Emergency Department use of Subdissociative-dose Ketamine for Treatment of Acute Pain

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Objectives

By the end of this presentation, participants will be able to:

- Understand pharmacology of subdissociative-dose ketamine

- Identify target patient populations for use of subdissociative / analgesic-dose ketamine

- Understand the “nuts and bolts” of administering analgesic-dose ketamine (including dosing, monitoring recommendations, adverse reactions and their management)

- Evaluate and address staff and patient perception of treatment
Why are novel pain medications needed?

- Pain is most common presenting complaint to the Emergency Department
...and we give A LOT of pain medications.
But we aren’t always great at it!

1. Pain may be under-treated
Under treatment of pain

“Pain in the Emergency Department: Results of the Pain and Emergency Medicine Initiative (PEMI) Multicenter Study”

- Only 60% of patients received analgesics
- Lengthy delays (median, 90 minutes; range, 0 to 962 minutes)
- 74% of patients were discharged in moderate to severe pain.
But we aren’t always great at it!

1. Pain may be under-treated

2. …or over-treated, leading to adverse effects (especially opioids)
But we aren’t always great at it!

1. Pain may be under-treated

2. …or over-treated, leading to adverse effects (especially opioids)

- **Acute effects**: respiratory depression, hypoxia, bradycardia, hypotension
- **Long-term effects** including opioid dependence/abuse, opioid-induced hyperalgesia (OIH)
Opioid-Induced Hyperalgesia

= state of increased pain sensitization caused by exposure to opioids

- Related to abnormalities in glutamate system, NMDA receptor upgrading

- Allodynia

- Morphine can INCREASE the pain
The History of Ketamine

- Synthesized in 1962 in attempt to find safer anesthetic alternative to PCP
  - because of PCP’s effects of hallucinations, mania, seizures
- First used on soldiers in WWII and Vietnam War
So, how does subdissociative-dose ketamine work?

- **Subdissociative**
  - 0.1-0.4mg/kg IV
  - *PAIN CONTROL*

- **Dissociative**
  - 1-2mg/kg IV
  - *SEDATION*
Mechanism of ketamine action

- Primarily acts as NMDA receptor antagonist
  - Belongs to family of receptors that mediate excitatory nerve transmission in the brain
  - Plays role in cellular mechanism for learning, memory
Mechanism of ketamine action

- Open NMDA channel allows Ca2+ ions to flow into the neuron
NMDA receptor antagonism

Blocks flow of Ca²⁺ ions into neuron

Blocked ability to process information

sensory less, analgesia, amnesia, state of DISSOCIATION
Strong pain stimuli activate NMDA receptors and produce hyperexcitability of neurons

- Increased sensitization, “wind up pain”, pain memory

Thus, Ketamine fights hyperalgesia and “wind up” pain

Ketamine disrupts many downstream, longer-lasting cellular processes such as gene expression, protein regulation
Mechanism of ketamine action

- Also acts on opioid, GABA, cholinergic receptors

- sympathetic nervous system

- Antidepressant effects (serotonin activation)

- Increases endogenous inhibition of pain sensation
  - Increases release of dopamine, norepinephrine; prevents uptake
What patient populations might benefit from subdissociative-dose ketamine?
(almost) ANYONE!!!
Many have developed significant opioid tolerance and opioid-induced hyperalgesia, making traditionally used medications (such as fentanyl, morphine, hydromorphone) ineffective.

Using high or frequent doses of opioids may also be unsafe because of progressive respiratory depression and cardiovascular effects (such as hypotension) despite lack of pain control.
Target population 2: patients at risk for adverse effects of opioids

- The elderly

- Patients at risk for hypoventilation
  - For example, patients with acute intoxication who are already at risk for respiratory depression

- Hemodynamically unstable patients
  - Trauma, Burn
Target population 3: refractory pain despite “typical” meds
Intravenous Subdissociative-Dose Ketamine Versus Morphine for Analgesia in the Emergency Department: A Randomized Controlled Trial


- 90 patients enrolled, 18-55 years old
  - Musculoskeletal, flank, back, abdominal pain
- Morphine 0.1mg/kg or Ketamine 0.3mg/kg IV
Ketamine > morphine at 15 minutes, but no significant difference in pain scores at 30 minutes

- Baseline pain scores: 8.6 versus 8.5
- 30min: 4.1 versus 3.9

- No significant difference in adverse effects
  - Ketamine patients reported increased minor adverse effects at 15 minutes
“Conclusion: Subdissociative intravenous ketamine administered at 0.3 mg/kg provides analgesic effectiveness and apparent safety comparable to that of intravenous morphine for short-term treatment of acute pain in the ED.”
Ketamine is SAFE + EFFECTIVE
So, how do we do give ketamine for acute pain?
So, how do we do give ketamine for acute pain?

**Patient preparation:**

- Cardiac and continuous SpO2 monitor

- Pre-ketamine vital signs (within 10 minutes of giving drug)
  - Then repeated q15minutes until patient back at baseline mental status
DOSING

0.1 – 0.4 mg/kg IV, with maximum bolus of 40mg

- average initial dose 10-20mg

- Onset of action: 30 seconds – 1 min
  - Peak effect: 1-5 minutes
  - Duration of action: 20-30 minutes
Or…
administer in 100mL 0.9% normal saline, infused over 10 minutes
Drip can be started after initial bolus:
0.1 – 0.3 mg/kg/hr IV

_to prepare:_ ketamine 100 mg in 100 mL of 0.9% NS to make a 1mg/mL drip
Adverse effects of subdissociative-dose ketamine

...aka what could go wrong?
Adverse effects of subdissociative-dose ketamine: **Cardiovascular**

- Arrhythmia *(tachycardia* most common)*
- Hypertension
Adverse effects of subdissociative-dose ketamine: **Psychiatric**

- Agitation, delirium, confusion
- Hallucinations
Adverse effects of subdissociative-dose ketamine: **Others**

- Transient hypertonia and/or tonic clonic movements
- Transient laryngospasm
- Increased salivation and respiratory secretions
- Apnea, respiratory depression
- Nausea, vomiting
- Increase in ICP (Intracranial Pressure) or intraocular pressure
- Cardiovascular: bradycardia, hypotension
Adverse effects are much less common than with DISSOCIATIVE-dose ketamine (ie for procedural sedation)
Adverse effects of subdissociative dose ketamine:

What do I do if these happen???
KEEP CALM AND GRAB THE BENZO'S
Adverse effects of subdissociative-dose ketamine: Management

Supportive care measures!
Managing adverse effects of ketamine: supportive care measures

- For **acute agitation**, hallucinations:
  - maintain calm, quiet environment, with dim lighting if possible
  - use benzo’s (lorazepam = Ativan; midazolam = Versed; etc)
Managing adverse effects of ketamine: supportive care measures

- For **respiratory** adverse reactions
  - reposition head/airway
  - apply supplemental oxygen as needed for hypoxia
  - use suction for airway secretions
  - bag-valve-mask assisted ventilation (or advanced airway techniques) as needed
Managing adverse effects of ketamine: supportive care measures

- For **nausea/vomiting**: ondansetron 4-8mg IV if not otherwise contraindicated
Managing adverse effects of ketamine: supportive care measures

- For hypotension: 500-1000mL 0.9% NS IV bolus if not otherwise contraindicated
So, who SHOULDN’T receive subdissociative-dose ketamine?
Absolute contraindications:

1. Allergy to ketamine
2. Age <3 months
3. Suspicion of acute primary psychotic condition such as schizophrenia
Relative Contraindications:

- Conditions in which elevated blood pressure would be hazardous
  - Acute angina
  - Acute heart failure
Relative Contraindications:

- Conditions in which elevated blood pressure would be hazardous
  - Acute angina
  - Acute heart failure
- Elevated intraocular pressure (such as acute glaucoma)
Relative Contraindications:

- Conditions in which elevated blood pressure would be hazardous
  - Acute angina
  - Acute heart failure
- Elevated intraocular pressure
- Patients with known or suspected upper airway obstruction
Relative Contraindications:

- Conditions in which elevated blood pressure would be hazardous
  - Acute angina
  - Acute heart failure
- Elevated intraocular pressure (such as acute glaucoma)
- Patients with known or suspected upper airway obstruction
- Cases in which elevated intracranial pressure is suspected (such as obstructive hydrocephalus) - CONTROVERSIAL
Relative Contraindications:

- Conditions in which elevated blood pressure would be hazardous
  - Acute angina
  - Acute heart failure
- Elevated intraocular pressure
- Patients with known or suspected upper airway obstruction
- Elevated ICP
- Acute thyrotoxicosis
Use caution with...

- Mild-moderate hypertension, tachycardia
- Neurotic traits
- Acute alcohol intoxication
Patient and Staff Perception of Treatment
Patient Perception

- It works!
- Decreased time to pain control
- Adverse effects should be discussed prior to giving the medication
Staff Perception: Initial

- “It’s too much work!”

- “It makes patients crazy.”

- “Drug-seekers love it.”
Staff Perception: After using it

- “It’s too much work!”
  → We do vital signs and put patients on monitors anyway!

- “It makes patients crazy.”

- “Drug-seekers love it.”
Staff Perception: Initial

- “It’s too much work!”
- “It makes patients crazy.”
  - Agitation/delirium are less common than with dissociative-dose ketamine
  - Adverse effects (agitation) are easily managed with lorazepam
- “Drug-seekers love it.”
Staff Perception: Initial

- “It’s too much work!”

- “It makes patients crazy.”

- “Drug-seekers love it.”

  Good! Their pain is treated effectively and they are ready to be discharged safely, more quickly than if traditional meds (opioids) were given.
Introducing a new Medication/Treatment

- Early adopters
- The Majority
- Late adopters
Staff Perception: Overall
Subdissociative-dose ketamine is a safe alternative to traditionally used pain medications in the Emergency Department, especially for:

1. Patients with chronic pain and on chronic opioids
2. Patients in whom opioids would be unsafe
   - Hypoventilation risk
   - Hypotensive
3. Patients with refractory pain (kidney stones, headaches, etc)
Ketamine primarily works as an NMDA receptor antagonist, but has activity at multiple other receptors as well.
The main adverse effects include:

- Tachycardia
- Hypertension
- Agitation
- Delirium
- Laryngospasm
- Increased airway secretions
SUMMARY

- Due to cardiovascular and respiratory effects, patients should be on cardiac and SpO2 monitor throughout treatment.

- Adverse effects can be managed by supportive care (especially benzo’s!)

- Since implementation of protocol for subdissociative-dose ketamine at our hospital, patient and staff perception has been positive.
Where to find our protocol

www.ena.org
Thank you!

Questions?

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CITATIONS


**Subdissociative Ketamine for Analgesia in Adults: Proposed protocol for use**

**Indication:** acute pain (traumatic or non-traumatic) in patients >16 years of age

**Mechanism of action:** primarily acts as NMDA receptor antagonist.
- Also acts on multiple other receptors including opioid, GABA, cholinergic; sympathetic nervous system
- Increases endogenous inhibition of pain sensation
- Prevents hyperalgesia and “pain wind up”

**Target patient populations:**
- Patients with severe pain refractory to other analgesics (including opioids such as morphine, hydromorphone, fentanyl; anti-inflammatory medications, such as toradol; acetaminophen). May be used as adjunct to these other medications, or as solo agent.
- Patients with chronic pain, especially those who are opioid-tolerant
  o Many patients on chronic opioids have developed significant opioid tolerance and opioid-induced hyperalgesia, making traditionally used medications (such as fentanyl, morphine, hydromorphone) ineffective.
  o Using high or frequent doses of opioids may also be unsafe because of progressive respiratory depression and cardiovascular effects (such as hypotension) despite lack of pain control.
- Patients at risk for compromised airway patency, hypoventilation, or hemodynamic instability if given opioid medications
  o Ketamine causes minimal central respiratory depression, so is safer for use in patients at risk for hypoventilation
  o Ketamine’s cardiovascular effects are usually stimulatory (ie, hypertension instead of hypotension), so safer for use in patients at risk for hypotension

**Contraindications:**
- **Absolute:**
  o Previous allergy to ketamine
  o Age < 3 months
  o Suspicion of acute psychotic condition including schizophrenia
- **Relative:**
  o Cases in which elevated intracranial pressure is suspected (such as hydrocephalus)
  o Elevated intraocular pressure (such as acute glaucoma)
  o Condition in which elevated blood pressure would be hazardous (such as acute angina, acute heart failure)
  o Use with caution in patients with acute alcohol intoxication
  o Acute thyrotoxicosis
  o Patients with known or suspected upper airway obstruction
Monitoring requirements for administration

- Continuous Cardiac and oxygen saturation monitoring established before administration
- Baseline vital signs (heart rate, blood pressure, respiratory rate, oxygen saturation) documented within 10 minutes prior to medication administration; then repeat vital signs every 15 minutes after medication administration, until patient returns to pretreatment level of awareness and verbalization
- Baseline and post-medication pain scores as per nursing protocol
- Notify physician/provider if:
  - heart rate <60 or >110
  - systolic blood pressure <90 or >180
  - respiratory rate <10
  - development of hallucinations or acute agitation or combativeness

Dose: 0.1 – 0.4 mg/kg IV, with maximum bolus of 40mg (average dose 10-20mg)

- Alternatively, 2mg/kg IM
- When given IV: administer over at least 1 minute; alternatively, may administer as IVP with 100mL 0.9% normal saline, infused over 10 minutes
- Following initial bolus, may be used as continuous infusion: 10-20mg/hr IV (to prepare: ketamine 100 mg in 100 mL of 0.9% NS to make a 1mg/mL drip)

Possible adverse reactions:

- Arrhythmia (tachycardia most common)
- Hypertension (hypotension less common)
- Recovery agitation, delirium, confusion
- Hallucinations
- Transient hypertonia and/or tonic clonic movements
- Transient laryngospasm
- Apnea, respiratory depression
- Nausea, vomiting
- Increased salivation and respiratory secretions
- Note: adverse reactions occur more commonly when medication is used at dissociative doses

Reversal agent: none

Management of adverse reactions: supportive care

- For respiratory adverse reactions: reposition head/airway, apply supplemental oxygen as needed for hypoxia, use suction for airway secretions, use bag-valve-mask assisted ventilation (or advanced airway techniques) as needed
- For acute agitation, hallucinations: maintain calm, quiet environment, with dim lighting if possible; see adjunctive medications below
- For nausea/vomiting: ondansetron 4-8mg IVP if not otherwise contraindicated
- For hypotension: 500-1000mL 0.9% NS IV bolus if not otherwise contraindicated

Adjunctive medications:
- benzodiazepines for agitation, hallucinations
  - lorazepam 0.02 – 0.04 mg/kg IV (maximum dose 2mg IV)
  - midazolam 0.01 – 0.05 mg/kg (average dose 0.5 – 4mg)
  - consider co-administration of benzodiazepine with ketamine
  - or, benzodiazepine can be administered in a PRN fashion (PRN agitation, hallucinations)
- consider giving hydromorphone 0.5-1mg IV for persistent pain

Selected articles with relevant data


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