Ketamine dosing for sedation in mechanically ventilated patients

Zsanett Kormanyos PharmD
Ketamine dosing for sedation in mechanically ventilated patients

Speaker: Zsanett Kormanyos, PharmD
PGY1 Resident, Parkview Health

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Luke Keller PharmD, BCPS, BCCCP

The speaker has no actual or potential conflict of interest in relation to this presentation.
Ketamine

- Mechanism of action:
  - NMDA receptor antagonist
  - Opioid receptor agonist
  - GABA receptor agonist
  - Ach receptor antagonist
  - Catecholamine release

- Rapid onset of action: 30 seconds (IV)
- Elimination half-life: 2-3 hours
- Lipophilic properties: CNS distribution

# Sedative Comparison

<table>
<thead>
<tr>
<th>Fentanyl</th>
<th>Propofol</th>
<th>Dexmedetomidine</th>
<th>Midazolam</th>
<th>Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallucination, Psychosis</td>
<td>↑ SBP/HR, arrhythmias</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory Depression</th>
<th>+</th>
<th>+++</th>
<th>+</th>
<th>+++</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Gut Motility</td>
<td></td>
<td>↓ SBP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolerance/Abuse</td>
<td>PRIS*</td>
<td>Bradycardia</td>
<td>Delirium/Agitation</td>
<td></td>
</tr>
</tbody>
</table>

*Propofol Infusion Syndrome


Literature Review

Groetzinger et al. Ketamine Infusion for Adjunct Sedation in Mechanically Ventilated Adults (2018)
- Retrospective review (N=91)
- Comparing **total daily doses** and **hourly rates of sedatives** before and after ketamine
- 63% had sedatives discontinued/reduced within 24 hours  → 36% propofol

Garber et al. Continuous Infusion Ketamine for Adjunctive Analgosedation in Mechanically Ventilated, Critically Ill Patients (2019)
- Retrospective review (N=104)
- Median **percent relative dose change** at 24 hours -20% (IQR -63.6 – 0.0) p=0.001, 71% had decreased **vasopressor** requirement

Known

- Reduction of concomitant sedative doses
- Does not depress hemodynamic parameters
- Can reduce vasopressor requirements

Unknown

- Ideal dose range

Sources:
## Ideal Dose Range

<table>
<thead>
<tr>
<th>Reference</th>
<th>Dose Range</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micromedex</td>
<td>8 – 66 mcg/kg/min</td>
<td>Umunna et al.</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>5 – 7.8 mcg/kg/min</td>
<td>Garber et al.</td>
</tr>
<tr>
<td></td>
<td>5.5 – 16.7 mcg/kg/min</td>
<td>Groetzinger et al.</td>
</tr>
<tr>
<td></td>
<td>Doses as high as 75 mcg/kg/min</td>
<td>Elamin et al.</td>
</tr>
</tbody>
</table>

**Table:** Ketamine (KETALAR) 500 mg in NS 250 mL infusion

- **Dose:** 0-7 mcg/kg/min
- **Weight Type:** Recorded, Ideal, Adjusted, Order-Specific
- **Titrating in increments of:** 0.1 mcg/kg/min
- **Dispense:** Every 48 hours

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Assessment Question #1

1. Which of the following best describes the mechanism of action of ketamine as a sedative agent?

• A. NMDA receptor agonist, hydrophilic
• B. NMDA receptor antagonist, hydrophilic
• C. NMDA receptor antagonist, lipophilic
• D. NMDA receptor agonist, lipophilic
Assessment Question #2

Which of the following patients would most likely benefit from the addition of ketamine to their sedative regimen?

- A. Patient admitted for hypertensive crisis, last recorded blood pressure of 167/125 mmHg and heart rate of 65 bpm
- B. Patient admitted for shock, currently requiring norepinephrine at 30 mcg/min, last recorded heart rate of 54 bpm
- C. Patient admitted for acute respiratory failure with a past medical history of schizophrenia, currently non-compliant with medications
- D. Patient admitted for acute myocardial infarction, now with new onset of atrial fibrillation, last recorded heart rate of 123 bpm
Purpose

• To compare the effectiveness of three different ketamine infusion dosing ranges in reducing the required doses of concomitant sedative agents in mechanically ventilated patients
Parkview Regional Medical Center (PRMC)

- Community hospital
- Tertiary care
- Level II trauma center
- 528 adult and pediatric inpatient beds
- 6 critical care units
Design

• Retrospective, single center study
• Time frame: 3 year
  • 08/01/2017 – 07/31/2020

<table>
<thead>
<tr>
<th>Low Dose Ketamine Group</th>
<th>Medium Dose Ketamine Group</th>
<th>High Dose Ketamine Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion rate ≤7 mcg/kg/min</td>
<td>Infusion rate 8-15 mcg/kg/min</td>
<td>Infusion rate &gt;15 mcg/kg/min</td>
</tr>
</tbody>
</table>
Inclusions

- Age >18
- ICU admission
- Ketamine titrated to RASS goal
- Ketamine for at least 4 hours

Exclusions

- Not receiving concomitant sedatives
- Receiving paralytics
- No documented RASS scores
- SARS-CoV-2 positive
# Outcomes

## Primary Outcome
- Difference in total sedative requirements 24 hours before and after ketamine initiation

## Secondary Outcomes
- RASS goal
- Time of mechanical ventilation
- Length of ICU stay

## Secondary Safety Outcomes
- New onset of arrhythmias
- Incidence of agitation/delirium
- Incidence of hallucination/psychosis
- Reason for ketamine discontinuation
Subgroup Analyses

<table>
<thead>
<tr>
<th>Hemodynamically Stable Patients</th>
<th>Hemodynamically Unstable Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Mean Arterial Pressure (MAP)</td>
<td>● Vasopressor Requirements</td>
</tr>
<tr>
<td>● Heart Rate (HR)</td>
<td></td>
</tr>
</tbody>
</table>

Ketamine initiation

6 hours 0 6 hours 12 hours 24 hours
Patient Population

N = 191

COVID (n=9)
Paralytics (n=52)
Ketamine Not Titrated to RASS (n=33)
No Concomitant Sedative (n=30)
Fixed Rate Ketamine (n=14)
Ketamine Infusion for <4 Hours (n=21)

Low Dose Ketamine  
 n=20

Medium Dose Ketamine  
 n=9

High Dose Ketamine  
 n=3
**Statistical Analysis**

- **High Dose Ketamine** group was excluded from statistical analysis due to low number of patients included.

<table>
<thead>
<tr>
<th>Test</th>
<th>Ordinal Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unpaired t-test</td>
<td>Normally distributed</td>
</tr>
<tr>
<td>Mann-Whitney U test</td>
<td>Non-normally distributed</td>
</tr>
<tr>
<td>Chi-square test</td>
<td>Categorical variables</td>
</tr>
</tbody>
</table>
# Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Low Dose Ketamine</th>
<th>Medium Dose Ketamine</th>
<th>p</th>
<th>High Dose Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, SD)</td>
<td>53.3 (± 15.6)</td>
<td>55.1 (± 14.1)</td>
<td>0.76</td>
<td>36.3 (±9.5)</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>12 (60.0)</td>
<td>5 (55.5)</td>
<td>0.82</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Ketamine Infusion Starting Dose (mcg/kg/min, IQR)</td>
<td>2 (0.6 – 2.0)</td>
<td>5.0 (2.0 – 10.0)</td>
<td>0.004</td>
<td>5.0</td>
</tr>
<tr>
<td>Highest Ketamine Infusion Rate in First 48 hours (mcg/kg/min, IQR)</td>
<td>6.0 (4.0-7.0)</td>
<td>10.2 (10.0-13.0)</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Ketamine Bolus Doses (n, %)</td>
<td>3 (15)</td>
<td>4 (44)</td>
<td>0.86</td>
<td>3 (100)</td>
</tr>
</tbody>
</table>
Results

Primary Outcome
Number of Sedatives in Addition to Ketamine

Before Ketamine Initiation
- 1 sedative: 34%
- 2 sedatives: 50%
- 3 sedatives: 6%
- 4 sedatives: 10%

After Ketamine Initiation
- 1 sedative: 31%
- 2 sedatives: 41%
- 3 sedatives: 25%
- 4 sedatives: 3%
## Changes in Sedative Requirements

<table>
<thead>
<tr>
<th></th>
<th>Low Dose Ketamine (n=20)</th>
<th>Medium Dose Ketamine (n=9)</th>
<th>High Dose Ketamine (n=3)</th>
<th>Total (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Sedatives Before Ketamine</td>
<td>46</td>
<td>21</td>
<td>8</td>
<td>75</td>
</tr>
<tr>
<td>Total Number of Sedatives After Ketamine</td>
<td>36</td>
<td>19</td>
<td>8</td>
<td>63</td>
</tr>
</tbody>
</table>

Fentanyl  
Midazolam  
Propofol  
Dexmedetomidine
## Total Fentanyl Dose Change

### Total Fentanyl Dose Change 24 Hours Before and After Ketamine Initiation

<table>
<thead>
<tr>
<th></th>
<th>Low Dose Ketamine (n=20)</th>
<th>Medium Dose Ketamine (n=9)</th>
<th>High Dose Ketamine (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients included</td>
<td>15</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Patients with a dose decrease (n, %)</td>
<td>6 (40.0)</td>
<td>3 (42.9)</td>
<td>0</td>
</tr>
<tr>
<td>Median dose change (mcg/hr, IQR)</td>
<td>26.68 (-17.16 – 54.79)</td>
<td>8.33 (-84.37 – 11.46)</td>
<td>41.15 (7.77 – 41.15)</td>
</tr>
</tbody>
</table>

\[ p=0.267 \]
Fentanyl Rate Change

<table>
<thead>
<tr>
<th></th>
<th>24 Hours Before Ketamine Initiation</th>
<th>At Ketamine Initiation</th>
<th>24 Hours After Ketamine Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Dose Ketamine</td>
<td>132</td>
<td>148</td>
<td>142</td>
</tr>
<tr>
<td>Medium Dose Ketamine</td>
<td>122</td>
<td>114</td>
<td>117</td>
</tr>
<tr>
<td>High Dose Ketamine</td>
<td>175</td>
<td>158</td>
<td>200</td>
</tr>
</tbody>
</table>
## Total Midazolam Dose Change

### Total Midazolam Dose Change 24 Hours Before and After Ketamine Initiation

<table>
<thead>
<tr>
<th></th>
<th>Low Dose Ketamine (n=20)</th>
<th>Medium Dose Ketamine (n=9)</th>
<th>High Dose Ketamine (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients included</td>
<td>3</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Patients with a dose decrease (n, %)</td>
<td>1 (33.3)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Mean dose change (mg/hr, IQR)</td>
<td>- 0.4 (±3.99)</td>
<td>-</td>
<td>2.1</td>
</tr>
</tbody>
</table>
Midazolam Rate Change

<table>
<thead>
<tr>
<th></th>
<th>24 Hours Before Ketamine Initiation</th>
<th>At Ketamine Initiation</th>
<th>24 Hours After Ketamine Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Dose Ketamine</td>
<td>10.0</td>
<td>7.3</td>
<td>4.8</td>
</tr>
<tr>
<td>High Dose Ketamine</td>
<td>5.0</td>
<td>10.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>
# Total Propofol Dose Change

## Total Propofol Dose Change 24 Hours Before and After Ketamine Initiation

<table>
<thead>
<tr>
<th></th>
<th>Low Dose Ketamine (n=20)</th>
<th>Medium Dose Ketamine (n=9)</th>
<th>High Dose Ketamine (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients included</td>
<td>7</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Patients with a dose decrease (n, %)</td>
<td>4 (57.1)</td>
<td>3 (80.0)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Median dose change (mcg/kg/min, IQR)</td>
<td>-8.69 (-17.92 – 4.45)</td>
<td>-8.43 (-26.08 – 3.04)</td>
<td>-44.35 (-59.13 – 44.35)</td>
</tr>
</tbody>
</table>

\[ p=0.639 \]
Propofol Rate Change

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>24 Hours Before Ketamine Initiation</th>
<th>At Ketamine Initiation</th>
<th>24 Hours After Ketamine Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Dose Ketamine</td>
<td>35</td>
<td>38</td>
<td>25</td>
</tr>
<tr>
<td>Medium Dose Ketamine</td>
<td>48</td>
<td>40</td>
<td>33</td>
</tr>
<tr>
<td>High Dose Ketamine</td>
<td>20</td>
<td>53</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Low Dose Ketamine (n=20)</td>
<td>Medium Dose Ketamine (n=9)</td>
<td>High Dose Ketamine (n=3)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------------</td>
<td>----------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Number of patients included</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Patients with a dose decrease (n, %)</td>
<td>4 (66.7)</td>
<td>0</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Mean dose change (mcg/kg/hr, SD)</td>
<td>-0.05 (±0.24)</td>
<td>0.22 (±0.05)</td>
<td>-0.14</td>
</tr>
</tbody>
</table>
Dexmedetomidine Rate Change

<table>
<thead>
<tr>
<th></th>
<th>24 Hours Before Ketamine Initiation</th>
<th>At Ketamine Initiation</th>
<th>24 Hours After Ketamine Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Dose Ketamine</td>
<td>0.48</td>
<td>0.80</td>
<td>0.75</td>
</tr>
<tr>
<td>Medium Dose Ketamine</td>
<td>0.55</td>
<td>1.30</td>
<td>1.53</td>
</tr>
<tr>
<td>High Dose Ketamine</td>
<td>1.00</td>
<td>1.50</td>
<td>1.50</td>
</tr>
</tbody>
</table>
Primary Outcome Summary

<table>
<thead>
<tr>
<th>Patients with a Sedative Dose Decrease (n, %)</th>
<th>Low Dose Ketamine (n=20)</th>
<th>Medium Dose Ketamine (n=9)</th>
<th>High Dose Ketamine (n=3)</th>
<th>Total (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (48.4)</td>
<td>6 (46.6)</td>
<td>3 (42.8)</td>
<td>24 (47.1)</td>
<td></td>
</tr>
</tbody>
</table>
RASS Goal

<table>
<thead>
<tr>
<th></th>
<th>Low Dose Ketamine</th>
<th>Medium Dose Ketamine</th>
<th>High Dose Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Goal</td>
<td>45%</td>
<td>78%</td>
<td>100%</td>
</tr>
<tr>
<td>Not at Goal</td>
<td>55%</td>
<td>22%</td>
<td></td>
</tr>
</tbody>
</table>

\[ p = 0.101 \]

<table>
<thead>
<tr>
<th></th>
<th>Low Dose Ketamine</th>
<th>Medium Dose Ketamine</th>
<th>High Dose Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oversedated</td>
<td>5</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Undersedated</td>
<td>4</td>
<td>3</td>
<td>-</td>
</tr>
</tbody>
</table>
Length of ICU Stay

![Graph showing length of ICU stay for different doses of ketamine.](image)

- **Low Dose Ketamine**: 11 days
- **Medium Dose Ketamine**: 12 days
- **High Dose Ketamine**: 6 days

Statistical Significance: $p=0.936$
Duration of Mechanical Ventilation after Ketamine Initiation

- Low Dose Ketamine: 3.6 days
- Medium Dose Ketamine: 2.8 days
- High Dose Ketamine: 1.5 days

*p = 0.532*
## Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Low Dose Ketamine</th>
<th>Medium Dose Ketamine</th>
<th>High Dose Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmias</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hallucination</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Agitation/Delirium (n, %)</td>
<td>6 (30.0)</td>
<td>3 (33.3)</td>
<td>-</td>
</tr>
<tr>
<td>Discontinuation (n, %)</td>
<td>12 (60.0)</td>
<td>7 (77.8)</td>
<td>3 (100.0)</td>
</tr>
<tr>
<td>Mortality (n,%)</td>
<td>6 (30.0)</td>
<td>2 (22.2)</td>
<td>2 (66.7)</td>
</tr>
</tbody>
</table>

### Reason for Ketamine Discontinuation

- **Delirium**: 6
- **Weaning Sedation**: 13
- **Extubation**: 2
- **Failure of therapy**: 1
Subgroup Analyses
Hemodynamically Stable Patients

MAP

- Minimum
- Average
- Maximum

Heart Rate

- Minimum
- Average
- Maximum
Hemodynamically Stable Patients

Number of Patients with a MAP < 65 mmHg or Heart Rate > 100 bpm

<table>
<thead>
<tr>
<th></th>
<th>Before Ketamine Initiation</th>
<th>After Ketamine Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP &lt;65 mmHg</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>HR &gt;100 bpm</td>
<td>4</td>
<td>11</td>
</tr>
</tbody>
</table>

p=0.028
Hemodynamically Unstable Patients

Vasopressor Requirements at Ketamine Initiation

- Total number of patients: 17
- Vasopressors started after ketamine initiation: 2
- Vasopressors discontinued after ketamine initiation: 6

Legend:
- 1 vasopressor
- 2 vasopressors
- 3 vasopressors
Hemodynamically Unstable Patients

Vasopressor Requirements in Norepinephrine Equivalents

- 6 Hours Before Ketamine: 6.0 Mcg/min
- At Ketamine Initiation: 9.5 Mcg/min
- 6 Hours After Ketamine: 13.0 Mcg/min
- 12 Hours After Ketamine: 9.0 Mcg/min
Hemodynamically Unstable Patients

Change in Vasopressor Dose Requirements 6 Hours After Ketamine Initiation

<table>
<thead>
<tr>
<th></th>
<th>At Ketamine Initiation</th>
<th>6 Hours after Ketamine Initiation</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median vasopressor dose* (mcg/min, IQR)</td>
<td>9.5 (4.8-21.3)</td>
<td>13.0 (3.0-28.0)</td>
<td>0.362</td>
</tr>
</tbody>
</table>

*Expressed in norepinephrine equivalents
Conclusion

• The study was unable to show that ketamine:
  • Can reduce concomitant sedative requirements
  • Can reduce vasopressor requirements
Limitations

- Small sample size
- Single center study
- Prescriber bias
- No information on severity of illness
Future Directions

• Further studies
  • Larger patient population
  • Longer time period

• Include baseline severity of illness
Acknowledgments

Special Thanks to:

- Michael Todt PharmD, BCCCP
- Luke Keller PharmD, BCPS, BCCCP
- Sarah Ferrell PharmD, BCPPS
References

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