Evolution of the Indications for Ketamine in the Emergency Department

Ketalgesia: /ke • tal • jēzəsiə/ noun Ketamine for analgesia in the Emergency Department

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Objectives

1. Understand the rationale behind ‘ketalgesia’ in the Emergency Department
2. Evaluate the available evidence for ‘ketalgesia’ in the Emergency Department
3. Assess clinical scenarios/patient populations where ‘ketalgesia’ may be a suitable option

Disclosures
The program chair and presenters for this continuing education activity have reported no relevant financial relationships.

“Opioid-sparing” analgesia
Ketamine. Part of your balanced pain plan. It’s not just for sedation anymore!

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KT is a 37 y/o African American female with poorly controlled Sickle Cell disease...

...weekly emergency department visits...

...on 100mcg transdermal fentanyl replaced q48h, and hydromorphone 8mg PO q6h PRN (which she takes ATC)...

...presents with severe pain radiating from her lower back, through her hips, and down to her knees

Given hydromorphone 2mg IV x 2 with minimal relief, heading towards PCA route (for the bazillionth time)....

....should ketamine be added to her ED pain regimen?

The ‘Why?’

A conundrum exists

Effective pain management

Oligo-analgesia

Patient satisfaction

Performance metrics /transparency

HCAHPs

The traditional solution....opioids

• Mazer-Amirshahi, et al., 2014
  ▪ Increased opioid analgesic prescribing among U.S. EDs from 2001-2010
    ▪ Absolute increase of 10.2%
    ▪ Relative increase of ~50%
  ▪ Stable rate of ED visits for painful conditions
    ▪ 2001: 47.1%; 2010: 51.1%

• Hoppe, et al., 2015
  ▪ 1 in 6 patients discharged with opioid analgesics

Are opioids really the answer?

ED visits related to prescription drug misuse/abuse, 2004-2011

Time for an alternative?

National Overdose Deaths

Source: National Center for Health Statistics, CDC Wonder
Why ketamine?

Various routes available (IM, IV, IN)
Kinetically advantageous
Minimal hemodynamic sequelae
Spontaneous respirations and laryngeal reflexes maintained

...because it works!!

- Origin as an analgesic
  - Perioperative setting
  - Oncology
  - Palliative care
- "Sub-dissociative" dosing
  - i.e. <1 mg/kg IV, <4 mg/kg IM, <3 mg/kg IN

Perioperative ketamine for acute pain

- Cochrane review from 1980-2004
- 37 RCTs of adult, perioperative patients (n=2240)
- Ketamine vs placebo (open-label analgesics permitted)
  - Sub-dissociative doses used (<1 mg/kg)
- Assessed pain intensity (pre-, peri-, post-), rescue analgesic consumption, adverse effects
- Ketamine reduced pain intensity, rescue analgesic requirements, or both in 27/37 trials
- Adverse effects mild or absent
- Ketamine reduced post-op N/V

Extrapolating the literature

- Not necessarily applicable to the ED
  - Epidural administration
  - Continuous infusions
  - Wide variability in dosing (0.05-1 mg/kg)
- General anesthesia may mask effects that would be unwanted in the awake patient
- Monotherapy?

The ‘How’

Ketamine has complex pharmacology!
Ketamine: Analgesic mechanisms

Perception

Descending Modulation

• µ-opioid receptor interaction
• Provides analgesia
• Augments µ-opioid receptor function
• May mitigate opioid receptor desensitization and tolerance

Noncompetitive NMDA-receptor antagonist
• NR2B subunit
• Decreases central sensitization of pain by inhibiting transmission of nociceptive signals
• May mitigate opioid-induced hyperalgesia

Descending Modulation
• δ-opioid receptor interaction
• Provides analgesia
• Augments mu-opioid receptor function
• May mitigate opioid receptor desensitization and tolerance

The ‘Literature’

PMID: 25716117

• Literature review of 4 RCTs (1998–2008)
• Significant heterogeneity precluding pooled analysis
• Mix of placebo-controlled vs. head-to-head
• Wide variability in dosing and pain scale use
• Different patient populations and etiologies (2 trials: procedural sedation > analgesia)
• No concluding evidence to support or refute ketamine for acute pain in the ED
• Included studies already dated upon publication

PMID: 25377395

• SPID:
  • Measures the difference between baseline and post-intervention scores of pain intensity
  • Widely reported in clinical trials assessing analgesic efficacy
  • Accounts for individual differences in perception of pain
  • Reflects analgesic efficacy over defined time period

Example:

<table>
<thead>
<tr>
<th>Pt 1:</th>
<th>Pt 2:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline score: 8</td>
<td>Baseline score: 5</td>
</tr>
<tr>
<td>30-minute score: 5</td>
<td>30-minute score: 2</td>
</tr>
<tr>
<td>60-minute score: 4</td>
<td>60-minute score: 0</td>
</tr>
<tr>
<td>SPID: 7 → %SPID: 44%</td>
<td>SPID: 8 → %SPID: 80%</td>
</tr>
</tbody>
</table>

Low-dose Ketamine Improves Pain Relief in Patients Receiving Intravenous Opioids for Acute Pain in the Emergency Department: Results of a Randomized, Double-blind, Clinical Trial

• N = 60 adults (18-65 yrs)
• 3 arms:
  • Morphine IV (0.1 mg/kg) + placebo
  • Morphine IV + ketamine IV (0.15 mg/kg)
  • Morphine IV + ketamine IV (0.3 mg/kg)
• Patients assessed at 30, 60, and 120 minutes
• Outcomes:
  • Primary: pain intensity reduction (Summed Pain Intensity Difference [SPID])
  • Secondary: rescue opioid analgesia (consumption and timing); adverse effects

SPID: Varying etiologies of pain between arms
Ketamine added to standard opioid analgesia (morphine) resulted in superior pain relief

- Ketamine NOT used as monotherapy
- Effects of ketamine appear dose-related
  - Efficacy
  - Adverse effects more prevalent
- Included those with chronic pain and opioid-tolerance, whose breakthrough pain persisted despite treatment with opioids prior to enrollment

Patient population:
- Age: 18-55 years
- ~70% abdominal pain w/ NRS ≥ 5
- Excluded extremes of weight (46-115kg)
- Opioid-naïve
- Hemodynamically stable

No history of:
- Head injury
- Seizures
- Renal/hepatic insufficiency
- Alcohol/drug abuse
- Psychiatric illness
Pain scores, vitals and adverse effects were reported at 5 time points:
- 15, 30, 60, 90, 120 minutes

Primary outcome: comparative reduction of NRS pain scores at 30 minutes

Secondary outcome: Need for rescue analgesia at 30 or 60 minutes

- Fentanyl 1 mcg/kg IV

PMID: 25817884

Ketamine appears to be a safe and effective alternative to morphine for acute pain relief

- Adverse effects more prevalent with ketamine
  - Minor: dizziness, disorientation, mood changes
  - Transient: rates similar after 30 minutes

- May not be ideal sole therapy for patients experiencing persistent acute pain

Limitations with statistical design
- Powered for superiority (≥ 1.3 diff in NRS between Ket and Mor)
- Intention to treat (ITT) supports superiority design
- Superiority not reached...can equivalency be claimed??

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Key Takeaways

- **Key Takeaway #1**
  - ED pain management is challenging. Effective, opioid-sparing analgesics are warranted to help mitigate some of these challenges.

- **Key Takeaway #2**
  - Ketamine (0.1-0.3 mg/kg IV) is safe and may be an effective alternative for select patient populations.

- **Key Takeaway #3**
  - Ketamine not ready for primetime as 1st line monotherapy.
  - Likely role as adjunctive therapy for acute, refractory pain.

Which of the following is true regarding the use of ‘ketalgesia’ in the ED?

- Current evidence suggests that monotherapy with ketamine is superior to morphine for acute pain.
- Adverse effects are comparable between ketamine and standard care (opioids).
- Ketamine may be an option for acute pain refractory to initial opioids.

Exploding Brains!
Ketamine in Traumatic Brain Injury

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Objectives

- Discuss the pathophysiology of secondary injury after traumatic brain injury (TBI).
- Review historical and updated literature to support the use of ketamine in patients with TBI.
- Evaluate the ketamine’s role compared to available alternatives.

84 year old male "found down" at the bottom of a staircase at home

- ABCDE
- Agitated, combative, needs a head CT...
- RSI vs Ketamine

34 year old male MVC (motorcycle), no helmet (…it’s Texas y’all)

- ABCDE
- Blood, teeth in airway...
- RSI w/ or w/o Ketamine

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Primary injury

Secondary injury

Cerebral blood flow
Autoregulation
Vasospasm
Cerebral metabolic dysfunction
Excitatory and oxidative stress
Edema

CPP → surrogate for CBF
CPP = MAP − ICP
ICP = Brain + CSF + Blood + Mass lesion

Ketamine ↑ ICP
Knowledge Assessment

- Which of the following is the best predictor of poor outcome in TBI?
  - A. GCS < 13 (ie, mental status)
  - B. SBP < 90 mm Hg
  - C. ICP > 10

2013 - Review

- Systematic review – ketamine for induction, maintenance, and sedation

  “...The use of ketamine in a controlled ventilation setting and in combination with other sedative agents has demonstrated no increase in ICP, which is the major concern of anesthesiologists regarding ketamine for patients with TBI.”

2014 Meta - Analysis

- Patients were on background sedatives
- If pCO2 was controlled by mechanical ventilation, ketamine in isolation would be well tolerated without ICP fluctuations

  “...the use of ketamine in severe TBI patients that are sedated and ventilated has little serious adverse effects, as demonstrated by the lack of complications identified in our review.”

2015 – Systematic Review

- 2/8 (20%) ↓ ICP within 10 minutes
- 2/8 (20%) ↑ ICP after administration

- No significant differences in CPP, neurologic outcomes, ICU length of stay, or mortality

  “...the use of ketamine in critically ill patients does not appear to adversely affect patient outcomes.”

- Degree and duration of hypotension ▸ poor neurologic outcome
- Avoid opioids, propofol, or benzodiazepines
84 year old male “found down” at the bottom of a staircase at home
34 year old MVC (motorcycle), no helmet (...it’s Texas y’all)

**ABCD**

Agitated, combative, needs a head CT...

**ABCDE**

Blood, teeth in airway...

**RSI vs Ketamine**

**RSI w/ or w/o Ketamine**

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**Seizures in patients with intracranial pathology**

No improvement in mortality or 6 month outcome (↓ MAP)

Significant morbidity

**Slow onset for RSI**

↓ MAP, ↑ CBF

See Propofol

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**Under Pressure?**

*Hypotension* has been associated with worsening secondary brain injury and increased morbidity and mortality

≥2 hypotensive episode with GCS < 13

Mortality RR 8.1 (95% CI 1.63-39.9)
### Key Takeaways

- **Key Takeaway #1**
  - Ketamine is unlikely to increase ICP with clinically appropriate induction doses

- **Key Takeaway #2**
  - Hypotension is associated with poor outcome – avoid at all costs

- **Key Takeaway #3**
  - Ketamine surrounded by dogma, read the literature for yourself!

### Ketamine is contraindicated in patients with known or suspected TBI?

- **True**
- **False**

### Ketamine in TBI - References


### Questions?

Which of the following is the best predictor of poor outcome in TBI?

- GCS < 13
- SBP < 90
- ICP > 10

**Ketalgiesia** - References