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### Ketamine dosing for sedation in mechanically ventilated patients

Zsanett Kormanyos PharmD

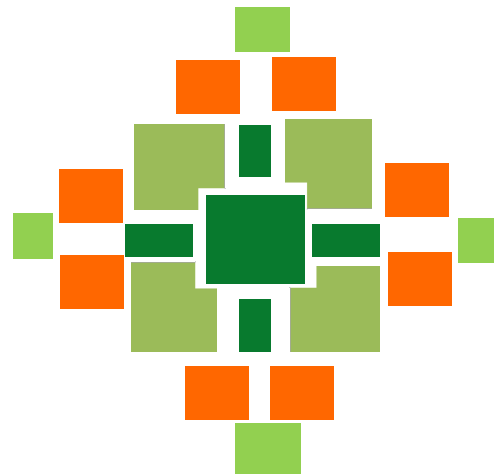
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# Ketamine dosing for sedation in mechanically ventilated patients



**Speaker:**

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**Mentors:**

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**Luke Keller PharmD, BCPS, BCCCP**

**04.28. - 04.30.2021.**  **PARKVIEW**

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

# Ketamine in Therapy

General  
Anesthesia

Procedural  
Sedation  
Off-label

Rapid  
Sequence  
Intubation  
Off-label

Acute Pain  
Off-label

Status  
epilepticus  
Off-label

**Analgo-  
sedation**  
Off-label

# Sedative Comparison

Fentanyl	Propofol	Dexmedetomidine	Midazolam	Ketamine
Respiratory Depression				Hallucination, Psychosis
+++	+++	+	+++	
↓ Gut Motility	↓ SBP			↑ SBP/HR, arrhythmias
Tolerance/Abuse	PRIS*	Bradycardia	Delirium/Agitation	

## \*Propofol Infusion Syndrome

Umunna BP, Tekwani K, Barounis D, Kettaneh N, Kulstad E. Ketamine for continuous sedation of mechanically ventilated patients. J Emerg Trauma Shock. 2015; 8(1):11-15  
 Groetzinger LM, Rivosecchi RM, Bain W, et al. Ketamine Infusion for Adjunct Sedation in Mechanically Ventilated Adults. Pharmacotherapy. 2018; 38(2): 181-188

# 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

# Ketamine in Practice

## Known

Reduction of concomitant  
**sedative** doses

Does not depress  
**hemodynamic** parameters

Can reduce **vasopressor**  
requirements

## Unknown

**Ideal dose range**

# Ideal Dose Range

ketamine (KETALAR) 500 mg in NS 250 mL infusion

Reference Links: 1. [Micromedex](#) 2. [Pediatrics](#)

Dose: 0-7 mcg/kg/min 5 mcg/kg/min 10 mcg/kg/min **0-7 mcg/kg/min**

Weight Type: Recorded Ideal Adjusted Order-Specific

Titrate in increments of: 0.1 mcg/kg/min Other May not titrate

Dispense: Dispense every 48 hours Label comments:

☐ Do not dispense doses

☐ Calculate rate from volume and admin over

**8 – 66**  
mcg/kg/min  
(Umunna et al.)

**5 – 7.8**  
mcg/kg/min  
(Garber et al.)

**5.5 – 16.7**  
mcg/kg/min  
(Groetzinger et al.)

Doses as high as  
**75** mcg/kg/min  
(Elamin et al.)



# Assessment Question #1

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

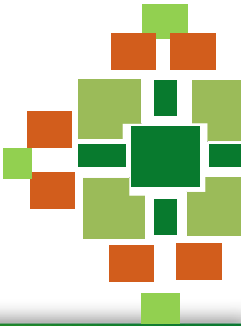
- A. NMDA receptor agonist, hydrophilic
- B. NMDA receptor antagonist, hydrophilic
- C. NMDA receptor antagonist, lipophilic
- D. NMDA receptor agonist, lipophilic

# 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

# Study Design



# 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

Low Dose Ketamine Group	Medium Dose Ketamine Group	High Dose Ketamine Group
Infusion rate $\leq 7$ mcg/kg/min	Infusion rate 8-15 mcg/kg/min	Infusion rate $>15$ mcg/kg/min

# 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



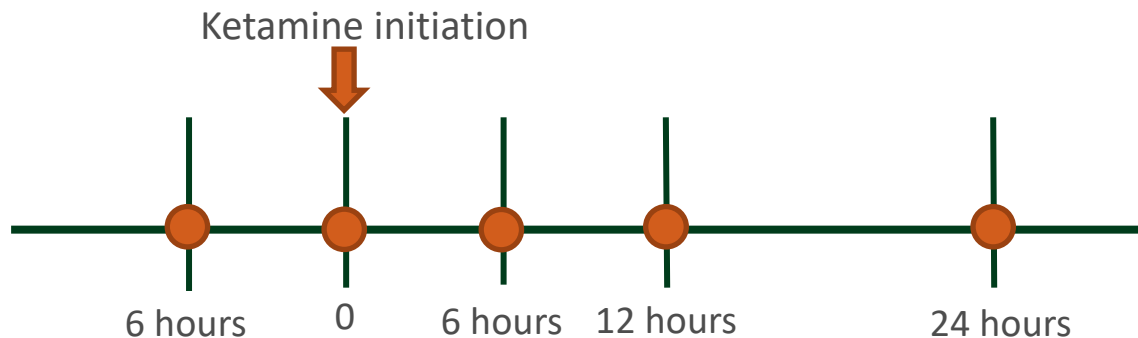
# Subgroup Analyses

## Hemodynamically Stable Patients

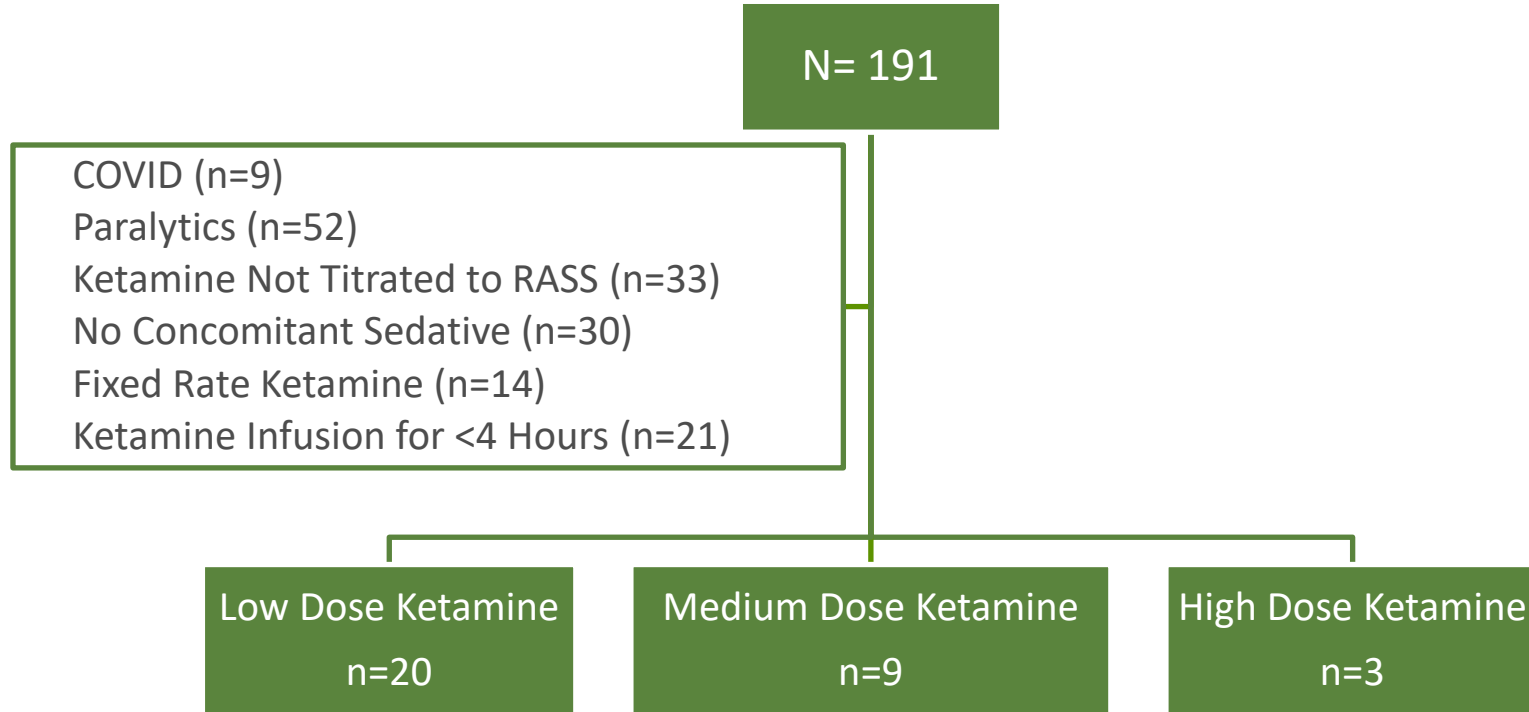
- Mean Arterial Pressure (MAP)
- Heart Rate (HR)

## Hemodynamically Unstable Patients

- Vasopressor Requirements



# Patient Population



# Statistical Analysis

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

Unpaired t-test

Normally distributed  
ordinal variables

Mann-Whitney U test

Non-normally  
distributed ordinal  
variables

Chi-square test

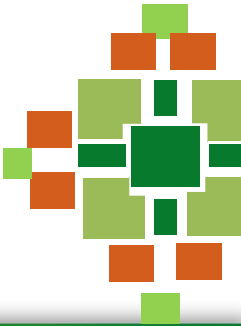
Categorical  
variables

# Baseline Characteristics

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

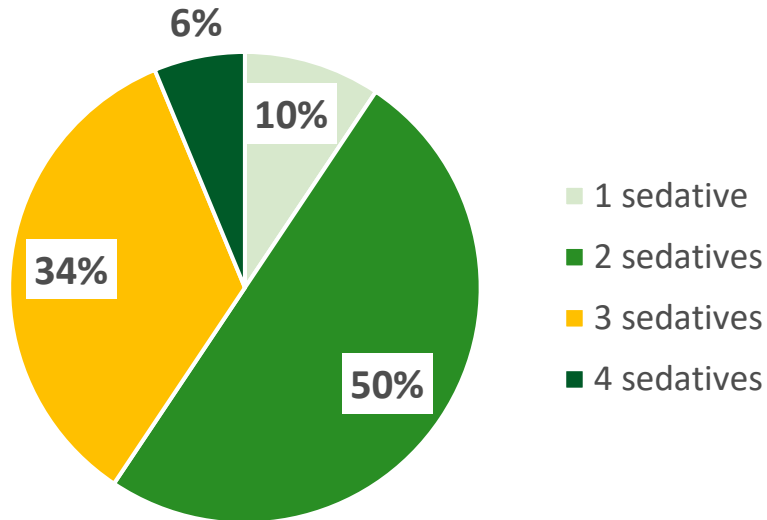
# Results

Primary Outcome

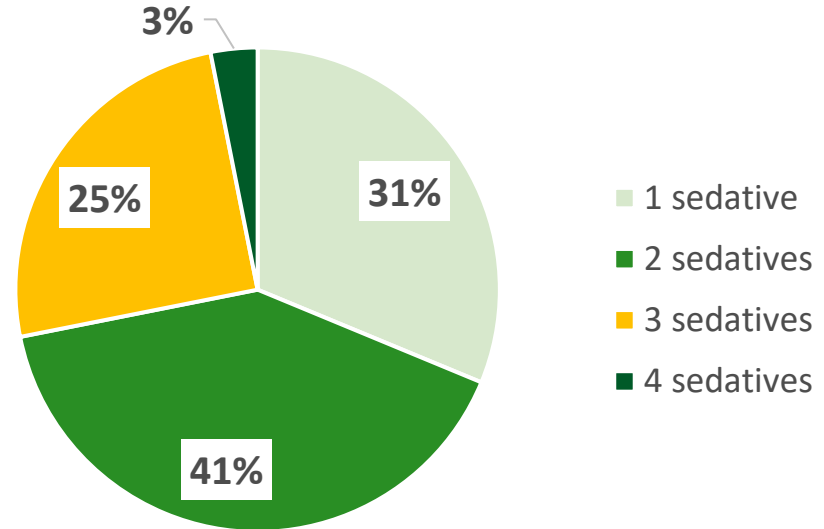


# Number of Sedatives in Addition to Ketamine

Before Ketamine Initiation



After Ketamine Initiation



# Changes in Sedative Requirements

	Low Dose Ketamine (n=20)	Medium Dose Ketamine (n=9)	High Dose Ketamine (n=3)	Total (n=32)
Total Number of Sedatives Before Ketamine	46	21	8	75
Total Number of Sedatives After Ketamine	36	19	8	63

Fentanyl

Midazolam

Propofol

Dexmedetomidine

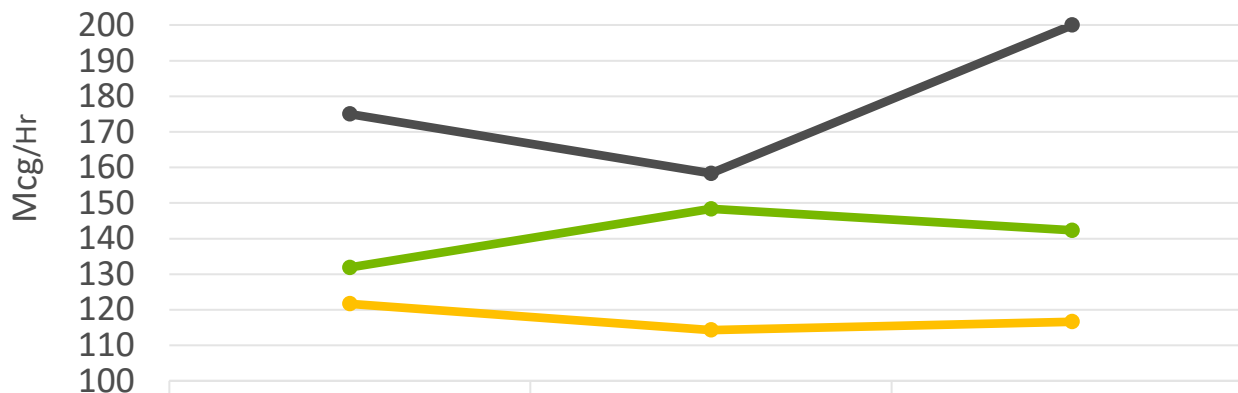
# Total Fentanyl Dose Change

Total Fentanyl Dose Change 24 Hours Before and After Ketamine Initiation

	Low Dose Ketamine (n=20)	Medium Dose Ketamine (n=9)	High Dose Ketamine (n=3)
Number of patients included	15	7	3
Patients with a dose decrease (n, %)	6 (40.0)	3 (42.9)	0
Median dose change (mcg/hr, IQR)	26.68 (-17.16 – 54.79)	8.33 (-84.37 – 11.46)	41.15 (7.77 – 41.15)
p=0.267			



# Fentanyl Rate Change



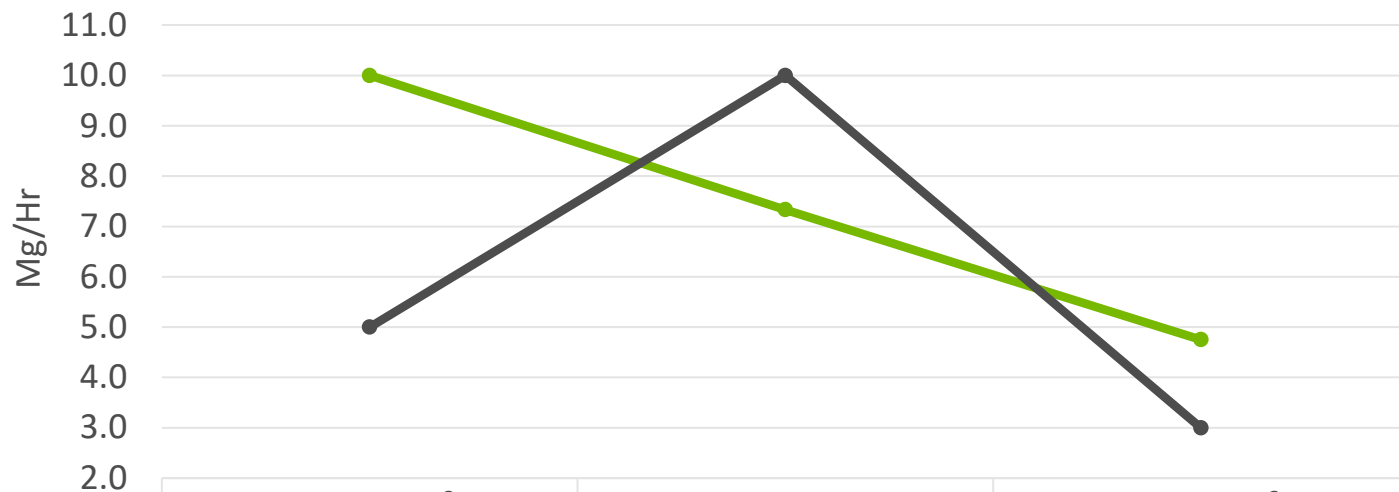
	24 Hours Before Ketamine Initiation	At Ketamine Initiation	24 Hours After Ketamine Initiation
Low Dose Ketamine	132	148	142
Medium Dose Ketamine	122	114	117
High Dose Ketamine	175	158	200

# Total Midazolam Dose Change

Total Midazolam Dose Change 24 Hours Before and After Ketamine Initiation

	Low Dose Ketamine (n=20)	Medium Dose Ketamine (n=9)	High Dose Ketamine (n=3)
Number of patients included	3	-	1
Patients with a dose decrease (n, %)	1 (33.3)	-	0
Mean dose change (mg/hr, IQR)	- 0.4 (±3.99)	-	2.1

# Midazolam Rate Change



—●— Low Dose Ketamine  
—●— High Dose Ketamine

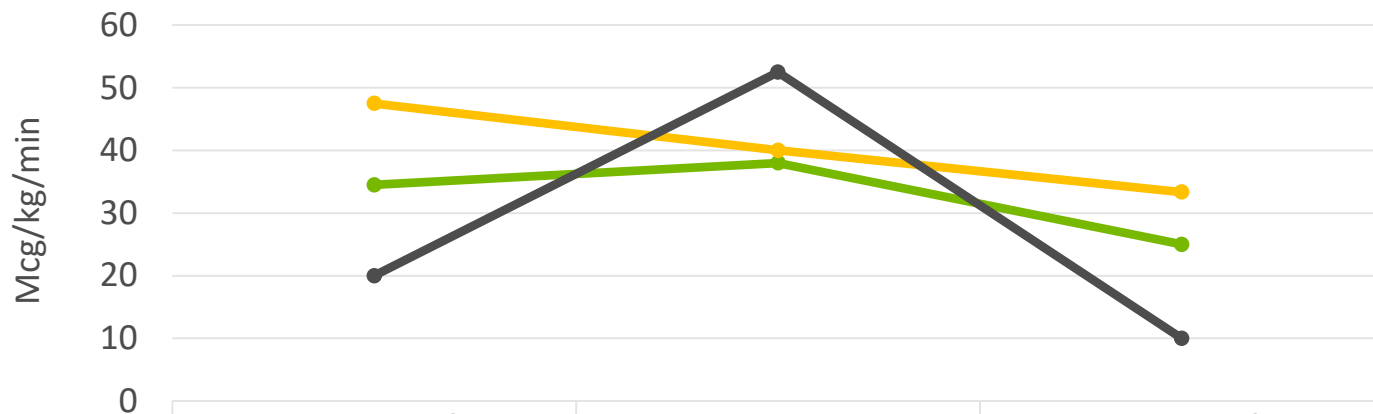
	24 Hours Before Ketamine Initiation	At Ketamine Initiation	24 Hours After Ketamine Initiation
Low Dose Ketamine	10.0	7.3	4.8
High Dose Ketamine	5.0	10.0	3.0

# Total Propofol Dose Change

Total Propofol Dose Change 24 Hours Before and After Ketamine Initiation

	Low Dose Ketamine (n=20)	Medium Dose Ketamine (n=9)	High Dose Ketamine (n=3)
Number of patients included	7	4	2
Patients with a dose decrease (n, %)	4 (57.1)	3 (80.0)	2 (100)
Median dose change (mcg/kg/min, IQR)	-8.69 (-17.92 – 4.45)	-8.43 (-26.08 – 3.04)	-44.35 (-59.13 – 44.35)
p=0.639			

# Propofol Rate Change



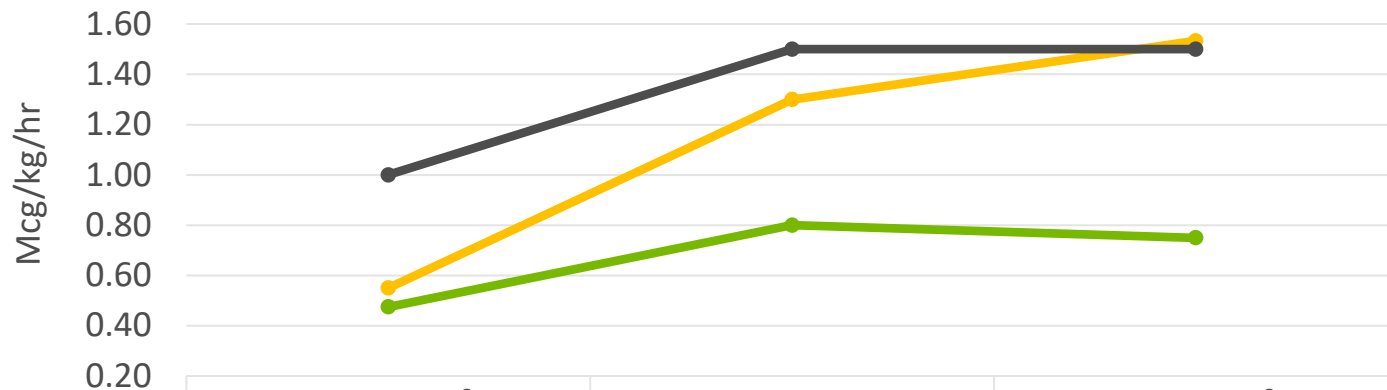
	24 Hours Before Ketamine Initiation	At Ketamine Initiation	24 Hours After Ketamine Initiation
Low Dose Ketamine	35	38	25
Medium Dose Ketamine	48	40	33
High Dose Ketamine	20	53	10

# Total Dexmedetomidine Dose Change

Total Dexmedetomidine Dose Change 24 Hours Before and After Ketamine Initiation

	Low Dose Ketamine (n=20)	Medium Dose Ketamine (n=9)	High Dose Ketamine (n=3)
Number of patients included	6	2	1
Patients with a dose decrease (n, %)	4 (66.7)	0	1 (100)
Mean dose change (mcg/kg/hr, SD)	-0.05 ( $\pm 0.24$ )	0.22 ( $\pm 0.05$ )	-0.14

# Dexmedetomidine Rate Change



	24 Hours Before Ketamine Initiation	At Ketamine Initiation	24 Hours After Ketamine Initiation
Low Dose Ketamine	0.48	0.80	0.75
Medium Dose Ketamine	0.55	1.30	1.53
High Dose Ketamine	1.00	1.50	1.50

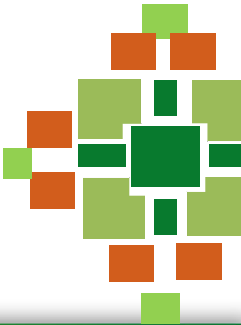
# Primary Outcome Summary

	Low Dose Ketamine (n=20)	Medium Dose Ketamine (n=9)	High Dose Ketamine (n=3)	Total (n=32)
Patients with a Sedative Dose Decrease (n, %)	15 (48.4)	6 (46.6)	3 (42.8)	24 (47.1)



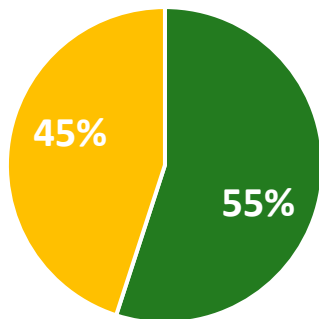
# Results

Secondary Outcomes



# RASS Goal

Low Dose Ketamine

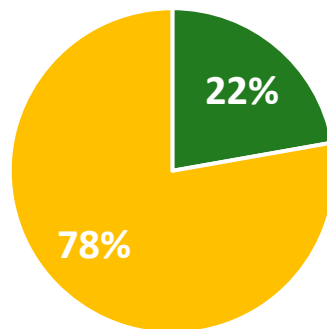


■ At Goal

■ Not at Goal

$p=0.101$

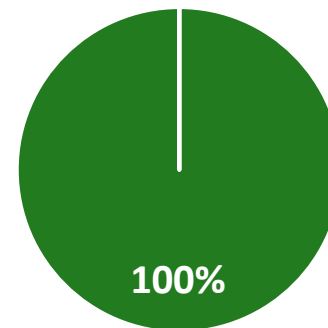
Medium Dose Ketamine



■ At Goal

■ Not at Goal

High Dose Ketamine



■ At Goal

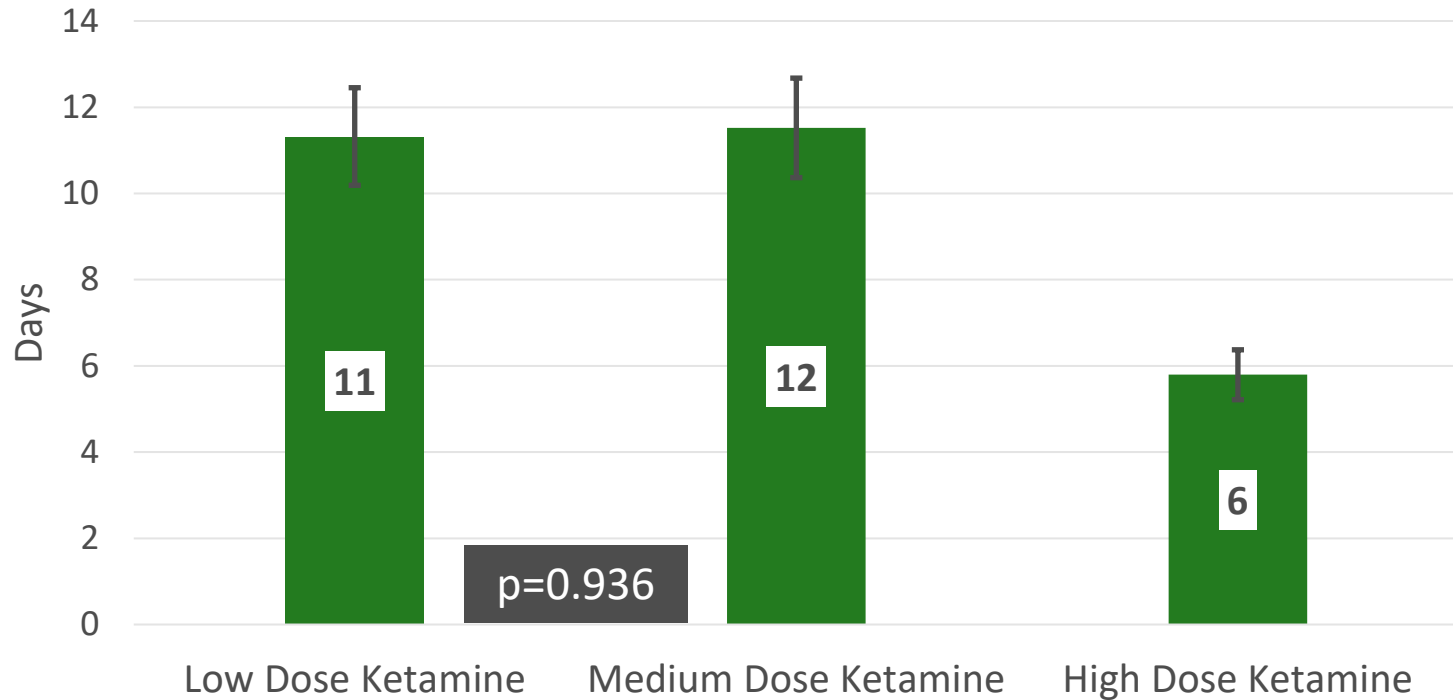
Low Dose  
Ketamine

Medium Dose  
Ketamine

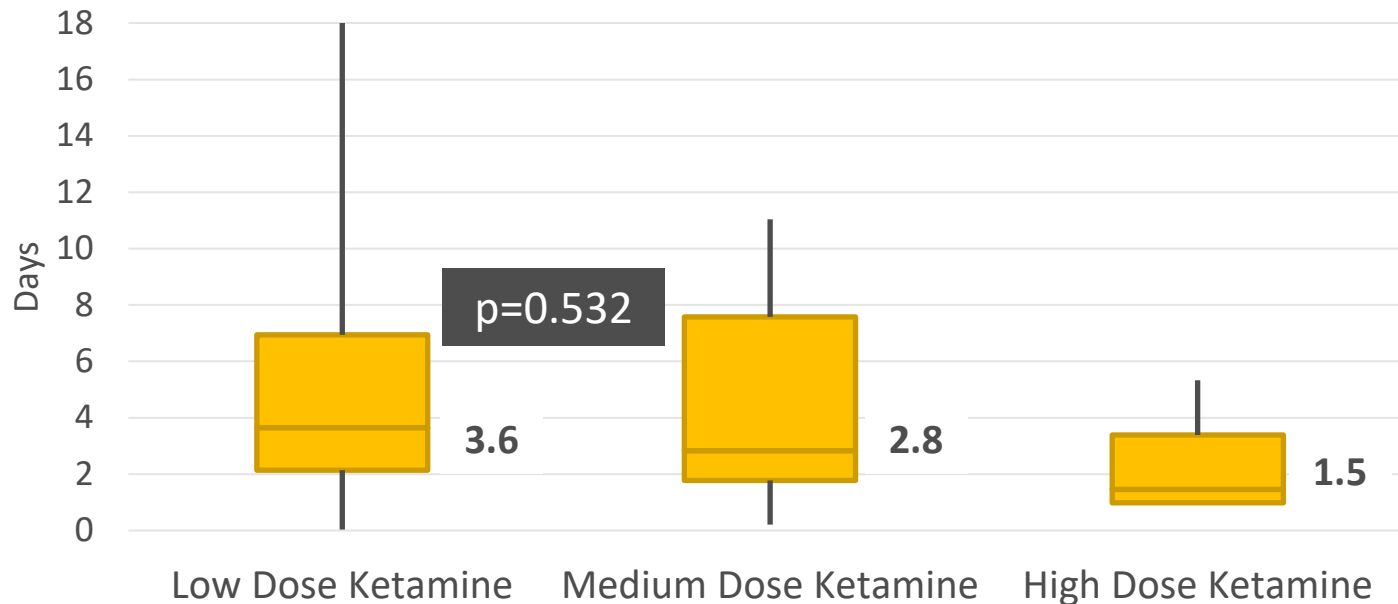
High Dose  
Ketamine

Not at Goal	Oversedated	5	3	-
	Undersedated	4	3	-

# Length of ICU Stay



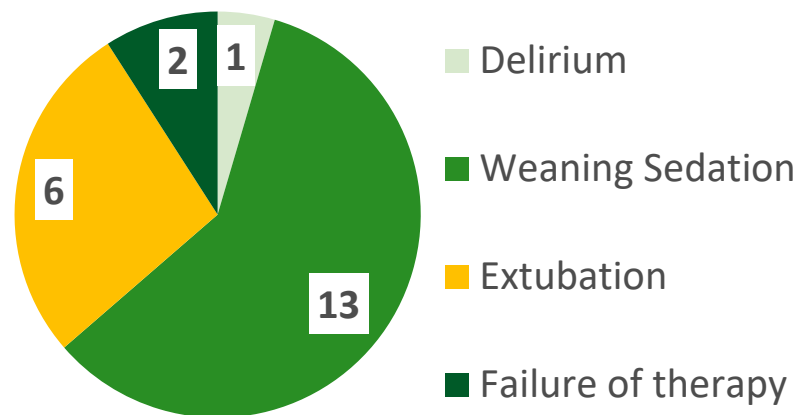
# Duration of Mechanical Ventilation after Ketamine Initiation



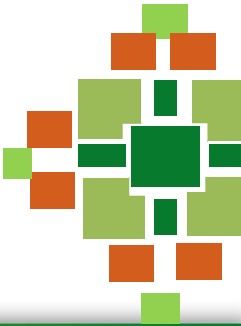
# Safety Outcomes

	Low Dose Ketamine	Medium Dose Ketamine	High Dose Ketamine
Arrhythmias	-	-	-
Hallucination	-	-	-
Agitation/ Delirium (n, %)	6 (30.0)	3 (33.3)	-
Discontinuation (n, %)	12 (60.0)	7 (77.8)	3 (100.0)
Mortality (n,%)	6 (30.0)	2 (22.2)	2 (66.7)

Reason for Ketamine Discontinuation

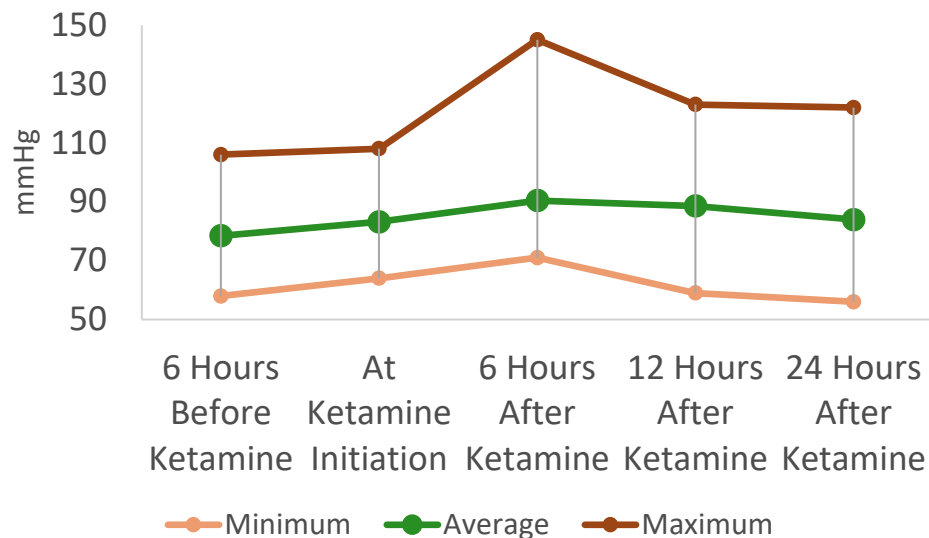


# Subgroup Analyses



# Hemodynamically Stable Patients

## MAP

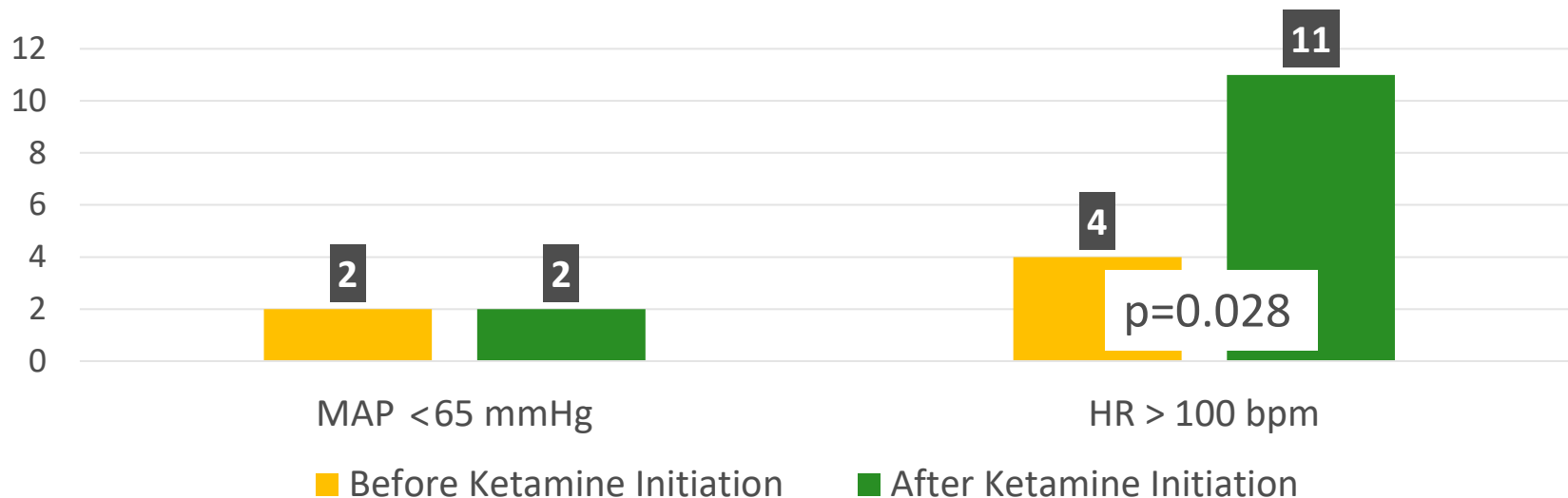


## Heart Rate



# Hemodynamically Stable Patients

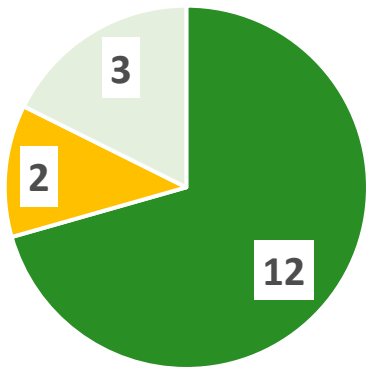
Number of Patients with a MAP < 65 mmHg or Heart Rate > 100 bpm





# Hemodynamically Unstable Patients

## Vasopressor Requirements at Ketamine Initiation

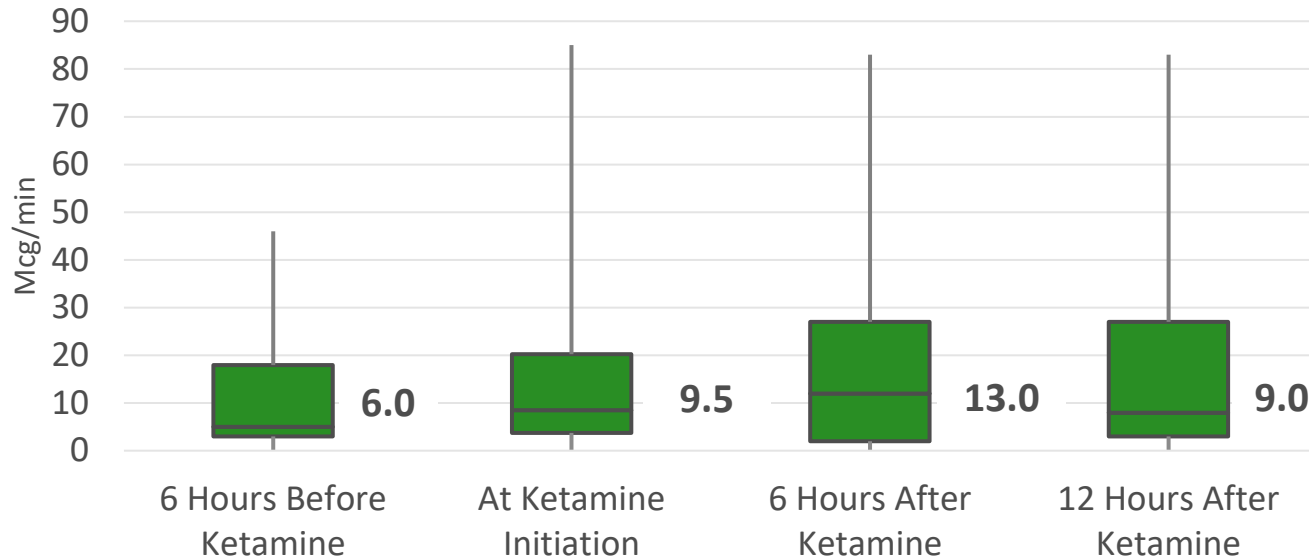


■ 1 vasopressor ■ 2 vasopressors ■ 3 vasopressors

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

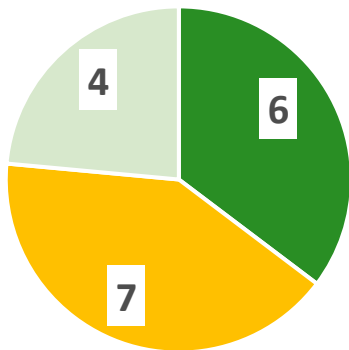
# Hemodynamically Unstable Patients

Vasopressor Requirements in Norepinephrine  
Equivalents



# Hemodynamically Unstable Patients

Change in Vasopressor Dose Requirements 6  
Hours After Ketamine Initiation



■ increase ■ decrease ■ no change

	At Ketamine Initiation	6 Hours after Ketamine Initiation	p
Median vasopressor dose* (mcg/min, IQR)	9.5 (4.8-21.3)	13.0 (3.0-28.0)	0.362

\*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:

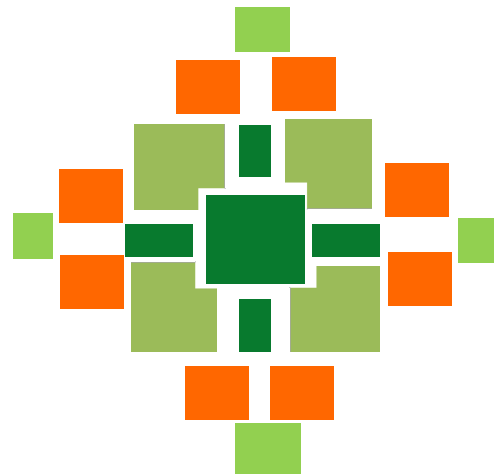
- **Michael Todt PharmD, BCCCP**
- **Luke Keller PharmD, BCPS, BCCCP**
- **Sarah Ferrell PharmD, BCPPS**

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4. Groetzing LM, Rivosecchi RM, Bain W, et al. Ketamine Infusion for Adjunct Sedation in Mechanically Ventilated Adults. Pharmacotherapy. 2018; 38(2): 181-188
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7. Miller AC, Jamin CT, Elamin EM. Continuous intravenous infusion of ketamine for maintenance sedation. Minerva Anesthesiol. 2011; 77:812-820
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9. IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp



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**PGY1 Resident, Parkview Health**

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