IV Ketamine for Acute and Chronic Pain

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Faculty/ Presenter Disclosure

- Faculty: Eli Adly

- Relationships with financial sponsors: None

Code :

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Objectives

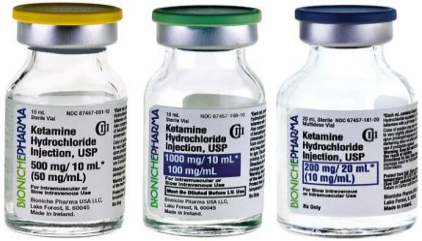
- Pharmacology , Side Effects and Relative Contraindications

- 2018 Consensus Guidelines on the Use of IV Ketamine Infusions for Acute and Chronic Pain Management

Why

Potential role : Depression & PTSD

Now, a team of pain medicine physicians are calling attention to the use of ketamine to combat chronic and acute postoperative pain.



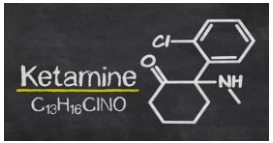
Sedative, Anesthetic, Amnestic, Antidepressant, Anti-asthma,

AND

ANALGESIC

Who, When , How

-Phencyclidine analog and dissociative anesthetic agent
-Maddox the chemist synthesized Phencyclidine 1958 , Park-Davis the pharmaceutical developed it and Dr Chen/Domino used it as an anesthetic in animals
-First used as a general anesthetic for huaman in the 1960s
-Reversible antagonism of the N-methyl-D-aspartate receptor
-NMDAr CNS (hippocampus, prefrontal) ; Agonist Glutamate
-Opioid
-Muscarinic /Nicotinic
-Monoaminergic
-GABA
-Na, K , Ca Channels



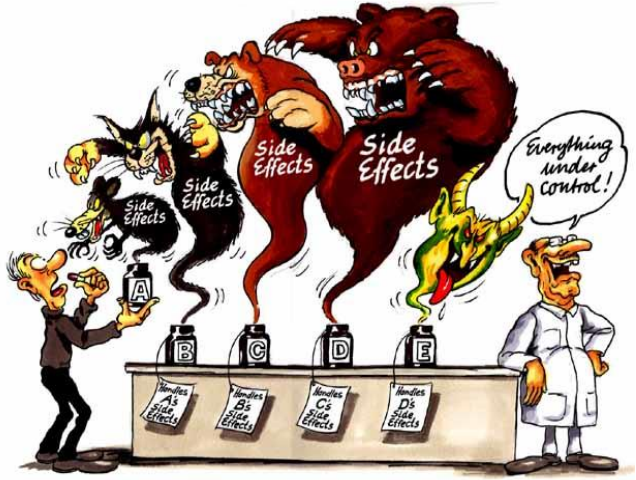
and several other receptors !

Side Effects

What are Special K's effects

Special K short term/side effects are...

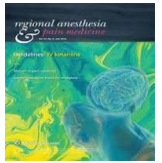
- Delirium
- Impaired attention span
- High blood pressure
- Depression
- Impaired motor function
- Bad dreams
- Respiratory failure
- Hallucinations
- Separated from the body
- Pleasant
- Sensory attachment
- Dry mouth
- Difficulty breathing
- Nervousness
- Nausea
- Vomiting
- Nightmares
- Double vision
- Muscle spasms
- Near-death experience
- Feelings of being paralyzed



Relative Contraindications

- Poorly controlled CVD : Acute CAD, Stroke , Uncontrolled BP/HR
- Psychiatric disorders such as Active Psychosis
- Raised ICP ?
- Raised IOP /Penetrating Eye Injury ?
- Acute Porphyria
- Severe/ Moderate Hepatic Disease
- Active Substance Abuse
- Pregnancy

Ketamine Infusion AND Acute Pain



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Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists

Schwenk, Eric S., MD*; Viscusi, Eugene R., MD*; Buvanendran, Asokumar, MD†; Hurley, Robert W., MD, PhD‡; Wasan, Ajay D., MD, MSc§; Narouze, Samer, MD, PhD‖; Bhatia, Anuj, MD, MBBS**; Davis, Fred N., MD††; Hooten, William M., MD‡‡; Cohen, Steven P., MD§§

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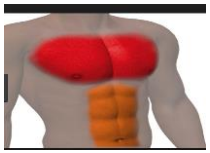
ASRA

ASRA PAIN MEDICINE

PHYSICIANS DEDICATED TO RELIEVING PAIN
the AMERICAN ACADEMY of PAIN MEDICINE
the voice of pain medicine

American Society of Anesthesiologists®

- ***Expected severe post-op pain:***



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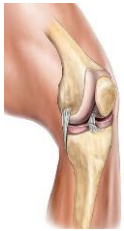


- ***Opioid tolerant/ dependent with acute pain (Sx or Exacerbation)***

-***Increased risk for opioid-related respiratory depression (OSA)***

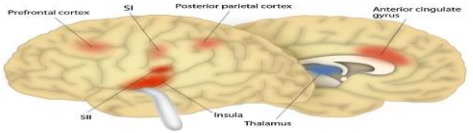
Sub-anesthetic dose :

0.5mg/kg bolus and 0.6mg/kg/hr intraop spine Sx

0.3 –0.5-mg/kg/IV bolus, +_ infusion (0.1–0.2 mg/kg/hr)

Opioid-naive : 0.05 -0.4 mg/kg/hr , opioid-tolerant : 0.05 -1 mg/kg/hr and OIH hyperalgesia: 1 mg/kg/hr

-Functional MRI : ↓ connectivity in pain perception somatosensory/ affective processing of pain (amygdala, insula and ant. cingulate cortex)



Moderate evidence supports use of subanesthetic IV ketamine bolus/infusion as adjuncts to opioids for perioperative analgesia

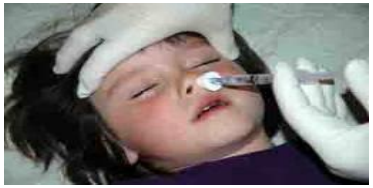
Recommended in the setting without intensive monitors :

Bolus: Do not exceed 0.35 mg/kg

Infusions: Do not exceed 1 mg/kg/hr

Evidence to Support Nonparenteral Ketamine for Acute Pain Management

-No FDA-approved nonparenteral formulations exist for PO or IN administration
-Published reports involved off-label use of compounded products (risk of contamination)



-IN Ketamine (1mg/kg) is beneficial for acute pain management up to 1 hour
-PO Ketamine (0.5 -1 mg/kg/TID), the evidence is less robust

Evidence for IV Ketamine PCA in Acute Pain

-No double-blind RCTs for IV Ketamine PCA
-Ketamine + Opioid IV-PCA : ↓Post-op pain intensity, Opioid consumption and AEs 2 recent SR

IV PCA Ketamine : Limited evidence
IV PCA Opioid + Ketamine : Moderate evidence supports

Staff /Setting for IV Ketamine Infusion

Supervising clinician:

A physician experienced with ketamine (anesthesiologist, critical care physician, pain physician, ER physician) , ACLS certified and trained in administering moderate sedation

Administering clinician:

RN or PA with formal training in safe administration of moderate sedation and ACLS certified

At the doses exceeding 1 mg/kg/hr :

Monitored setting , resuscitative equipment and immediate access to rescue medications & personnel who can treat emergencies ***although this dose may vary based on individual characteristics***

Ketamine Infusion AND Chronic Pain

CHRONIC AND INTERVENTIONAL PAIN

SPECIAL ARTICLE

OPEN

Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists

Steven P. Cohen, MD,† Anuj Bhatia, MBBS, MD,‡ Asokumar Buvanendran, MD,§ Eric S. Schwenk, MD,||*
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Ketamine in Chronic Pain Management

NMDA receptor : Memory / Cognition, Central Sensitization/ Windup, Opioid tolerance/ Hyperalgesia
Ketamine : Affecting the Sensory-Discriminative System, Modulating the Affective-Motivational component of pain

- SCI, PHN, CRPS, Fibromyalgia, Chronic Ischemic Pain, Migraine headache ,...

No evidence for intermediate or long-term improvements in chronic pain (except in CRPC)
Moderate evidence for improvement in chronic pain up to 3 months

Serial infusions in Chronic vs Acute Pain : Abuse Potential (Opioid Risk Tool), Cystitis and Hepatic Dysfunction

Insufficient evidence on preinfusion testing prior IV Ketamine
- Liver Dysfunction/ ↑risk of Liver Toxicity (Etoh, hepatitis), or ↑doses/ Frequent intervals: LFTs
- High risk CVS events : Baseline ECG

Dose/Duration Response Relationship ?

-Dose 0.006 to 0.75 mg/kg/hr and the duration of the infusions ranged from 5 min- 2 hrs

- Higher Doses
- Longer duration
- Dose Cutoff Threshold
- Continuous vs Boluses
- Repeat Infusions

No RCTs on low vs high-dose infusions

Moderate evidence for higher doses, longer duration and more frequent administration

Reasonable to start with a single, outpt infusion at 80 mg over 2 hrs and reassess before initiating further treatments

Maher Review : Higher the dose and longer the duration, longer the improvement in pain

Noppers Review : Infusions <2 hrs unlikely to provide benefit >48 hrs

Evidence on PO Ketamine following infusions

Low-level evidence for PO (150 mg/d or 0.5 mg/kg as follow-up therapy following IV infusions

Moderate evidence for IN (1–5 sprays or 0.2–0.4 mg/kg for breakthrough pain

-PO Ketamine has significant **Abuse** potential and a high street value (Hx of Abuse)
-Reasonable to try a IN/PO Ketamine or PO Dextromethorphan
(↑cost and resources for IV infusions)

Evidence on Preemptive/Rescue Medication

Premedication:

Limited evidence on BZD / α2 agonists

No evidence on antidepressant, antihistamine, or anticholinergic

Rescue :

Midazolam : ↓ psychomimetics/ sympathomimetics/ nausea

Haloperidol :↓ psychomimetics

Clonidine :↓ psychomimetics/ sympathomimetics

ACLS Meds

Evidence on Positive Response to Ketamine

30% pain relief or greater
12.8% improvement in Oswestry Disability Index score
20% or greater reduction in opioid use

Duration of benefit:
3 W or more following a single outpt infusion
6 W or more following an inpt or series of infusions

"Series" of infusions should be tailored to patient response;
Limiting these to no more than 6-12 treatments per year is reasonable

Conclusion

Powerful/ Inexpensive tool for Acute/Chronic Pain

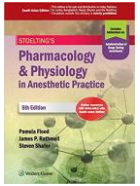
Its use will continue to expand

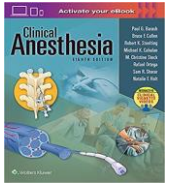
More research : Selection Criteria, Ideal Dosing, treatment regimen & long-term risks

TABLE 6. Summary of ASRA/AAPM/ASA Recommendations for Ketamine Infusions for Chronic Pain

Recommendation Category	Recommendation	Level of Evidence*
Indications	(1) For spinal cord injury pain, there is weak evidence to support short-term improvement	(1) Grade C, low certainty
	(2) In CRPS, there is moderate evidence to support improvement for up to 12 wk	(2) Grade B, low to moderate certainty
	(3) For other pain conditions such as mixed neuropathic pain, fibromyalgia, cancer pain, ischemic pain, headache, and spinal pain, there is weak or no evidence for immediate improvement	(3) Grade D, low certainty
Dosing range and dose response	(1) Bolus: up to 0.35 mg/kg	(1) Grade C, low certainty
	(2) Infusion: 0.5 to 2 mg/kg per hour, although dosages up to 7 mg/kg per hour have been successfully used in refractory cases in ICU settings	(2) Grade C, low certainty
	(3) There is evidence for a dose-response relationship, with higher dosages providing more benefit. Total dosages be at least 80 mg infused over a period of >2 h	(3) Grade C, low certainty
Relative contraindications	(1) Poorly controlled cardiovascular disease, pregnancy, active psychosis	(1) Grade B, low certainty
	(2) Severe hepatic disease (avoid), moderate hepatic disease (caution)	(2) Grade C, low certainty
	(3) Elevated intracranial pressure, elevated intraocular pressure	(3) Grade C, low certainty
	(4) Active substance abuse	(4) Grade C, low certainty
Role of oral NMDA receptor antagonist as follow-on treatment	(1) Oral ketamine or dextromethorphan, and intransal ketamine can be tried in lieu of serial infusions in responders	(1) Grade B, low certainty for oral preparations, moderate certainty for intranasal ketamine
Preinfusion tests	(1) No testing is necessary for healthy individuals	(1) Grade C, low certainty
	(2) In individuals with suspected or at high risk of cardiovascular disease, baseline ECG testing should be used to rule out poorly controlled ischemic heart disease.	(2) Grade C, low certainty
	(3) In individuals with baseline liver dysfunction or at risk of liver toxicity (eg, alcohol abusers, people with chronic hepatitis), and those who are expected to receive high doses of ketamine at frequent intervals, baseline and postinfusion liver function tests should be considered on a case-by-case basis	(3) Grade C, low certainty
Positive response	(1) A positive response should include objective measures of benefit in addition to satisfaction such as ≥30% decrease in pain score or comparable validated measures for different conditions (eg, Oswestry Disability Index for back pain)	(1) Grade C , low-to-moderate certainty
Personnel and monitoring	(1) Supervising clinician: a physician experienced with ketamine (anesthesiologist, critical care physician, pain physician) who is ACLS certified and trained in administering moderate sedation	(1) Grade A, low certainty
	(2) Administering clinician: registered nurse or physician assistant who has completed formal training in safe administration of moderate sedation	(2) Grade A, low certainty
	(3) Setting: at dosages exceeding 1 mg/kg per hour, a monitored setting containing resuscitative equipment and immediate access to rescue medications and personnel who can treat emergencies should be used, although this dose may vary based on individual characteristics	(3) Grade A, low certainty

References





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