Inpatient Ketamine Infusion to Treat Acute Pain Crisis Refractory to Opioids in Sickle Cell Disease

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• Pacira Pharmaceuticals: one time honoraria for serving on nursing advisory board

Objectives

• Identify specific factors that complicate effective pain control during acute pain crises in sickle cell disease in the acute care setting
• Discuss the actual and potential beneficial effects of ketamine infusion for sickle cell disease patients with acute pain crises and with chronic pain
• Create a plan for using ketamine infusions to treat acute and chronic pain conditions in the acute care setting
Management of Sickle Cell Pain Crisis

- Effectively treat pain
  - Parenteral opioid therapy
    - (morphine, hydromorphone, fentanyl)
  - IV PCA preferred
  - AVOID meperidine (risk of seizures)
  - NSAIDs, local heat, other adjunctive measures
  - Medication offered around the clock, not “PRN” (use PCA or sustained-release, standing doses)
  - Transition to oral short-acting opioid pain medication
  - Be sure any other factors are recognized and addressed
  - No evidenced based strategy: expert opinion

Pain in Sickle Cell Disease

- Acute, intermittent, unpredictable, severe episodes called “crisis”
  - Typical duration said to be 7-10 days
  - Associated by some patients with death
  - Onset may occur in early infancy
  - Chronic pain may develop in adolescence and adulthood
    - Not necessarily acute vaso-occlusion
  - Other pain still occurs (e.g. injury, menses, SLE)
    - To be distinguished from acute vaso-occlusion

PAIN TYPE ORIGINS & SYNDROMES

- Nociceptive
  - Deep somatic: Vaso-occlusion, bone infarction, priapism
  - Superficial somatic: Leg ulcers
  - Visceral: Splenic/hepatic sequestration, splenic infarction, cholelithiasis

- Neuropathic
  - Peripheral neuropathy: Vaso-occlusion, neuropathies
  - Central neuropathy: CNS damage, central sensitization (?)

- Mixed
  - Vaso-occlusion

- Breakthrough
  - Incident (movement): Vaso-occlusion, skeletal damage
  - Nonincident: Transient flares of pain during analgesia

Adapted from Niscola, Pain Medicine 10:470, 2009
Adult SCD Pain Common, but Managed at Home

PISCES data from 31,017 daily pain diaries from 232 patients

- Crisis – Utilization: 3.5%
- Crisis – No utilization: 12.7%
- Pain – Not Crisis: 38.3%
- No Pain: 45.5%


Chronic Pain in SCD

- Tissue infarction/fibrosis
- Everything else that affects humans: abnormal processing of nociceptive pain
- Central sensitization
  - Allodynia: increased nociception to normally innocuous stimuli
  - Hyperalgesia: excessive painful response to a painful stimulus
- Unfortunately, in SCD there are lots of such ongoing stimuli


Sickle Cell Pain and Catastrophizing

- Catastrophizing:
  - High degree of aversion associated with pain-eliciting situations
  - Pay more attention to pain sensations
  - Rumination, magnification of pain
  - Helplessness when dealing with pain

- For sickle cell patients:
  - Higher than in other pain groups (e.g. RA, spinal cord injury, back pain)
  - Associated with depression and lower quality of life
  - Worse in people with milder syndromes - fewer chronic symptoms, less opportunity to adapt

A Citero, Pain 133:39, 2007
Challenges and Complexities

- Acute Sickle Cell Pain with Baseline Chronic Pain
  - Chronic opioid therapy
  - Significant opioid tolerance
  - Poor response to parenteral opioid therapy
  - Poor response to non-opioid adjuvants
  - Opioid rotation ineffective or unavailable (allergy, intolerance, refusal)
  - Opioid induced hyperalgesia (OIH)
  - High readmission rates
  - Poor or no outpatient management
  - Poor medication compliance - opioid withdrawal
  - Development of chronic neuropathic pain through sensitization of spinal neurons from repeated noxious stimuli

Opioid Tolerant Patient

- Acute pain management in the opioid tolerant patient presents a significant challenge to nurses
- Opioid only based analgesic regimens are usually marginally effective and dose escalation increases patient risk and provider concern
- Multimodal analgesic techniques recommended by national practice guidelines are not always feasible or sufficient
- This situation results in poor quality pain management, patient suffering, and staff frustration and dissatisfaction

Opioid Induced Hyperalgesia (OIH)

- A state of nociceptive sensitization caused by exposure to opioids. The condition is characterized by a paradoxical response whereby a patient receiving opioids for the treatment of pain could actually become more sensitive to certain painful stimuli.
- Characteristics
  - Worsening pain over time in spite of and because of increases in opioid dose
  - Nociceptive sensitization
  - Area of pain more diffuse
  - Pain of lesser quality and harder to pinpoint
What is Ketamine...

- IT IS NOT AN OPIOID
- It’s a dissociative anesthetic that works as a NMDA receptor antagonist
- Used as an anesthetic - profound analgesia
- Produces catatonic state, psychotomimetic effects during recovery ("dissociative" state)
- Analgesia maintained in sub-anesthetic low doses
- Can be very effective in crisis situation: tolerant patient with severe pain, unresponsive to high dose opioids

Ketamine

- Opioid tolerance and the development of neuropathic pain both involve activation of NMDA receptors
- Ketamine as an NMDA receptor antagonist may represent a “2-for-1” type intervention, helping to overcome tolerance to opioids as well as attenuating neural sensitization
- Through blocking the N-methyl-D-aspartate (NMDA) receptor, ketamine impairs sensitization of spinal neurons to noxious stimuli and may, therefore, impede development of and blunt neuropathic pain.

Mechanism of Action

- Inhibits binding of excitatory amino acids (glutamate, aspartate) to the N-methyl-D-aspartate (NMDA) receptor in the CNS, blocking the transmission of painful stimuli
- NMDA antagonism produces analgesia, limits the development of opioid tolerance and hyperalgesia
- Elevates circulating epinephrine and norepinephrine leading to increased HR, BP, cardiac output, and vascular resistance
- No respiratory depressant effects when given in low doses
Mechanism of Action

- Strong pain stimuli activate NMDA receptors and produce hyperexcitability of dorsal root neurons.
- This induces central sensitization - the "wind-up phenomenon" - and hyperalgesia.
- NMDA antagonism can reverse/limit hyperalgesia and the wind-up phenomenon.

NMDA Receptor and Tolerance

- Repeated μ opioid receptor activation via prolonged large dose opioid use leads to increased NMDA receptor activity and the development of tolerance.
- Ketamine has been shown to block this increased NMDA activity and can prevent the development of tolerance.
Fig. 2. In sensitization and opioid tolerance-related phenomena, pathologic pain is an expression of neuronal plasticity. After activation of intracellular kinase cascades, transcription-independent phosphorylation of key membrane receptors and channels, such as the N-methyl-D-aspartate (NMDA) receptor, is initiated. This increases neuronal excitability for tens of minutes after cessation of the initiating stimulus. Long-term hypersensitivity is also regulated by mitogen-activated protein kinases (MAP kinases) via transcription of gene products. Protein kinase (PK) C, a series of other protein kinase families, and nitric oxide (NO)/cGMP/PKG are activated after NMDA-mediated increases in intracellular calcium (Ca\(^{2+}\)) or µ-opioid receptor binding to opioid receptors. Increased Ca\(^{2+}\) stimulates Ca\(^{2+}\)/calmodulin, and Ca\(^{2+}\)/calmodulin kinase (CaMK) pathways. These and inflammatory transmitters stimulate adenylcyclase – cAMP–PKA signaling. Several cascades then converge on MAP kinases, such as the extracellular signal-regulated kinases (ERK). These processes facilitate association of key signaling molecules with postsynaptic density (PSD) proteins in the NMDA receptor. This leads to kinase phosphorylation of NMDA receptor subunits and up-regulation of NMDA receptor currents. Enhanced downstream signaling ensues and, in this vicious circle, potentiates NMDA receptor function and synaptic efficacy and, thus, pain sensitization. In long-term hypersensitivity, CaMK and inflammation-related signaling kinases converge on MAP kinases, such as p38MAP kinases, which is followed by phosphorylation of promoters with the initiation of gene transcription. The cAMP response element binding protein (CREB), MAP kinases, and CaMKIV may also cause transcription via direct phosphorylation of gene promoters. Intervention with ketamine blocks NMDA receptor currents and connected downstream signaling. Regarding pain sensitization and opioid phenomenon, a common mechanism underlying ketamine’s preventive action appears to be the perturbation of increased assembly of PSD proteins – tyrosine kinase – NMDA receptor protein subunits. This reduces phosphorylation and functional NMDA receptor up-regulation. In the future, the cascades presented may evolve as important targets for new pain reducing drugs with similar but more specific responses than those caused by ketamine.

\[\text{\[triangle-headed upwards arrow\]} = \text{pathophysiological increase or activation,}\]
\[\text{\[triangle-headed downwards arrow\]} = \text{pathophysiological decrease or reduction,}\]
\[\text{\[up arrow\]} = \text{increase or activation related to severe pain or opioid use,}\]
\[\text{\[down arrow\]} = \text{decrease or reduction related to ketamine blockade.}\]

Nervous System Plasticity allows persistent pain and continuous use of opioids to lower pain thresholds, cause central sensitization leading to the “Wind-Up” phenomenon, and contribute to pathologic pain.

Pharmacokinetics

- Metabolized and then conjugated in the liver before being excreted in the urine, with minimally active metabolites.
- Onset of 1-2 minutes
- Duration of action 60 minutes.
- Half-life is 2.5 hours

Selected Literature

- 3 Systematic Reviews: Carstensen & Moller 2010; Laskowski et al. 2011; Bell et al. 2006 (Cochrane Review)
- Consistently found or showed a trend towards
  - Reduced postop opioid needs and PONV
  - Increased time to rescue analgesic
  - Generally well tolerated
  - Heterogeneity of trials acknowledged as a limitation
- UCH Ketamine MUE: Baumgartner & Lyda 2013
  - 12 months; 95 patients; stopped in 21 patients, 4 for HTN/Tachy
  - 43 patients (45%) required transfer from M-S unit
  - Did not look at pain scores or opioid consumption
UCH Ketamine Study in Sickle Cell Disease

• Background
  • Sickle cell disease (SCD) is characterized by hemolytic anemia and vaso-occlusion, which can lead to acute and chronic pain (i.e. recurrent sickle cell pain crises)
  • There are no current evidence-based treatment strategies for SCD pain
  • A small subset of this population requires chronic opioid medications for pain control, which poses greater risk of opioid dependence, tolerance and opioid-induced hyperalgesia
  • Anecdotal case reports suggest ketamine is a useful analgesic adjunct in decreasing pain scores and opioid consumption

• Objectives
  • Characterize the effects of ketamine infusion on inpatient opioid intake
  • Characterize the effects of ketamine infusion on inpatient pain scores
  • Compare opioid prescription dose requirements at admission and discharge

• Population
  • All adult patients with SCD who were admitted to the University of Colorado Hospital (UCH) Anschutz Inpatient Pavilion with chief complaint of a sickle cell pain crisis between January 2009 and December 2016
  • Patients whose pain was refractory to opioids and were treated with continuous ketamine infusion
UCH Ketamine Study in Sickle Cell Disease

**Data Collection**
- Number of eligible ketamine infusion episodes and control episodes per patient
  - Ketamine episodes: Data collected from day preceding initial ketamine infusion to discharge
  - Non-ketamine episodes (control): Data collected from admission to discharge
- Total dose of opioids given each day for each ketamine and non-ketamine episode, converted to PO morphine equivalents per day (MED, mg)
- Pain scores using Numeric Rating Scale (0-10 pts), averaged for each day in each ketamine and non-ketamine episode
- Opioid prescription dosage (MED) at admission and discharge for each episode
- Incidence of discontinued ketamine infusions due to adverse side effects

**Data Analysis**
- Linear mixed-effects regression was used to analyze trends in opioid intake and pain scores over time with and without ketamine infusion
- Repeated measures were accounted for using random intercepts
UCH Ketamine Study in Sickle Cell Disease

- Population Characteristics
  - 60 ketamine infusion episodes in 9 patients
  - 12 non-ketamine infusion episodes in 6 patients

- Inpatient Opioid Intake
  - Ketamine: Significant decrease in opioid dose by 55.42 MED (SE=13.42 mg, p<0.0001) on average each day of the infusion
  - Non-ketamine: Significant increase in opioid dose by 79.7 MED (SE=18.99, p<0.0001) on average each day of admission
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- **Pain Scores**
  - Ketamine: Significant decrease in pain scores by 0.11 pts/day ($SE=0.024$, $p<0.0001$) on average each day of the infusion
  - Non-ketamine: Decrease in pain scores by 0.039 pts/day ($SE=0.031$, $p=0.21$) on average each day of admission

- **Opioid Prescriptions**
  - Ketamine infusion does not appear to reduce opioid dosage when admission MED was compared to discharge MED after ketamine infusion

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- **Ketamine Discontinuations**
  - 6 ketamine infusions (9.62%) discontinued due to adverse side effects:
    - Altered neurological state (hallucinations, confusion)
    - Dizziness and lightheadedness
    - Sedation

UCH Ketamine Study in Sickle Cell Disease

- **Conclusions**
  - Ketamine infusion beneficially serves as an analgesic adjunct in managing sickle cell pain by significantly reducing opioid intake and pain scores
  - The use of ketamine may also help to reduce the risks of opioid tolerance and opioid-induced hyperalgesia
  - Pain scores are more significantly reduced when managed with ketamine as an analgesic adjunct than with opioids and other analgesics alone
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• Limitations
  • Analyses include outlier episodes in ketamine and non-ketamine infusion groups
  • Non-ketamine infusion episodes were not identified for 3 patients
  • Unreported pain scores from 14 ketamine infusion episodes and 2 non-ketamine infusion episodes
  • Inconsistent time frame between ketamine and non-ketamine data collection

UCH Nursing Guideline
Low Dose Ketamine Infusion Analgesia

• Suitable candidates for analgesic dose ketamine are those with
  • uncontrolled moderate to severe pain refractory to conventional therapies such as epidural infusion, IVPCA, nerve blocks, opioids, and non-opioid therapies.
  • it may be particularly helpful for those with a history of chronic opioid use and tolerance, neuropathic pain, or intolerable side effects from conventional therapies.

Low Dose Ketamine Infusion Dosing

• There is great variance in individual response to intended and unintended effects
• Dose ranges are suggested starting and end points
• The patient response should guide dosing adjustments
• As with opioid drugs, the phrase “the dose that works is the dose that works” applies.
• The goal is maximize the beneficial effects of ketamine and minimize opioid escalation
What Do you Need to Watch For?

- BP greater than 180/100
- HR greater than 120
- PT excessively agitated or sedated
- Pt complaining of hallucinations
- Anxiety related side effects can be treated with lorazepam

Other Random Facts

- Telemetry and continuous pulse ox at all times.
- Pump must be checked by 2 RNs like PCAs
- You CAN NOT "Y" in any other meds into a ketamine line. Must be run through own line.
- Pts should be placed on a bed alarm.

When Do You Document

- BP, HR, pain level every 15min for the first hour
- Then 2 hrs x 2hrs
- Q4 hours for remainder of administration
- Check VS Q30min after any dose change.
What Do You Document?

- BP, HR, O2, RR
- Pain intensity, sedation level
- Side effect/complications
- Evaluation of patient response to intervention.
- Pt and family education

Ketamine Breakdown Sheet

**What does it do?**

- NMDA antagonist that works in the CNS
- Analgesia and limits opioid tolerance
- IV onset: 30 seconds and full effect in 1 min
- Duration: 60 min
- Half-life: 2.5 hours

**What do you need to know?**

- Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that works in the CNS.
- NMDA antagonism produces analgesia and limits the development of opioid tolerance.
- IV onset: 30 seconds and full effect in 1 min.
- Duration: 60 min.
- Half-life: 2.5 hours.

**Adverse Effects**

- Nausea and vomiting
- Vivid dreams
- Hallucinations
- Anxiety
- Hypertension
- Nystagmus

**What do you need to know?**

- Acute Pain Service will manage the Ketamine infusion at a dose from 1-3mg/hr. Concentration is 1mg/cc.
- Max dose for any bolus is 5mg.
- Contraindications:
  - Absolute: Psychosis
  - Relative: Poorly controlled hypertension, angina, congestive heart failure, stroke, PTSD, recent head injury.

**Anxiety/hallucination Reduction Treatment of Choice**

- Benzodiazepines—usually lorazepam.

**Monitoring**

- Telemetry and continuous pulse ox at all times.
- Initiation of infusion:
  - BP, HR, pain level every 15 min for the first hour.
  - Then every 2 hrs for 1 hr, then every 4 hrs.
- Q4 hours for remainder of administration.
- Check VS 30 min after any dose change.

**Dose and pump must be checked by 2 RNs upon arrival to the floor with any rate changes, and at change of shift.

**Documentation**

- Blood pressure, heart rate, pulse ox, respiratory rate.
- Pain intensity, sedation level.
- Side effect/complications.
- Evaluation of patient response to intervention.
- Patient and family education.
UCH Ketamine Policy

Table 1. Low-Dose Intravenous Ketamine for Analgesia for Patients.

**NOTE** Due to the variable patient response to continuous infusion dosing, the doses listed below are based on a guide.

<table>
<thead>
<tr>
<th>Clinical Area</th>
<th><strong>Usual Dose/Rate</strong></th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>ICU, PCU, Preop, PACU</td>
<td>Continuous Infusion: 1-50 mg/hr; ICU level care should be considered for dosing above 30 mg/hr</td>
<td>Acute Pain Service is available for dosing assistance. The APG will order and manage all infusions outside the ICU</td>
</tr>
<tr>
<td>Pain Medicine Clinic</td>
<td>Continuous Infusion: 1 mg/min and increase by 1 mg/min every 5 min up to 8 mg/min (max dose: usually less than 100 mg in 30 min)</td>
<td></td>
</tr>
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Final Thoughts

References