Why Emergency Departments Love Ketamine

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Course Description:

- This course will discuss the use of ketamine in Emergency Departments (EDs) for the management of pain and procedural sedation in adults, children and high risk populations. Ketamine has been used for years in pediatric procedural sedation but has now become the “go-to-drug” for adult sub-dissociative analgesia in ED, trauma, and prehospital settings and in patients with chronic opioid use or those at high risk for addiction.
Disclosures

- Phyllis Hendry, MD, FACEP, FAAP (Principal Investigator)
- Sophia Sheikh, MD, FACEP (Sub-Investigator)
- Pain Assessment and Management Initiative (PAMI)
- Funded by Florida Medical Malpractice Joint Underwriting Association, Alvin E. Smith Safety of Health Care Services Grant: 2014-2018
Learning Objectives

- Discuss the pharmacology, dosing and routes of administration for ketamine in adults and children.
- Describe ketamine's indications for sub-dissociative analgesia in the ED, trauma and prehospital settings.
- List patient safety concerns in regard to utilizing ketamine in the ED and prehospital setting for analgesia including side effects, monitoring and discharge planning.
- Discuss the inclusion of ketamine in multimodal ED pain protocols.
Background

- Review of ED pain management challenges to promote understanding of ketamine popularity
- History of ketamine
Pain in the ED: Background and Barriers

1. Pain is often the main reason why patients come to the ED
   • 45-78% of ED presenting complaints related to pain
   • Acute pain is common reason for 911 calls

2. Care in the ED often adds to a patient’s pain
   • IV insertion, wound care, fracture reduction

3. Pain can be a barrier to communication
   • Impedes ability to obtain history and exam
Pain in the ED: Background and Barriers

4. Need to balance analgesia and sedation with adverse effects, especially at the extremes of age

5. Medications that did not work at home unlikely to work in ED
   - Require escalation of analgesia treatment
   - Lack of protocols
Pain in the ED: Background and Barriers

6. Patient credibility and provider biases
   - Unique population of patients often with mental illness, substance abuse and co-morbidities leading to bias
   - Limited means or time to verify patient’s history
   - Drug-seekers vs drug-diverters vs legitimate pain
7. Overall error prone environment

- Same drug used for multiple conditions in varying dosages and routes
- Frequent interruptions
- Management of hundreds of different disease states and injuries requiring use of hundreds of medications
- Variable team members and levels of experience
Trying to Balance Pain Management While......

- Dealing with opioid addiction crisis
- Receiving pressure to decrease readmissions and triage to discharge times
- Performing painful procedures
- Searching for the “perfect drug” - is it ketamine?
History
From DPT* to Ketamine

- ED analgesic and sedative experience began with:
- Chronic pain: sickle cell disease, cancer pain, migraines
- Procedural sedation and analgesia (PSA): pediatric and adult
- Rapid sequence induction (RSI) for emergent intubation and ongoing sedation for mechanically ventilated patients

*DPT = Demerol, Phenergan, and Thorazine
Historical Perspective

- Limited options in 1980s
  - “Brutocaine” → DPT injections
  - “Lytic Cocktail” → lethargy, seizures, long acting, extrapyramidal symptoms
  - Called into question in early to mid 1990’s

- 1990’s
  - DPT injections → midazolam +/- morphine → ketamine in kids
  - Limited monitoring and accountability
“Newer drugs are available that may provide safe and effective sedation and analgesia . . . including midazolam, fentanyl, ketamine, and propofol.”

- Increase in adverse events leading to Joint Commission standards for sedation outside of the OR
Popularity of Ketamine in Pediatrics

- Very popular for use in procedural dissociative sedation in 1990s as pediatric EM developed as a specialty
  - IM or IV
  - Rapid onset and short half life
  - Amnesia, sedation and analgesia
- Also used for mechanically ventilated children with asthma and procedures in children with shock
ACEP Clinical Practice Guideline for ED Dissociative Sedation: 2011 Update
SM Green, MG Roback, RM Kennedy, B Krauss
- Revision of 2004 guideline, several prior recommendations disproved.
- Sufficient ED research in adults to support expansion of ketamine use beyond children.
Absolute contraindications- schizophrenia, even if currently stable or controlled with medications; age < 3 months

Head trauma removed as a relative contraindication while retaining previous concerns relating to CNS masses, abnormalities or hydrocephalus.

Door opened for ketamine usage in all ages and trauma
Ketamine Timeline

**1960’s**
- Ketamine first synthesized -- Calvin Stevens
- Patented in U.S. as an anesthetic & sedative in humans

**1970’s**
- FDA approved for human use—primarily in pediatrics and elderly
- Battlefield anesthetic during Vietnam War
- Sedative agent for uncooperative children
- FDA approved for human use—primarily in pediatrics and elderly
- Battlefield anesthetic during Vietnam War
- Sedative agent for uncooperative children

**1980’s**
- Decline in use due to increased illicit use and emergence reactions
- Ketamine first used to treat pain-1989

**1990’s**
- Ketamine declared a Schedule III Drug, controlled substance in the U.S.

**2000’s**
- Increased use in treatment of acute & chronic pain
- Ketamine as treatment for depression
Ketamine Pharmacology

- Blockade of N-methyl D-aspartate (NMDA) receptors, peripheral Na+ channels and μ-opioid receptors providing sedation, amnesia, and analgesia.
  - R(−) vs S(+) ketamine
    - S(+) enantiomer provides better analgesia (4x potent) but more auditory/visual disturbances
- High lipid solubility
  - Allows rapid crossing of the blood-brain barrier,
  - Quick onset of action (peak concentration at 1 minute-IV)
- Rapid recovery to baseline (duration 5-15 minutes).
Ketamine Indications

- Used in ED and ICU settings for procedures via *dissociative amnesia* and analgesia.
  - Higher doses are used than for analgesia alone

- Ketamine used in ED, EMS and military settings in *subdissociative* doses either as *adjunct to opioid analgesics* or as *solo agent analgesic*. 
Ketamine Advantages

- Preserves airway patency, ventilation and cardiovascular stability

- Small doses may increase analgesic potency of opioids
  - Opioid-resistant pain
  - Trauma patients with hemodynamically instability

- Multiple routes- intravenous (IV), intramuscular (IM), intranasal (IN) and oral (PO)
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<td>IV: 1 mg/kg; IM: 4-5 mg/kg</td>
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+PAMI Pain Management and Dosing Guide
*Dosing not well established. Studies have used 0.5-9 mg/kg.*
Additional Indications for Ketamine

- Antidepressant effects that can influence the ‘emotional’ coloring of pain
- PTSD symptom reduction by blocking glutamate via NMDA receptor blockade.
- Excited Delirium Syndrome
- Anti-inflammatory
- Metabolism blockage of morphine
Ketamine Controversies

- Who can administer and where?
  - ED vs OR
  - Nurse vs physician
- Monitoring
- Indications and age
- Long term effects
Why EDs Love Ketamine: Short Version

- Fast, short acting
- Multiple routes
- Multiple uses
- Usually no apnea or hypotension
- Comfort zone from years of using in pediatric emergencies

If it is safe for kids it must be safe for everyone
# Dissociative Dose Ketamine for PSA

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Procedural Sedation and Analgesia (PSA)

- Use of pharmacologic agents to provide anxiolysis, analgesia, sedation, and motor control during procedures or diagnostic tests.
  - Reduces discomfort, apprehension and potential unpleasant memories associated with procedures
  - Commonly used for a variety of indications
Fracture reduction & orthopedic procedures
Burn & wound debridement
Cardioversion, endoscopy or bronchoscopy
IV or blood draw lumbar puncture
Chest tube insertion
Radiographic studies in agitated or uncooperative patients
Abscess incision & drainage
Laceration repair
Foreign body removal
Ketamine Side Effects in PSA

- Common:
  - Nausea, vomiting, mild increase in HR and BP
  - Pretreatment with ondansetron

- Uncommon
  - Laryngospasm, emergence reactions, nightmares
Ketamine Combinations

- Ketamine and midazolam
- Ketamine and atropine
- Ketamine and propofol = “Ketofol”
  - Prepare 1:1 mixture of ketamine and propofol (10mg/1ml concentration of each drug)
  - Anticipate single dose of 0.75 mg/kg Ketamine + 0.75mg/kg of propofol
# Sub-dissociative Dose Ketamine (SSDK)

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Why New Interest in SDDK?

- Increased military usage—ED/EMS treatments often based on successful military medical care
- 2011: Committee on Tactical Combat Casualty Care (CoTCCC) guidelines recommends 20 mg IV or 50 mg IM/IN as initial dose
- Defense Health Board authorized SDDK for battlefield/pre-hospital analgesia
Why New Interest in SDDK?

- Opioid epidemic
  - Interest in use of non-opioid treatments in the ED
  - Opioid-free EDs- reality check
  - Alternatives To Opiates (ALTOSM) Program

Patient advocacy; HCAHPS scores; Patient safety

DEA, TJC, Regulatory agencies

Tug-of-war
Conflicting priorities
SDDK for Analgesia in the ED

- SDDK for analgesia has been well documented in various settings such as cancer, palliative, and perioperative care, the military and in chronic therapy for neuropathic pain.
SDDK for Analgesia in the ED

- Why not the ED?
  - ED physicians comfortable using for PSA, especially in pediatrics
    - Use < 5% for adult PSA in 2011 but has increased
  - Many proposed contraindications disproven, remaining concerns over emergence phenomenon
  - Growing ED and pre-hospital literature over past 10 years
<table>
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<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Potential emergence reaction</td>
<td>88%</td>
</tr>
<tr>
<td>Concerns or restrictions on use</td>
<td>42%</td>
</tr>
<tr>
<td>Limited literature on adult use compared to children</td>
<td>29%</td>
</tr>
<tr>
<td>Can’t use in patients with hypertension</td>
<td>17%</td>
</tr>
<tr>
<td>Better drugs available</td>
<td>17%</td>
</tr>
<tr>
<td>Potential laryngospasm</td>
<td>8%</td>
</tr>
<tr>
<td>Ignorance</td>
<td>4%</td>
</tr>
<tr>
<td>Nursing concerns</td>
<td>4%</td>
</tr>
<tr>
<td>Stigma</td>
<td>4%</td>
</tr>
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</table>

SDDK for Analgesia:
Suggested in 4 ED patient populations:

1. Acute traumatic and non-traumatic pain
2. Awake patients needing brief painful procedures
3. Patients with chronic pain on high-doses of opioids experiencing intractable breakthrough pain
4. Patients experiencing pain along with emotional distress

Acute Pain in the ED
Ketamine vs Opioids

Ketamine adjunct better than opioids alone

- **Lester et al. 2010**
  - 54% (19 out of 35) of patients reported pain relief after opioids failed. No adverse events.

- **Johansson et al. 2009**
  - improved pain scores with ketamine + morphine in prehospital long-bone fractures
Ketamine vs opioids

Ketamine adjunct better than opioids alone

- TL Ahern et al. 2013 - ketamine + hydromorphone
  - profound pain reduction at 5 minutes, where the mean and median reduction in NRS was 6.0 and 7.5
  - 46% of subjects reported complete resolution of pain
  - higher rate of nausea compared to hydromorphone alone (25% vs 7%)
Ketamine vs opioids

Ketamine adjunct equal to opioids alone

- Ahmadi et al 2014
  - ketamine + midazolam = morphine in closed limb fractures

- Motov et al. 2015
  - No difference in pain score reductions or proportion with complete pain relief between morphine (0.1 mg/kg) and ketamine (0.3 mg/kg) groups
  - Ketamine group with higher side effects (dizziness, disorientation)
Ketamine vs Opioids

Morphine vs. ketamine

Miller et al. 2015

–ketamine was not superior to morphine in the maximum change of NRS pain scores
–maximum reduction in NRS pain scores was 5 minutes for ketamine vs 100 minutes for morphine
–vital signs, adverse events, provider and nurse satisfaction scores were similar
Best SDDK Adjunct Dosing?

- Beaudoin et al. 2014
  - ketamine 0.3 mg/kg more effective than 0.15 mg/kg as morphine adjunct
  - Minor adverse events
Review of 4 RCT Trials in the ED

- In patients with moderate-severe pain failing conventional therapies, is the administration of SDDK, compared to placebo, safe and effective in pain control?
  - Primary outcome- difference in pain score
  - Secondary outcome- adverse events and reduction in opioids consumed
Review of 4 RCT Trials- Conclusions

- Four RCTs with methodologic limitations failed to provide convincing evidence to either support or refute the use of SDDK for acute pain control in the ED.
- SDDK may result in satisfactory pain control and the incidence of adverse events seems to be limited.
- SDDK may play a role in reducing the need for additional opioids.
- Most trials reported pain reduction within 5 minutes of initiating therapy.

Bottom Line

- SDDK may play a role as an adjunct in failed monotherapy
- 0.3 mg/kg dosing better than 0.1 mg/kg
- Low risk of side effects
- May reduce additional opioid use
- Shorter time to pain reduction compared to morphine
Ketamine Infusions in the ED
Ketamine Infusions

- Used at least since the 1980s
- Used for peri-operative, chronic and acute pain
- Short-lived analgesic effect as a bolus
  - peaks in few minutes, duration 10-15 min
- Suggested dosing: 0.1-0.25 mg/kg bolus + 0.2-1 mg/kg/h
ED Ketamine Infusions for Acute Pain

Goltser et al. 2015 (case series)

- 14 pts with acute or acute exacerbations of chronic disease
- Low-dose (0.2-0.4 mg/kg) ketamine infusions
- 33% history of chronic opioid medications
- 86% failed opioid medications in the ED
- 79% (11) had significant improvement
  - 2 patients reported mild adverse effects
ED Ketamine Infusions for Acute Pain

Golster et al. 2015 (case series)

- Short infusions of low-dose ketamine (0.3 mg/kg over 10 minutes) demonstrated significantly less side effects (6%) with effective analgesia (87%) compared with bolus dosing.
ED Ketamine Infusions for Acute Pain

Ahern et al. 2015- 38 pts

- 15 mg IV ketamine + 20 mg/h infusion x 1 hr
- Pain score reduction similar to IV morphine
- 34% “very bothersome” psychomimetic side effects
- 84% patients said they would want ketamine again
- Ketamine responders?
  - 31% (12) no rescue analgesia
  - Group with most profound drop in pain score

ED Ketamine Infusions for Acute Pain

- Ideal patient? Limited studies but consider
  - Chief Complaint:
    - undifferentiated abdominal pain
    - trauma
    - musculoskeletal pain
    - sickle cell pain
    - cancer pain
    - known opioid tolerance

Intranasal Ketamine in the ED
Intranasal Ketamine in the ED

- Appealing in overcrowded resource limited EDs

- Bioavailability 45%

- Suitable for acute or breakthrough pain

- Exact dose difficult to control
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<th>Dose</th>
<th>Max Dose</th>
<th>Comments</th>
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<tr>
<td>Ketamine</td>
<td>0.5-1.0 mg/kg</td>
<td>Limited data</td>
<td>Use with caution until further studied</td>
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*Always use the MOST concentrated formulation with an atomizer.

+ Dosing range not well established. Studies have used 0.5-9 mg/kg.
Intranasal Ketamine in the ED

- Graudins et al. 2015 (PICHFORK ED RCT)
  - IN ketamine and fentanyl equivalent in pediatric limb injuries
  - Ketamine more minor adverse events (78 vs 40%)
  - 3 patients with moderate degree of sedation

- Shrestha R et al. 2016
  - Age > 8 years
  - 0.7 mg/kg IN ketamine (given by drop) showed significant pain relief 79% of patients at 15 minutes
    - increased to 100% at 30 and 60 minutes.
Intranasal Ketamine in the ED

- **Andolfatto et al. 2013**
  - Clinically significant reduction in VAS pain scores seen in 88% of adult and pediatric patients with orthopedic injuries (IN 0.5-0.75 mg/kg)

- **Yeaman et al. 2013**
  - 1 mg/kg provided 30 min of analgesia in children age 3-13 yrs with mod-to-severe limb pain.
  - 82% reported reduction of $\geq 20$mm
Intranasal Ketamine in the ED - Bottom line

- Studies including children reported overall better pain relief compared to the one adult-only study
  - IN ketamine as first line in pediatric pts
  - IN ketamine as adjunct in adult pts with poor opioid response or in opioid-dependent pts
Topical, Oral and Sublingual Ketamine

- Not currently used in the ED settings
- Used in chronic wound and chronic pain conditions outside the ED
- Future ED use?
Multimodal Pain Management Using Ketamine
Multimodal Therapy Rationale

- Multimodal therapy and algorithms are now commonly used pre and post surgery to decrease opioid use and adverse events, improve function and promote successful discharge home
- Many analgesics are synergistic
- Fewer side effects with lower dosages
- Multimodal management just beginning in ED settings
Alternatives To Opiates (ALTOSM) Program

Alexis LaPietra, DO
Medical Director of Emergency Medicine Pain Management
St. Joseph’s Regional Medical Center
Extremity Fracture or Joint Dislocation

- Ketamine Intranasal 0.5 mg/kg (concentration 50 mg/mL)
  - MAX dose 50 mg; MAX volume per nare 1 mL
- Nitrous Oxide titrate up to 70%
- Acetaminophen 1000 mg PO
- Ultrasound Guided Regional Anesthesia
  - Joint Dislocation
    - Lidocaine 0.5 % peri-neural infiltration (MAX 5 mg/kg)
  - Extremity Fracture
    - Ropivacaine 0.5% peri-neural infiltration (MAX 3 mg/kg)
Acute on Chronic Radicular LBP (Opiate Tolerant)

- Acetaminophen 1000 mg PO
- Ibuprofen 600 mg PO OR ketorolac 30 mg IV/IM
- Muscle Relaxant
- Gabapentin (neuropathic pain) – 300 mg PO
- Dexamethasone 8 mg IV

- Lidocaine patch
- Trigger Point Injection(s)
- Ketamine 0.1-0.3 mg/kg in 50 cc NS over 10 min; then 0.1 mg/kg/hour infusion until pain is tolerable
Ketamine for Excited Delirium Syndrome
Excited Delirium Syndrome

- Increase in potent synthetic stimulatory drugs available through the internet and dealers
  - Severely agitated patients pose potential safety threat to themselves, prehospital personnel, and ED staff
  - Benzodiazepines and antipsychotics typically used for treatment
    - Problems with time to onset, elimination time, and over-sedation requiring intubation
## Excited Delirium Syndrome

- Ketamine faster onset, procedural sedation dosing
- Monitoring? Requirements for PSA, none for EDS

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Ketamine Safety Considerations

- Adverse events - varying definition
- Special populations
- Monitoring
- Discharge planning
Adverse Events

- Ahern T.L. et al. 2015
  - Low adverse event rate within 1 hour (30, 6%) mostly transient and moderate to mild
  - No laryngospasm, apnea, HTN emergency or cardiac arrests
  - 1.5% (7) experienced hypoxia BUT 4 pts concurrently received hydromorphone
    - 5% rate of hypoxia associated with hydromorphone (Chang et al 2011)

Adverse Events

- Ahern T.L. et al. 2015
  - 1% (5) emesis, no aspiration
  - 3.5% (18) psychomimetic or dysphoric reactions
    - Only 3 required intervention
  - No significant change in heart rate or blood pressure

Ketamine Increased ICP Concern

- Neuroprotective properties
  - $S^+\text{-ketamine}$ increases cerebral blood volume

- Theoretical concern of increased ICP after ketamine dosing
  - Preliminary and methodologically limited studies indicating this may not be true in sedated mechanically-ventilated pts
Ketamine and Dysphoria

- Mild dysphoria can occur at sub-dissociative dosing
  - Dissociative range (1-2 mg/kg IV) – emergence phenomenon
  - Rates from 3.5-26%, transient

- Patients reporting negative dissociative effects may still report high satisfaction at discharge (Ahern T et al. 2013)

- Patients should be warned about possible effects and a calm environment should be created
### Ketamine Pitfalls

**Is goal sedation or analgesia?**

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- **Confusion about indication**
- **Wrong dose selection**
- **Over-sedation, apnea**
Monitoring
What Monitoring is Required for Ketamine?

- Clear monitoring guidelines for PSA
- Currently no guidelines or studies exist regarding what type of monitoring should be used with SDDK
- IN medications?
• Example of monitoring for inpatient ketamine infusion.

• What about the ED?

• What about ketamine bolus dosing?

• Intranasal?

Discharge Planning after Ketamine
Certain Conditions Should be met Before a Patient can be Considered Safe for Discharge after PSA:

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<th>Alert, oriented and back to pre-sedation baseline (Modified Aldrete Score $\geq 9$)</th>
<th>Stable vital signs, respiratory and cardiac functions</th>
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<td>Tolerating fluids and no emesis</td>
<td>Patient is ambulatory and demonstrating normal activity (age/developmentally appropriate)</td>
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<td>Sufficient time post-administration of IV medications</td>
<td>Airway is patent with protective reflexes intact</td>
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Discharge Planning for Patients with Pain

- Discharge planning should take into account ED pain medications received, comorbidities and transportation home.
  - How will patient be safely transported home or to another facility?
  - Is patient ambulating at baseline without assistance?
  - Are there still ongoing ketamine effects (i.e. lethargy, emesis, dysphoria)?
Summary

- Ketamine is rapidly gaining favor in the ED and EMS settings
- Relatively safe compared to other options
- Comfort zone for ED and EMS providers
- Dramatic increase in ED/EMS related ketamine research
- Numerous routes and indications
- Potential to avoid opioids
Thank you!

Please share your comments, suggestions, or protocols

Email: Sophia.Sheikh@jax.ufl.edu or Phyllis.Hendry@jax.ufl.edu

Call: 904-244-4986

Website: http://pami.emergency.med.jax.ufl.edu
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