Low-dose Ketamine for Prehospital Analgesia

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Disclosures

- IRB Status: Exempt Status Approved
- Co-investigators: Amanda Woloszyn; Eric Lowe; Adam Whiteley; Ryan Merritt; Greg Pishotta; David Claudio
- Conflicts of Interest: None
- Project Sponsorship: None

Learning Objectives

1. Describe the advantages and disadvantages of using ketamine for prehospital analgesia

2. Outline appropriate dosing, administration, and patient monitoring of prehospital ketamine analgesia

Pre-Test Questions

1. Which of the following are advantages of using low-dose ketamine for analgesia in the prehospital setting?
   a. Lack of hypotensive effects, possible blood pressure increase
   b. Synergistic analgesia with opioids
   c. Little to no respiratory depression/adverse effects on airway reflexes
   d. A and B
   e. All of the above

2. Which of the following adverse effects are associated with ketamine?
   a. Hypertension
   b. Catalepsy
   c. Nystagmus
   d. A and C
   e. All of the above

Background

Low-dose Ketamine Analgesia

- NMDA receptor antagonist
  - Enhances DA activity, α- and β- agonist activity
  - Augments the action of opioids at C-fiber synapses
- Doses ≤0.5 mg/kg used for analgesia
  - Referred to as "sub-dissociative" doses
- Rarely cause significant adverse effects
  - Easily treated with low-dose benzodiazepines
- Pharmacokinetics for analgesia
  - Onset: 30 seconds (IV)
  - Duration: 20-45 minutes (IV)
Prehospital Ketamine

Advantages
- Hemodynamic benefits
- Minimal respiratory impairment
- Minimal cardiac impairment
- Synergistic with opioids
- Very good safety profile
- Rapid onset
- Multiple uses and routes

Disadvantages
- Psychological effects
- Nausea, dizziness
- Emergence reactions
- Use in patients at risk of hypertensive complications
- Requires training for optimal use and administration
- Preparations/packaging not ideal for low-dose use

Prehospital Ketamine Analgesia

- Large, prospective studies have concluded that prehospital ketamine administration by trained, non-physician responders is safe and effective7,8,11,12,13
- Ketamine has been widely-adopted for prehospital use
  - UK, Australia, many rural, limited-resource countries2,3,4,12,13
  - US military and backcountry/wilderness EMS operations2,4,5,11
- Prehospital ketamine analgesia in Gallatin Valley, MT
  - Potentially useful for AMR Bozeman operation
  - Prolonged extrications and transport durations
  - Traumatic injury common
    - Often related to outdoor recreation

American Medical Response Bozeman

- Emergency & non-emergency medical transport service
- Approximately 42 paramedics and EMTs
- Annual average ~3,600 calls
  - Wide variety of calls from farm to ski injuries
- Serves the Gallatin County area
  - Geographically vast, rural, and mountainous area
  - Extensive opportunities for outdoor recreation
  - Population nearly 100,000 people

MT Prehospital Treatment Protocols

- Restrictions on the use of ketamine14
  - Only for analgesia
  - Only at low, sub-dissociative doses
    - 0.1-0.5 mg/kg
  - Only for IV administration
  - Only may use if SBP > 100 mmHg
  - May not use for chest pain or pain of suspected cardiac origin

Study Objectives

- Implement a safe and effective process for AMR Bozeman to use low-dose ketamine for analgesia
- Evaluate pain in AMR patients before and after ketamine administration
- Evaluate adverse effects experienced by AMR patients after ketamine administration
- Assess the paramedics’ level of satisfaction, opinions, and concerns with low-dose ketamine analgesia

Methods
**Study Design and Protocols**

- Prospective, observational study
  - Pilot study for low-dose, prehospital ketamine use
- Prehospital protocol for ketamine analgesia
  - Developed by pharmacists in collaboration with AMR
  - Designed in accordance with MT state EMS protocols
- Pharmacist developed ketamine analgesia field protocol
  - Dosing chart included
  - Copy posted inside of every ambulance

**Ketamine Protocol Summary**

- Indications
  - Pain of traumatic origin
  - Opioid refractory pain
  - Chronic pain exacerbation in opioid-tolerant patient
- Contraindications
  - Hypersensitivity to ketamine
  - Chest pain of suspected cardiac origin
  - Hypertension could be problematic
  - SBP <100 mmHg

**Ketamine Protocol Summary**

- Dosing: 0.2 mg/kg, MAX 20 mg
- Administration: Slow IV push over 60 seconds
- Monitoring: BP, SpO₂, mental status, pain ratings, ECG
- Mediating Adverse Effects:
  - Agitation & ≥12 y.o. → midazolam 1mg IV
  - Agitation & <12 y.o. → midazolam 0.5mg IV
  - Laryngospasm → bag-valve-mask, airway maneuvers
  - Hypersalivation → atropine 0.5 mg IV

**Ketamine Field Protocol**

**Ketamine Education**

- Pharmacist-led ketamine education for paramedics
  - Training prior to protocol implementation mandatory
  - Focus on ketamine for prehospital analgesia
- Ketamine “go live” date - 11/1/2015
  - Pilot study planned for 11/1/2015 - 4/30/2016
  - Data collected on a rolling basis throughout

**Wrap-up and Statistical Analysis**

- Data collection through 4/30/15
  - End of ketamine pilot study
- Summarize and analyze final results
- Evaluate subjective feedback from paramedics, providers, and patients
- Statistical analysis through Montana State University
  - Pain score changes with ketamine
  - Descriptive statistics on parametric data
Preliminary Results

Patient and Run Information

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Age (years)</td>
<td>38.8</td>
<td>32</td>
<td>14 - 84</td>
</tr>
<tr>
<td>Patient Weight (kg)</td>
<td>78</td>
<td>60</td>
<td>54 - 113</td>
</tr>
<tr>
<td>Total distance (miles)</td>
<td>11.9</td>
<td>13.2</td>
<td>2.7 - 23.2</td>
</tr>
<tr>
<td>Duration (minutes)</td>
<td>71.6</td>
<td>67.5</td>
<td>31 - 196</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=15)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>9</td>
<td>60%</td>
</tr>
<tr>
<td>Morphine + Ketamine</td>
<td>4</td>
<td>26.7%</td>
</tr>
<tr>
<td>Fentanyl + Ketamine</td>
<td>6</td>
<td>40%</td>
</tr>
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Indication for Ketamine

<table>
<thead>
<tr>
<th>Indication</th>
<th>Patients (n=15)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain of traumatic origin</td>
<td>5</td>
<td>33.3%</td>
</tr>
<tr>
<td>Both no/poor response to opioids and pain of traumatic origin</td>
<td>7</td>
<td>46.7%</td>
</tr>
<tr>
<td>No/poor response to opioids</td>
<td>1</td>
<td>6.7%</td>
</tr>
<tr>
<td>Chronic pain exacerbation</td>
<td>1</td>
<td>6.7%</td>
</tr>
<tr>
<td>Both refused opioids and pain of traumatic origin</td>
<td>1</td>
<td>6.7%</td>
</tr>
</tbody>
</table>

Ketamine Protocol Compliance

<table>
<thead>
<tr>
<th>Ketamine Administered per Protocol</th>
<th>Patients (n=15)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>12</td>
<td>80%</td>
</tr>
<tr>
<td>No</td>
<td>3</td>
<td>20%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of Deviation from Protocol</th>
<th>Patients (n=3)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intentional</td>
<td>2</td>
<td>66.7%</td>
</tr>
<tr>
<td>Unintentional</td>
<td>1</td>
<td>33.3%</td>
</tr>
</tbody>
</table>

Ketamine Pain Score Changes

<table>
<thead>
<tr>
<th>Pain Scores with Ketamine Administration</th>
<th>Patients (n=15)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both pre- and post-ketamine pain scores</td>
<td>12</td>
<td>80%</td>
</tr>
<tr>
<td>Missing either or both pain scores</td>
<td>3</td>
<td>20%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change in Pain Score with Ketamine</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>-3.25</td>
<td>-3</td>
</tr>
<tr>
<td>Patients given ketamine per protocol</td>
<td>-3.5</td>
<td>-3.5</td>
</tr>
</tbody>
</table>

Ketamine Results and Adverse Effects

<table>
<thead>
<tr>
<th>Result</th>
<th>Patients (n=15)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>12</td>
<td>80%</td>
</tr>
<tr>
<td>Unresolved</td>
<td>2</td>
<td>13.3%</td>
</tr>
<tr>
<td>Deteriorated*</td>
<td>1</td>
<td>6.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Patients (n=15)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>No adverse effects</td>
<td>12</td>
<td>80%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>6.7%</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>1</td>
<td>6.7%</td>
</tr>
<tr>
<td>Dissociation*</td>
<td>1</td>
<td>6.7%</td>
</tr>
</tbody>
</table>

*Off protocol administration – dosing error
Ketamine and Morphine Subgroup

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of morphine given prior to ketamine administration</td>
<td>5 mg 1/4 10 mg 3/4</td>
</tr>
<tr>
<td>Ondansetron administered</td>
<td>3/4</td>
</tr>
<tr>
<td>&quot;Improved&quot; after ketamine administration</td>
<td>4/4</td>
</tr>
</tbody>
</table>

Pain Score Changes for K + M Subgroup

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine pain score change</td>
<td>-3</td>
<td>-3</td>
</tr>
</tbody>
</table>

Ketamine and Fentanyl Subgroup

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of fentanyl given prior to ketamine administration</td>
<td>0 mcg 1/6 50 mcg 2/6 100 mcg 2/6 150 mcg 1/6</td>
</tr>
<tr>
<td>Ondansetron administered</td>
<td>4/6</td>
</tr>
<tr>
<td>&quot;Improved&quot; after ketamine administration</td>
<td>4/6</td>
</tr>
</tbody>
</table>

Pain Score Changes for K + F Subgroup

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine pain score change</td>
<td>-3</td>
<td>-3.5</td>
</tr>
</tbody>
</table>

Hemodynamic & Respiratory Changes

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP change after ketamine*</td>
<td>+ 6.2 mmHg</td>
<td>+ 6 mmHg</td>
</tr>
<tr>
<td>Time between ketamine administration and BP*</td>
<td>21 minutes</td>
<td>19 minutes</td>
</tr>
</tbody>
</table>

*Excludes:
-3 patients with no post-ketamine BP
-1 patient given 10x protocol dose (SBP +42 mmHg)

- No trends or notable changes in HR, RR, or SpO2 with ketamine
- 11/14 patients had EKG monitoring – all normal sinus rhythm

Discussion

Summary of Preliminary Results

- Most common indications
  - Pain of traumatic origin
  - No/poor response to opioids
- Efficacy
  - 12/15 patients “improved” after ketamine
  - Average pain score decrease of -3
- Safety
  - 2 ADR at protocol doses: dizziness and dysphoria
  - Midazolam not attempted for side effect mediation
- Hemodynamic response
  - Average BP increase of 6.2 mmHg

Ketamine Drug Error - First Patient

- Received ketamine 140 mg IV instead of 14 mg IV
  - Experienced paramedic
  - Occurred despite dosing chart posted in ambulance
- Patient experienced classic dissociative ketamine anesthesia
  - Obtunded, eyes open but not focused
  - Maintained airway and SBP +42 mmHg
  - Verbally and physically non-responsive
- Ketamine 10 mg/mL in 20 mL vials
  - Lowest available concentration, smallest vial size
  - Maximum administration amount of 20 mg in 2 mL
  - Huge education point during paramedic training
Ketamine Drug Error - Response

- Medication error occurred 11/07/2015
- Ketamine box pulled from the ambulances
- Action taken prior to further use of ketamine
  1. 3 ml syringe added to box and replaced at refill
  2. Additional copy of the laminated protocol "cheat sheet" must be included in or on the box
  3. Paramedics required to participate in a skills verification conversation with Dr. Lowe
- Next ketamine administration delayed until 11/19/2015

Off-Protocol Ketamine Use

- IM ketamine 25 mg per online medical control
  - Unable to establish IV access after 2 attempts
  - First and only analgesic given
    - "Improved". 3 on pain scale
- Lower dose per patient preference
  - Refused opioids due to history of opioid abuse
  - Agreed to a 10 mg (0.1 mg/kg) dose of ketamine
  - Small improvement seen (-1 on pain scale)

Conclusion

Preliminary Conclusions

- Positive overall experience with ketamine analgesia in the field
- Seems to be safe and effective for analgesia
  - Ketamine medication error safer in overdose vs. opioids
  - Seems to be a mild increase in BP at low doses
- Patient satisfaction/response generally good
  - Dysphoria in 1 patient that received ketamine per protocol
  - Midazolam may have resolved dysphoria, but was not given
- Recommend making ketamine permanently available in the field as an option for analgesia

Next Steps and Future Directions

- Reevaluate ketamine protocol based on results
  - Indications, contraindications, dosing, monitoring
- Respond to future MT prehospital protocol changes
  - Eliminate/change minimum SBP for ketamine
  - Expansion of indications, routes, doses

Questions?
Post-Test Questions

1. Which of the following are advantages of using low-dose ketamine for analgesia in the prehospital setting?
   a. Lack of hypotensive effects, possible BP increase
   b. Synergistic analgesia with opioids
   c. Little to no respiratory depression/adverse effects on airway reflexes
   d. A and B
   e. All of the above

2. Which of the following adverse effects are associated with ketamine?
   a. Hypertension
   b. Catatopy
   c. Nystagmus
   d. A and C
   e. All of the above

Contact Information

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References