PAINWEEK®

Why Emergency Departments Love Ketamine

Sophia Sheikh, MD, FACEP
Phyllis Hendry, MD, FACEP, FAAP

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

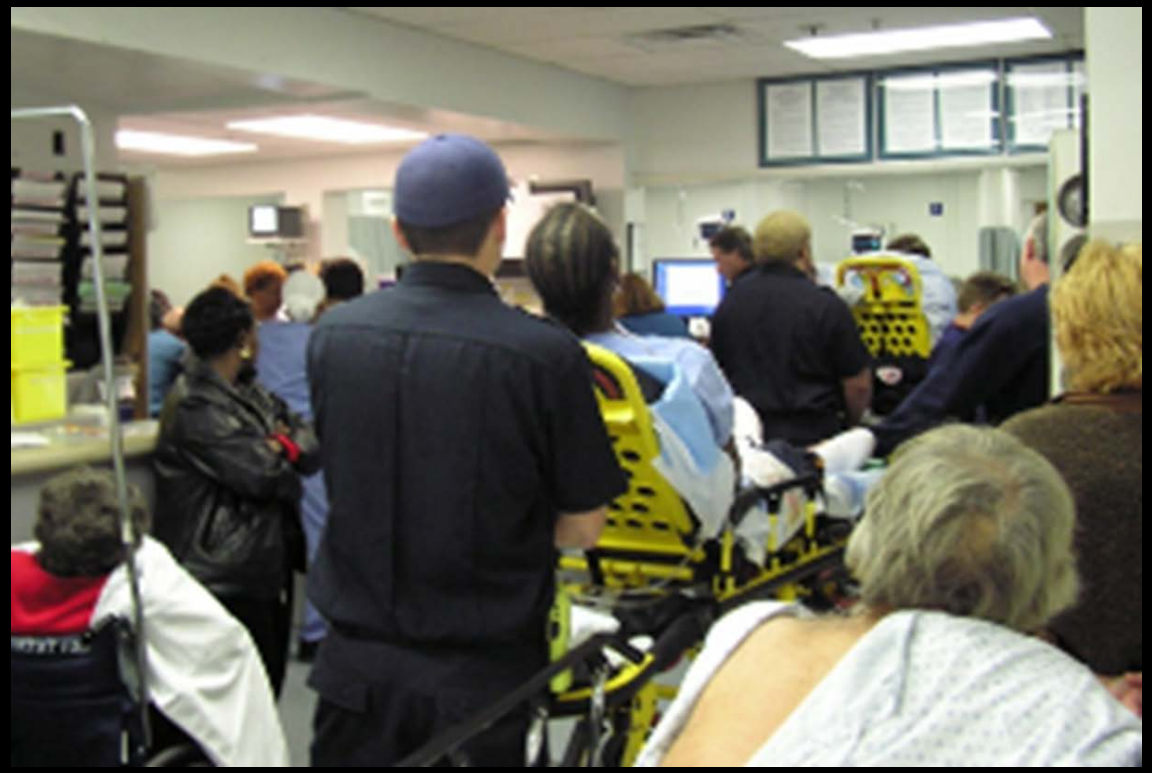
- 6. Patient credibility and provider biases
  - Unique population of patients often with mental illness, substance abuse and co-morbidities leading to bias
  - Limited means or time to verify patient's history
  - Drug-seekers vs drug-diverters vs legitimate pain

Pain in the ED: Background and Barriers

- 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


XIII.—No. 636.] NEW YORK, SATURDAY, MARCH 6, 1869.
THE COUNTRY DOCTOR.—[Drawn by A. R. Waud.]


RESTAURANT
PAIN & COLD MEDICINE
SOMEONE SPECIAL WHO LOVES ME WENT TO NEW ORLEANS AND GOT ME THIS BOX OF Pralines COMPANY
LIQUOR BEER WINE
PRALINES
SELECT

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

American Academy of Pediatrics:
Reappraisal Of Lytic Cocktail/DPT For The Sedation
Of Children, Committee On Drugs.
Pediatrics. April 1995

- "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.

ACEP Clinical Practice Guideline for ED Dissociative Sedation: 2011 Update

- 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

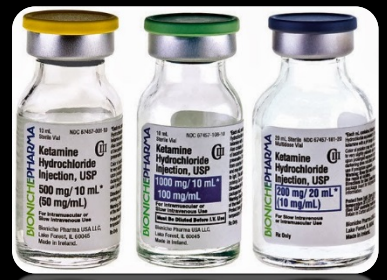
- FDA approved for human use—primarily in pediatrics and elderly
- Battlefield anesthetic during Vietnam War
- Sedative agent for uncooperative children

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)

Ketamine Indications+

Indications	Starting Dose
Procedural Sedation	IV: Adult 0.5-1.0 mg/kg, Ped 1-2mg/kg; IM: 4-5 mg/kg
Sub-dissociative Analgesia	IV: 0.1 to 0.3 mg/kg, initial starting dose max initial dose variable (10-20 mg) IM: 0.5-1.0 mg/kg; IN*: 0.5-1.0 mg/kg
Excited Delirium Syndrome	IV: 1 mg/kg; IM: 4-5 mg/kg

+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

Indications	Starting Dose
Procedural Sedation	IV: Adult 0.5-1.0 mg/kg, Ped 1-2mg/kg; IM: 4-5 mg/kg

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)

Ketamine Indications	
Indications	Starting Dose
Sub-dissociative Analgesia	IV: 0.1 to 0.3 mg/kg, initial starting dose max initial dose variable (10-20 mg) IM: 0.5-1.0 mg/kg; IN*: 0.5-1.0 mg/kg

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

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

Physician's reasons for ketamine underuse in adult patients- 2013	
Potential emergence reaction	88%
Concerns or restrictions on use	42%
Limited literature on adult use compared to children	29%
Can't use in patients with hypertension	17%
Better drugs available	17%
Potential laryngospasm	8%
Ignorance	4%
Nursing concerns	4%
Stigma	4%

Richards JR et al. Low-dose ketamine analgesia: patient and physician experience in the ED. Am J of Emergency Medicine (2013) 31, 390–394

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

Herring AA. Emerging applications of low-dose ketamine for pain management in the ED. The American Journal of Emergency Medicine 2013;31(2):416–419

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 (0.3mg/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
  - Sin et al. Subdissociative-dose ketamine for acute pain in the ED. Academic Emergency Medicine 2015;22:251–257

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

Sin et al. Subdissociative-dose ketamine for acute pain in the ED. Academic Emergency Medicine 2015;22:251–257

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

Ahern TL. Herring AA. Miller S. Frazee BW. Low-Dose Ketamine Infusion for Emergency Department Patients with Severe Pain. Pain Medicine 2015; 16: 1402–1409

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

Ahern TL. Herring AA. Miller S. Frazee BW. Low-Dose Ketamine Infusion for Emergency Department Patients with Severe Pain. Pain Medicine 2015; 16: 1402–1409

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

Intranasal*			
Medication	**Dose**	**Max Dose**	**Comments**
Ketamine+	**0.5-1.0 mg/kg Large range**	**Limited data**	**Use with caution until further studied**

*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 >/=20mm

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

Ketamine Indications	
Indications	Starting Dose
Procedural Sedation	IV: Adult 0.5-1.0 mg/kg, Ped 1-2mg/kg; IM: 4-5 mg/kg
Sub-dissociative Analgesia	IV: 0.1 to 0.3 mg/kg, initial starting dose max initial dose variable (10-20 mg) IM: 0.5-1.0 mg/kg; IN*: 0.5-1.0 mg/kg
Excited Delirium Syndrome	IV: 1 mg/kg; IM: 4-5 mg/kg

Adverse events- varying definition

Special populations

Monitoring

Discharge planning

Ketamine Safety Considerations

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)

TL Ahern et al. The first 500: initial experience with widespread use of low-dose ketamine for acute pain management in the ED. American Journal of Emergency Medicine 33 (2015) 197–201

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

TL Ahern et al. The first 500: initial experience with widespread use of low-dose ketamine for acute pain management in the ED. American Journal of Emergency Medicine 33 (2015) 197–201

Ketamine Increased ICP Concern

- Neuroprotective properties
  - S+-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

Confusion about indication

Is goal sedation or analgesia?

Wrong dose selection

Over-sedation, apnea

Ketamine Indications	
Indications	Starting Dose
Procedural Sedation	IV: Adult 0.5-1.0 mg/kg, Ped 1-2mg/kg; IM: 4-5 mg/kg
Sub-dissociative Analgesia	IV: 0.1 to 0.3 mg/kg, initial starting dose max initial dose variable (10-20 mg) IM: 0.5-1.0 mg/kg; IN*: 0.5-1.0 mg/kg
Excited Delirium Syndrome	IV: 1 mg/kg; IM: 4-5 mg/kg

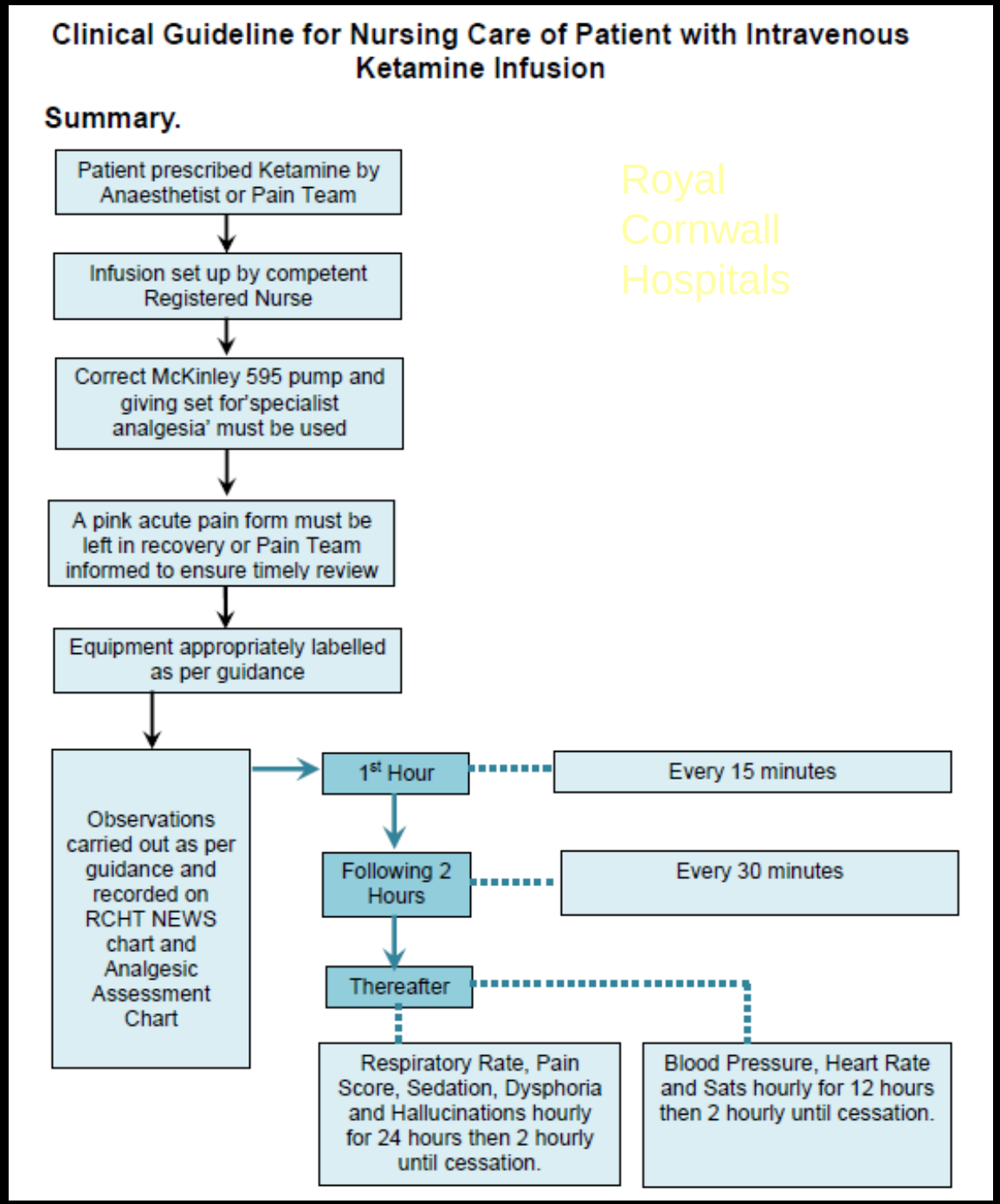
Monitoring

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?

http://www.rcht.nhs.uk/DocumentsLibrary/RoyalCornwallHospitalsTrust/Clinical/Pain/IntravenousKetamineInfusionNursingGuidelines.pdf



Discharge Planning after Ketamine

Certain Conditions Should be met Before a Patient can be Considered Safe for Sischarge after PSA:

Alert, oriented and back to pre-sedation baseline (Modified Aldrete Score ≥ 9)	Stable vital signs, respiratory and cardiac functions
Tolerating fluids and no emesis	Patient is ambulatory and demonstrating normal activity (age/developmentally appropriate)
Sufficient time post-administration of IV medications	Airway is patent with protective reflexes intact

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

Questions

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

References

- Thomas SH. Management of pain in the emergency department. ISRN Emergency Medicine. 2013;2013. doi:10.1155/2013/583132.
- Chen R. Reappraisal of lytic cocktail/demerol, phenergan, and thorazine (DPT) for the sedation of children. The Journal of Em ergency Medicine. 1995;13(6):867. doi:10.1016/0736-4679(96)81893-2.
- Sprenger T, Valet M, Woltmann R, Zimmer C, Freynhagen R, Kochs EF, et al. Imaging pain modulation by subanesthetic S-(+)-ketamine.Anesth Analg 2006;103(3):729-37 IARS.
- Wang J, Goffer Y, Xu D, Tukey DS, Shamir DB, Eberle SE, et al. A single subanesthetic dose of ketamine relieves depression-like behaviors induced by neuropathic pain in rats. Anesthesiology 2011;115(4):812-21.
- Machado-Vieira R, Salvadore G, Diazgranados N, Zarate CA. Ketamine and the next generation of antidepressants with a rapid onset of action. Pharmacol Ther 2009;123(2):143-5.
- Qi X, Evans AM, Wang J, Miners JO, Upton RN, Milne RW. Inhibition of morphine metabolism by ketamine. Drug Metab Dispos 2010;38:728-31.
- Loix S, De Kock M, Henin P. The anti-inflammatory effects of ketamine: state of the art. Acta Anaesthesiol Belg 2011;62:47-58.
- Butler FK, Kotwal RS, Buckenmaier III CC, et al. A Triple-Option Analgesia Plan for Tactical Combat Casualty Care: TCCC Guidelines Change 13-04. Journal of Special Operations Medicine. 2014;14(1).
- Defense Health Board. Prehospital Use of Ketamine in Battlefield Analgesia 2012-03. In: Department of Defense; 2012.

References

- Mercer SJ. 'The drug of war' —a historical review of the use of ketamine in military conflicts. J R Nav Med Serv 2009;95:145-50.
- Bennett GJ. Update on the neurophysiology of pain transmission and modulation: focus on the NMDA receptor. J Pain Symptom Manage 2000;19:S2–S6.
- Hocking G, Cousins MJ. Ketamine in chronic pain management: an evidence-based review. Anesth Analg 2003;97:1730–9.
- Himmelseher S, Durieux ME. Ketamine for perioperative pain management. Anesthesiology 2005;102:211–20.
- Talwic QA. A review of the use of ketamine in pain management. J Opioid Manag 2013;9:379–88.
- DuPen A, Shen D, Ersek M. Mechanisms of opioidinduced tolerance and hyperalgesia. Pain Manag Nurs 2007;8:113 –21.
- Bredlau A, McDermott MP, Adams HR, et al. Oral ketamine for children with chronic pain: a pilot phase 1 study. J Pediatr 2013 ;163:194–200.
- Mercadante S, Lodi F, Sapio M, Calligara M, Serretta R. Long-term ketamine subcutaneous continuous infusion in neuropathic cancer pain. J Pain Symptom Manage 1995;10:564–8.
- Niesters M, Martini C, Dahan A. Ketamine for chronic pain: risks and benefits. Br J Clin Pharmacol 2014;77:357 –67.
- Richards JR et al. Low-dose ketamine analgesia: patient and physician experience in the ED. American Journal of Emergency Medicine (2013) 31, 390–394.
- Scheppke KA, Braghiroli J, Shalaby M, Chait R. Prehospital Use of IM Ketamine for Sedation of Violent and Agitated Patients.Western Journal of Emergency Medicine. 2014;15(7):736-741. doi:10.5811/westjem.2014.9.23229.
- Herring AA. Emerging applications of low-dose ketamine for pain management in the ED. The American Journal of Emergency Medicine 2013;31(2):416–419.

References

- Lester L, Braude DA, Niles C, Crandall CS. Low-dose ketamine for analgesia in the ED: a retrospective case series. Am J Emerg Med 2010;28:820-7.
- Johansson P, Kongstad P, Johansson A. The effect of combined treatment with morphine sulphate and low-dose ketamine in a prehospital setting. Scand J Trauma Resusc Emerg Med 2009;17:61.
- TL Ahern et al. Effective analgesia with low-dose ketamine and reduced dose hydromorphone in ED patients with severe pain. American Journal of Emergency Medicine 31 (2013) 847–851.
- Chang AK, Bijur PE, et al. Randomized clinical trial comparing the safety and efficacy of a hydromorphone titration protocol to usual care in the management of adult emergency department patients with acute severe pain. Ann Emerg Med 2011 Oct;58(4):352–9.
- Chang AK, Bijur PE, et al. Safety and efficacy of rapid titration using 1mg doses of intravenous hydromorphone in emergency department patients with acute severe pain: the "1+1" protocol. Ann Emerg Med 2009;54(2):221–5.
- Ahmadi O, Isfahani MN, Feizi A. Comparing low-dose intravenous ketamine-midazolam with intravenous morphine with respect to pain control in patients with closed limb fracture. Journal of Research in Medical Sciences : The Official Journal of Isfahan University of Medical Sciences. 2014;19(6):502-508.
- Motov et al. Intravenous Subdissociative-Dose Ketamine Versus Morphine for Analgesia in the Emergency Department: A Randomized Controlled TrialAnn Emerg Med. 2015;66:222–229
- Miller J, Schauer S, Ganem V, et al. Low-dose ketamine vs morphine for acute pain in the ED: a randomized controlled trial. Am J Emerg Med. 2015;33:402-408.

References

- Beaudoin et al .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. Academic Emergency Medicine 2014;21:1194–1202.
- Sih Kendra et al. Ketamine in Adult Emergency Medicine: Controversies and Recent Advances. Ann Pharmacother 2011;45:1525-34.
- S. Patil, M. Anitescu. Efficacy of outpatient ketamine infusions in refractory chronic pain syndromes: a 5-year retrospective analysis 13 (2) (2012), pp. 263–269.
- R.F. Bell, J.B. Dahl, R.A. Moore, E. Kalso. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev (2009).
- W.T. Zempsky, K.A. Loiselle, J.M. Corsi, J.N. Hagstrom. Use of low-dose ketamine infusion for pediatric patients with sickle cell disease-related pain. Clin J Pain, 26 (2010), pp. 164–167.
- Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: A review of current techniques and outcomes. Pain 1999;82(2):111–25.
- Weinbraum AA. Non-opioid IV adjuvants in the perioperative period: Pharmacological and clinical aspects of ketamine and gabapentinoids. Pharmacol Res 2012;65(4):411–29.
- Peltoniemi MA et al. Ketamine: A Review of Clinical Pharmacokinetics and Pharmacodynamics in Anesthesia and Pain Therapy. Cli n Pharmacokinet DOI 10.1007/s40262-016-0383-6 (dosing).

References

- A. Gurnani, P.K. Sharma, R.S. Rautela, A. Bhattacharya. Analgesia for acute musculoskeletal trauma: low-dose subcutaneous infusion of ketamine. Anaesth Intensive Care, 24 (1996), pp. 32–36.
- Goltser A, Soleyman-Zomalan E, Kresch F, Motov S. Short (low-dose) ketamine infusion for managing acute pain in the ED: case-report series. Am J Emerg Med. 2015 Apr;33(4):601.e5-7.
- Ahern TL. Herring AA. Miller S. Frazee BW. Low-Dose Ketamine Infusion for Emergency Department Patients with Severe Pain. Pain Medicine 2015; 16: 1402–1409.
- Peltoniemi MA et al. Ketamine: A Review of Clinical Pharmacokinetics and Pharmacodynamics in Anesthesia and Pain Therapy. Clin Pharmacokinet DOI 10.1007/s40262-016-0383-6.
- Graudins et al. The PICHFORK (Pain in Children Fentanyl or Ketamine) Trial: A Randomized Controlled Trial Comparing Intranasal Ketamine and Fentanyl for the Relief of Moderate to Severe Pain in Children With Limb Injuries. Annals of Emergency Medicine 2015;65(3):248–254.
- Shrestha R, Pant S, Shrestha A, Batajoo KH, Thapa R, Vaidya S. Intranasal ketamine for the treatment of patients with acute pain in the emergency department. World J Emerg Med. 2016;7(1):19-24.
- Andolfatto G, Willman E, Joo D, Miller P, Wong WB, Koehn M, et al. Intranasal ketamine for analgesia in the emergency department: a prospective observational series. Acad Emerg Med 2013; 20: 1050–4.
- Yeaman F, Oakley E, Meek R, Graudins A. Sub-dissociative dose intranasal ketamine for limb injury pain in children in the emergency department: A pilot study. Emerg Med Australas 2013; 25: 161–7.
- TL Ahern et al. The first 500: initial experience with widespread use of low-dose ketamine for acute pain management in the ED. American Journal of Emergency Medicine 33 (2015) 197–201.

References

- Finch PM, Knudsen L, Drummond PD. Reduction of allodynia in patients with complex regional pain syndrome: a double -blind placebo-controlled trial of topical ketamine. Pain 2009;146:18–25.
- Gewandter JS, Mohile SG, Heckler CE, Ryan JL, Kirshner JJ, Flynn PJ, et al. A phase III randomized, placebo-controlled study of topical amitriptyline and ketamine for chemotherapy inducedperipheral neuropathy (CIPN): a University of Rochester CCOP study of 462 cancer survivors. Support Care Cancer. 2014;22:1807–14.
- Tam E. Furlan AD. Transdermal lidocaine and ketamine for neuropathic pain: A study of effectiveness and tolerability. Open Journal J 2012;6:58-64.
- Woo KY et al. Evidence-based approach to manage persistent wound-related pain. Curr Opin Support Palliat Care 2013, 7:86–94.
- Kundra P et al. Oral ketamine and dexmedetomidine in adults' burns wound dressing—A randomized double blind cross over study. Burns 3 9 (2 0 1 3) 1 1 5 0 – 1 1 5 6.
- Rolan P, Lim S, Sunderland V, Liu Y, Molnar V. The absolute bioavailability of racemic ketamine from a novel sublingual formu lation. Br J Clin Pharmacol. 2014 Jun;77(6):1011-6.
- Motov S. Nelson L. Advanced Concepts and Controversies in Emergency Department Pain Management. Anesthesiology Clinics 2016.
- Green SM. Let's "Take 'Em Down" With a Ketamine Blow Dart. Annals of Emergency Medicine 2016;67(5) :588 -290.
- Chang AK, Bijur PE, Gallagher E. Randomized clinical trial comparing the safety and efficacy of a hydromorphone titration pro tocol to usual care in the management of adult emergency department patients with acute severe pain. Ann Emerg Med 2011;58(4):352–9.
- Jennings PA et al. Morphine and Ketamine Is Superior to Morphine Alone for Out-of-Hospital Trauma Analgesia: A Randomized Controlled Trial. Ann Emerg Med. 2012;59:497-503.

References

- Zeiler FA, Teitelbaum J, West M, Gillman LM. The ketamine effect on ICP in traumatic brain injury. Neurocrit Care. 2014;21:163–73.
- F.X. Marcoux, J.E. Goodrich, M.A. Dominick. Ketamine prevents ischaemic neuronal injury. Brain Res, 452 (1988), pp. 329 – 355.
- J. Albanese, S. Arnaud, M. Rey, L. Thomachot, B. Alliez, C. Martin. Ketamine decreases intracranial pressure and electroencephalographic activity in traumatic brain injury patients during propofol sedation. Anesthesiology, 87 (1997), pp. 1328–1334.
- R.S. Sehdev, A.D.A. Symmons, K. Kindl. Ketamine for rapid sequence induction in patients with head injury in the emergency department. Emerg Med Australas, 18 (2006), pp. 37–44.
- Pfenninger E, Grunert A, Bowdler I, et al: The effect of ketamine on intracranial pressure during haemorrhagic shock under the conditions of both spontaneous breathing and controlled ventilation. Acta Neurochir 1985; 78:113–118.
- Schwedler M, Miletich DJ, Albrecht RF: Cerebral blood flow and metabolism following ketamine administration. Can Anaesth Soc J 1982; 29:222–226.
- Shackelford SA, Fowler M, Schultz K, et al. Prehospital pain medication use by U.S. Forces in Afghanistan. Mil Med. 2015;180(3):304-309.

References

- Ahern T, Herring A, Stone M, Frazee B. Effective analgesia with low-dose ketamine and reduced dose hydromorphone in ED patients with severe pain. Am J Emerg Med 2013;31(5):847–51.
- GalinskiM, Dolveck F, Combes X, Limoges V, Smail N, Pommier V, et al.Management of severe acute pain in emergency settings: ketamine reduces morphine consumption. Am J Emerg Med 2007;25(4):385–90.
- Richards JR, Rockford RE. Low-dose ketamine analgesia: patient and physician experience in the ED. Am J Emerg Med 2013;31(2):390–4.
- Zou L, Tian SY, Quan X, Ye TH. Psychedelic effects of subanesthetic doses of ketamine. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2009;31:68-72.
- Witt N, Coynor S, Edwards C, Bradshaw H. A Guide to Pain Assessment and Management in the Neonate. Current Emergency and Hospital Medicine Reports. 2016;4:1-10.
- Saarenmaa E et al. Ketamine for procedural pain relief in newborn infants. Arch Dis Child Fetal Neonatal Ed. 2001 Jul; 85(1): F53-6.
- CDC. National Center for Health Statistics. Centers for Disease Control and Prevention. http://www.cdc.gov/nchs/fastats/pregr isk.htm. Accessed August 9.
- Sharma S. (2003) Shock and Pregnancy. www.emedicine.com/med/topic3285.htm.
- Newton E. (2003) Trauma and Pregnancy. www.emedicine.com/med/topic3268.htm.
- Seiler RJ. Management of Pain During Pregnancy. http://www.osteopathic.org/inside -aoa/events/omed/omed-presentations/documents/aoaam-seiler.pdf. Accessed August 8, 2016.

References

- Svenson JE. et al. Ketamine for prehospital use: new look at an old drug. The American Journal of Emergency Medicine 2007:25(8):977–980
- http://www.rcht.nhs.uk/DocumentsLibrary/RoyalCornwallHospitalsTrust/Clinical/Pain/IntravenousKetamineInfusionNursingGuidelines.pdf.
- Newman DH, Azer MM, Pitetti RD, Singh S. When is a patient safe for discharge after procedural sedation? The timing of adverse effect events in 1367 pediatric procedural sedations. Ann Emerg Med 2003; 42:627.
- Pre-hospital Pain Management for Adults, Children, and Special Populations. University of Florida College of Medicine - Jacksonville Department of Emergency Medicine, Pain Management and Assessment Initiative (PAMI): A Patient Safety Project, August 9, 2016. Retrieved from http://pami.emergency.med.jax.ufl.edu/.
- Procedural Sedation and Analgesia (PSA) for Adults and Children in the Emergency Setting, University of Florida College of Medicine - Jacksonville Department of Emergency Medicine, Pain Management and Assessment Initiative (PAMI): A Patient Safety Project, August 9, 2016. Retrieved from http://pami.emergency.med.jax.ufl.edu/.
- Pain Assessment and Management Initiative. http://pami.emergency.med.jax.ufl.edu/resources/dosing-guide/.