</td>
<td>- Allergy to ketamine</td>
</tr>
<tr>
<td></td>
<td>- Weight &lt;46 kg or &gt;115 kg</td>
</tr>
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### Intervention

- Ketamine 0.3 mg/kg via IV push (over 5 minutes)
- Ketamine 0.3 mg/kg mixed in 100 mL NS via short infusion (over 15 minutes)
- If patients still desired pain medication, they were offered IV morphine 0.1 mg/kg as a rescue analgesic

### Outcomes

#### Primary Outcomes:

- Overall rates of specific side effects and specific severity levels of the side effects rated from 0-4 on the Side Effects Rating Scale for Dissociative Anesthetics (SERSDA)
- Severity of agitation and/or sedation rated by RASS score
- These were measured at 15, 30, 60, 90, and 120 minutes post administration

#### Secondary Outcomes:

- Analgesic efficacy (NRS score)
- Changes in vital signs
- Need for rescue analgesia

### Statistics

Student t-tests, chi square tests

### Baseline Characteristics

- N= 48 (IVP: 24, SI 24)
- Baseline characteristics similar (i.e. age, gender, chief complaint, etc.)
- Mean age: early 40s
- Mean baseline pain score: >8 in both groups

### Results

**Primary Outcome:**

Side effects - Feeling of Unreality on SERSDA
- IVP: 91.7%
- IV infusion 54.2%
- P=0.008
- NNH: 3
- SERSDA= side effects rating scale for dissociative anesthetics

Rates of Sedation (RASS)
- RAAS scale at 5 minutes was greater in the IVP group
- Median RAAS – 2.0 versus 0.0
- P=0.01
Secondary Outcomes

- No difference in reduction in pain scores, change in vital signs or need for rescue analgesia

<table>
<thead>
<tr>
<th>Conclusion</th>
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<tbody>
<tr>
<td>Low-dose ketamine given as a short infusion is associated with significantly lower rates of feeling of unreality and sedation with no difference in analgesic efficacy in comparison to intravenous push.</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Critique</th>
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<tbody>
<tr>
<td>Strengths</td>
</tr>
<tr>
<td>Randomized, double-blind</td>
</tr>
<tr>
<td>Limitations</td>
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<tr>
<td>Single center</td>
</tr>
<tr>
<td>Small patient size</td>
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</tbody>
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Conclusion

I. Overall

a. Ketamine is safe
   i. No major adverse effects occurred in the literature review studies
   ii. Higher rate of minor side effects, but usually short lived and tolerable

b. Ketamine is effective
   i. LDK alone is comparable to morphine 0.1 mg/kg
   ii. LDK as an adjunct to opioids improved pain control versus IV opioids alone

II. Treatment Recommendations

a. Multimodal approach to pain management is recommended
   i. Use combination of non-pharmacologic treatments, non-opioids and opioids if necessary

b. When should ketamine be considered?
   i. NRS score >6
   ii. Patients who use opioids chronically
   iii. Opioids are contraindicated
   iv. Opioids not tolerated by patient
   v. Opioids are ineffective
   vi. Opioids are not desired by the patient
   vii. Opioids are not desired by the physician

c. How should ketamine be given?
   i. Ketamine 0.3 mg/kg in 100 mL NS over 15 minutes

Figure 2. Pain Ladder

<table>
<thead>
<tr>
<th>Severe (7-10)</th>
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</thead>
<tbody>
<tr>
<td>APAP +/- NSAID</td>
</tr>
<tr>
<td>IV opioids</td>
</tr>
<tr>
<td>Ketamine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate (4-6)</th>
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</thead>
<tbody>
<tr>
<td>APAP +/- NSAID</td>
</tr>
<tr>
<td>PO/IV Opioids</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Mild (0-3)</th>
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</thead>
<tbody>
<tr>
<td>APAP +/- NSAID</td>
</tr>
</tbody>
</table>

Non-Pharmacologic treatments, nerve blocks, muscle relaxants, antidepressants, anticonvulsants if applicable
Fig. 3 Ketamine Algorithm

Age 18-69 years old and NRS score >6

- Chronic opioid user
- Non-chronic opioid user
- Contraindication or intolerance, opioids not desired

IV Opioid + Ketamine 0.3 mg/kg IVPB over 15 minutes

IV opioid Reassess in 15 minutes

Ketamine 0.3 mg/kg IVPB over 15 minutes

If pain score still >5, administer ketamine 0.3 mg/kg IVPB over 15 minutes

Exclusion:
- Pregnancy/breastfeeding
- Psychiatric illness
- Altered mental status
- Acute heart failure
- Acute coronary syndrome
- Uncontrolled hypertension
- Advanced liver disease
- Headache

Fig. 4 Summary of Pain Management

Establish realistic pain goals
Educate patient/caregiver on goals and regimen
Consider pharmacologic and non-pharmacologic treatment options
Continually reassess patient's pain and monitor efficacy and side effects
References