Ketamine & Lidocaine Use During Vaso-Occlusive Crisis

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Abbreviations

SCD- Sickle Cell Disease
VOC- Vaso-occlusive crisis
RBC- Red blood cell
NMDA- N-Methyl-D-aspartate
NRS- Numeric rating scale
BPM/BPM- beats per minute/breaths per minute

AE- Adverse event
MDE- Morphine dose equivalent
ER- Emergency room
PCA- Patient controlled analgesia
MME- Morphine milligram equivalent
AMS- Altered mental status

Objectives

Discuss background and current therapy for pain management in patients with SCD during a VOC
Evaluate available literature regarding ketamine and lidocaine infusions for pain management
Draw conclusions about appropriate use of ketamine and lidocaine use during VOC treatment

Statistics

197,000 ER visits due to VOCs per year, averaging nearly 2 visits per patient

SCD ER visits are:
4 times higher than for those with congestive heart failure
13 times higher for those with HIV

86% of patients with SCD were hospitalized for VOCs over a 5-year study
How do we treat pain in VOC currently?

Background

Sickle Cell Disease

Complications of SCD

- Acute Chest Syndrome
- Aplastic Crisis
- Parvovirus B19
- Splenic Sequestration
- Infections

- Chronic Anemia
- Neurological Complications
- Skeletal Disease
- Renal Disease
Vaso-Occlusive Crisis

- Most common reason for hospitalization
- May occur as early as 6 months of age presenting as dactyilitis
- Clinical presentation includes:
  - Sudden onset of pain in the extremities
  - Chest pain
  - Lower back and joint pain

PATHOPHYSIOLOGY

- Multi-step pathway involving sickled RBCs, leukocytes, endothelial cell and plasma proteins
- Sickled RBCs have increased adhesive properties and an increased activation of adhesion receptors.

COMMON TRIGGERS

- Infection
- Dehydration
- Stress
- Air pressure changes
- Temperature changes

Standard of Care Medications for VOC

NON-OPIOID PAIN MANAGEMENT
- Acetaminophen
- Ibuprofen
- Naproxen
- Ketorolac

OPIOID PAIN MANAGEMENT
- Hydrocodone
- Oxycodeone
- Methadone
- Morphine injection
- Morphine PCA

Non-Pharmacologic Pain Management

- Massage Therapy
- Physical Therapy
- Heating Pads
- Relaxation techniques
- Tai Chi
- Meditation
- Acupuncture
- Pet therapy
Ketamine

- Non-competitive antagonist of NMDA receptors which blocks glutamate and acts as an anesthetic
- Significant improvement in pain and a reduction in opioid consumption in 83% of patients
- Could be an effective option for patients with opioid-induced hyperalgesia

Lidocaine

- Amide local anesthetic with analgesic, anti-hyperalgesic and anti-inflammatory properties
- Blocks voltage-gated sodium channels and inhibits NMDA receptors
- Systemic administration has shown analgesic activity in patients with perioperative pain, cancer pain and chronic neuropathic pain

Literature Review

Journal of Pain & Palliative Care Pharmacotherapy: Intravenous Lidocaine as an Adjuvant for Pain Associated with Sickle Cell Disease
Study Methods

Objective
- Evaluate the efficacy and safety of IV lidocaine use in adult patients with SCD

Trial Design
- Retrospective chart review
- 11 patients with SCD who have received IV lidocaine during a previous hospital admission

Patient Population

Inclusion
- 18 years of age and over
- Received at least 1 lidocaine infusion
- Diagnosis of SCD

Exclusion
- Prisoners and pregnant patients

Endpoints
- Opioid requirement at 24 hours pre- and post-lidocaine challenge
- Pain score

Baseline Characteristics

Number of Patients (n=11) [%]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (years)</td>
<td>31.1 (20-40 years)</td>
</tr>
<tr>
<td>Ethnicity (African American)</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Seizure History (yes)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Cardiac History (yes)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Alpha- or beta-blocker (no)</td>
<td>11 (100)</td>
</tr>
</tbody>
</table>

Results

<table>
<thead>
<tr>
<th>Table 1: Pre-, post- and 24 hours post-lidocaine challenge pain scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rating</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*Note: The table is not entirely visible in the image.*

*Patients who score above the threshold during the entire period have alphabetical letters or numbers next to each submission.*
Results

**TABLE 1. Morphine dose equivalent (MDE) for clinically successful IV lidocaine trials**

<table>
<thead>
<tr>
<th>Patient letter</th>
<th>MDE 24 hours pre-lidocaine challenge (mg)</th>
<th>MDE 24 hours post-lidocaine challenge (mg)</th>
<th>MDE percent change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-A</td>
<td>15.400</td>
<td>2200</td>
<td>-73.6</td>
</tr>
<tr>
<td>2-A</td>
<td>20.400</td>
<td>6220</td>
<td>-28.4</td>
</tr>
<tr>
<td>2-B</td>
<td>21.000</td>
<td>19.400</td>
<td>-7.6</td>
</tr>
<tr>
<td>5</td>
<td>1400</td>
<td>340</td>
<td>-76.6</td>
</tr>
<tr>
<td>10-A</td>
<td>13.100</td>
<td>7480</td>
<td>-73.6</td>
</tr>
<tr>
<td>10-B</td>
<td>2700</td>
<td>3330</td>
<td>+22.2</td>
</tr>
<tr>
<td>10-C</td>
<td>1520</td>
<td>1600</td>
<td>+5.3</td>
</tr>
<tr>
<td>11</td>
<td>3591</td>
<td>2750</td>
<td>-30</td>
</tr>
<tr>
<td>Mean</td>
<td>9419.6</td>
<td>5093.8</td>
<td>-32.2</td>
</tr>
</tbody>
</table>

Conclusions

- IV lidocaine infusion was effective as adjuvant pain therapy for patients with SCD
- One patient admitted 3 separate times over a 1 year time period had clinical success with IV lidocaine during each admission
- An initial infusion of 100mg of lidocaine over 30 minutes, followed by 0.5 mg/kg/hr IV of lidocaine titrated to 20% pain reduction was the most common dosing strategy
- More research is needed specifically for lidocaine infusion in patients with SCD

Study Limitations & Critiques

- Retrospective chart review, with a sample size of only 11 patients
- Pain scores are subjective and vary between patients
- There was no standardized protocol for IV lidocaine use during this time
- Other non-opioid and non-pharmacologic pain management therapies were not reported allowing practice variations for adjuvant pain management

Journal of Pain & Palliative Care Pharmacotherapy: Low-Dose Ketamine Infusion for Adjunct Management during Vaso-occlusive Episodes in Adults with Sickle Cell Disease: A Case Series
Study Methods

**Objective**
- Examine the use of adjunct subanesthetic doses of ketamine opioids for treatment of refractory pain in SCD

**Trial Design**
- Retrospective case series of five patients admitted to the ICU with prolonged VOC

**Intervention**
- Continuous infusion of low dose ketamine (max 5mcg/kg/min)

Patient Population

**Inclusion**
- Ketamine infusion order from 2010-2014
- Ketamine infusion for at least 24 hours in the ICU
- 18 years old and older
- Diagnosis of SCD

**Exclusion**
- Ketamine administered via bolus dosing only
- Used for another indication

**Endpoints**
- Ketamine dose and duration
- Oral MME before and after ketamine therapy
- NRS scores
- RASS scores
- AEs

Baseline Characteristics

### Table 1. Baseline characteristics for patients with SCD during hospital admission for VOCs.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline average pain score, NRS</td>
<td>8</td>
<td>9</td>
<td>6</td>
<td>7</td>
<td>not recorded</td>
</tr>
<tr>
<td>Patient psychiatric history</td>
<td>Depression</td>
<td>None</td>
<td>Depression</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>History of VHS</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Past medical history</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Days with VHS symptoms</td>
<td>34</td>
<td>25</td>
<td>24</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Hospital LOS, days</td>
<td>308</td>
<td>1200</td>
<td>999</td>
<td>739</td>
<td>240</td>
</tr>
<tr>
<td>Adjuvant care or pain management consult</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### Table 2. Analgesic and inpatient adjunctive therapy.

<table>
<thead>
<tr>
<th>Analgesic therapy</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUcidone</td>
<td>200</td>
<td>240</td>
<td>90</td>
<td>240</td>
<td>300</td>
</tr>
<tr>
<td>IV</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Morphine</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Propofol</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>RASS</td>
<td>10</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Patient response to therapy</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Discharge opioid dose, MME/day</td>
<td>300</td>
<td>1200</td>
<td>999</td>
<td>739</td>
<td>240</td>
</tr>
</tbody>
</table>
Conclusions

- Low dose ketamine infusion in addition to other opioid and non-opioid therapies may reduce pain
  - Specifically in patients requiring high dose opioids without adequate control during VOCs
  - Initiation at a moderate dose of 5mcg/kg/min was more effective than starting lower and titrating
  - No serious complications were associated with low dose ketamine infusions
  - Further study is needed to explore the role of ketamine use in these patients

Study Limitations & Critiques

- Retrospective case series with only 5 patients
- Standardized doses of various medications were not utilized during ketamine infusions
- Heterogeneity of patients makes comparisons between them difficult
- Changes in opioid regimens and adjuvant therapies occurred during hospitalization

Scandinavian Journal of Pain:
Low Dose Ketamine versus Morphine for Acute Severe Vaso-occlusive Pain in Children: A Randomized Controlled Trial
Study Methods

Objective
• Compare maximal pain reduction of ketamine to morphine as measured by the NRS

Trial Design
• Prospective, double blind, non-inferiority RCT
• 240 children at the Mulago National Referral and Teaching Hospital in Uganda

Intervention
1 mg/kg IV ketamine vs. 0.1 mg/kg IV morphine

Patient Population

Inclusion
• Age 7-18 years old
• Severe acute painful crisis

Exclusion
• Oxygen <90%
• BP >180mmHg or <90mmHg
• HR >120bpm or <90bpm
• RR >30bpm or <10bpm
• AMS
• History of stroke

Endpoints
• Maximum change on NRS from baseline
• Time to max analgesic effect
• AEs and outlying vital signs
• Incidence of treatment failure

Baseline Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ketamine ± SD</th>
<th>Morphine ± SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>11.8 ± 3.4</td>
<td>11.8 ± 3.6</td>
<td>0.49</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>30.8 ± 11.9</td>
<td>30.0 ± 12.2</td>
<td>0.31</td>
</tr>
<tr>
<td>Female</td>
<td>77 (64.2%)</td>
<td>78 (65.0%)</td>
<td>0.89</td>
</tr>
<tr>
<td>No Prior Medication</td>
<td>89 (74.2%)</td>
<td>78 (65%)</td>
<td>0.12</td>
</tr>
<tr>
<td>NRS Pain Score</td>
<td>8.9 ± 1.2</td>
<td>9.2 ± 1.0</td>
<td>0.93</td>
</tr>
<tr>
<td>Extremity Pain</td>
<td>60 (50%)</td>
<td>58 (48.3%)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Results & Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Ketamine ± SD</th>
<th>Morphine ± SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall change in NRS (%)</td>
<td>66.4 ± 29.9</td>
<td>61.3 ± 28.7</td>
<td>0.18</td>
</tr>
<tr>
<td>Overall time to max effect (min)</td>
<td>19.8 ± 14.4</td>
<td>34.1 ± 22.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of max effect (min)</td>
<td>60.0 ± 28.7</td>
<td>58.5 ± 10.3</td>
<td>0.47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Nystagmus</th>
<th>Dysphoria</th>
<th>Dizziness</th>
<th>Allergy</th>
<th>Nausea/ Vomiting</th>
<th>Saliva</th>
<th>Pruritus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>18</td>
<td>12</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Morphine</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
Results

• Steady trend of reduced pain over time
• Differences noted at 25 and 30 minutes
• Rapid 25% decrease in NRS in the ketamine group
• Increase in NRS in the morphine group

Fig. 3: Mean Numeric Rating Score as a percent change from baseline over time.

Conclusions

• Low dose ketamine was as effective as morphine in maximal change of NRS from baseline
• Both had an overall reduction of greater than 50%
• Ketamine had a shorter time to max effect compared to morphine
• Patients receiving ketamine had an 11-fold increase in side effects

Study Limitations & Critiques

• Single center trail could limit generalizability
• Children under the age of 7 were not included
• Set time intervals for pain checks limit ability to know exact onset and duration of pain relief
• Ketamine specific AEs like nystagmus may have created a potential for un-blinding.

How do we currently treat pain in VOC currently?
How do we treat pain in VOC currently?

Opioid Pain Management
- Hydrocodone
- Oxycodone
- Methadone
- Morphine injection
- Morphine PCA

Non-Narcotic Pain Management
- Acetaminophen
- Ibuprofen
- Naproxen
- Ketorolac
- Ketamine
- Gabapentin

Non-Pharmacologic Pain Management
- Massage Therapy
- Physical Therapy
- Heating Pads
- Relaxation techniques
- Acupuncture
- Pet therapy

Conclusion
- Additional pain management therapies, beyond opioids, are needed for patients experiencing recurrent VOCs.
- Lidocaine and ketamine infusions as adjunct to current pain management therapies have shown some benefit in adult and pediatric patients.
- More research is needed, especially with lidocaine infusions, with larger patient populations to further examine the benefits and long term effects of these therapies.

References
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Leslie Getchell, PharmD

Questions?