Supplemental Digital Content

Methods:

Data collected to describe institution demographics included type of hospital, geographic location, total number of hospital and ICU beds, use of ICU pain/sedation and ketamine guidelines, and restrictions around ketamine use including need for ICU level of care and/or mechanical ventilation, and if titration is allowed by a nurse (Table S3). Type of pain, agitation, and delirium screening tools used by each institution were also collected (Table S4).

Data collected to describe patient demographics included median age, race, ethnicity, sex, weight, height, admitting diagnosis, co-morbidities, history of substance abuse, APACHE II score, allergies, intolerances or known clinical failure to other analgesics, sedatives, and antipsychotics, type of ICU, percentage requiring mechanical ventilation, vasopressors, and continuous neuromuscular blockers, hospital location where ketamine was initiated, and if ketamine was started before or after intubation (Table 1, S5, and S6)

Table S1 Adverse Effect Endpoint Definitions

Hemodynamic Endpoint	Definition
Hypertension	MAP > 105 mmHg, administration of an antihypertensive agent to treat acute hypertension, 25% decrease in vasopressor infusion rate, or decrease in two or more vasopressor infusion rates
Hypotension	MAP < 65 mmHg, start of a new vasopressor agent, administration of a fluid bolus > 500 ml to increase BP, 25% increase in any vasopressor infusion rate, or any increase in two or more vasopressor infusion rates
Tachycardia	HR >120 BPM without an increase in vasopressor dose (norepinephrine, dopamine, epinephrine, or dobutamine) within 15 minutes prior to HR measurement, administration of a new antiarrhythmic or rate-controlling medication, or requiring electrical cardioversion
Bradycardia	HR < 50 BPM not caused by administration of a rate controlling medication/antiarrhythmic within 15 minutes prior to HR measurement or administration of atropine
Cardiac Abnormalities	Atrial fibrillation, ventricular tachycardia, ventricular fibrillation, myocardial infarction, or heart block
Emergence Reaction	Chart documentation of hyperexcitability, restlessness, agitation, confusion, or hallucinations, prescription of a benzodiazepine or antipsychotic in the 4 hours surrounding CI ketamine

	discontinuation, or new delirium presenting in the 4 hours after CI ketamine discontinuation
Oral secretions	Presence of copious secretions, need for increased suctioning, or need for medication to manage secretions

MAP: mean arterial pressure; BP: blood pressure; HR: heart rate; BPM: beats per minute; CI: continuous infusion

Definitions were decided upon study author's clinical knowledge and experience

Table S2 Patient Distribution by Institution

Institution	Number of Patients	Institution	Number of Patients
Advent Health	21	Parkview Regional Medical Center	56
Augusta University Medical Center	44	Robert Wood Johnson University Hospital	21
Dartmouth-Hitchcock Medical Center	13	Rush University Medical Center	1
Erie County Medical Center	8	Sarasota Memorial Hospital	2
Flagstaff Medical Center/Northern Arizona Healthcare	8	St. Dominic Hospital	7
Froedtert Menomonee Falls Hospital	32	Texas Health Harris Methodist Fort Worth	42
Froedtert Hospital	1	University Hospital New Jersey	4
Inova Fairfax Medical	1	University of Maryland Medical Center	10
Kaleida Health	3	University of New Mexico Hospital	1
Lakes Region General Hospital	1	University of Rochester Medical Center	79
Loma Linda University Health	1	Vidant Medical Center	16
Lutheran Health Network	12	Wellstar Cobb Hospital	1

Mercy Hospital St Louis/ Saint Louis University	5		

Table S3: Institutional Demographics (n=25)

Demographics	n (%)
Type of hospital	
University teaching	13 (52)
Community non-teaching	8 (32)
Community teaching	4 (16)
Hospital location region[a]	
Northeast	8 (32)
Southeast	7 (28)
Midwest	6 (24)
Southwest	3 (12)
West	1 (4)
Total hospital beds	
101-249	2 (8)
250-499	6 (24)
500-749	10 (40)
750-1000	6 (24)
>1000	1 (4)
Total ICU beds (excluding neonatal ICU)	
<10	1 (4)
11-25	1 (4)
26-50	7 (28)
51-75	6 (24)
>75	10 (40)
Indications included in CI ketamine guideline (n=17)	
ICU pain and agitation	17 (100)
Intractable pain/acute pain only	10 (58.8)
Status epilepticus	5 (29.4)
Status asthmaticus	3 (17.6)
Palliative care	1 (5.9)
ICU admission required for CI ketamine, yes	12 (48)
Non-ICU locations CI ketamine allowed (n=13)	
Step-down/PCU	12 (92)
Emergency room	10 (77)
Floor	8 (62)
MV requirement for CI ketamine, yes	
Invasive or non-invasive	15 (60)
Invasive only	10 (40)
Titratable nursing administration permitted, yes	18 (72)

Presented as n (%); Abbreviations: ICU: intensive care unit; CI: continuous infusion; PCU: progressive care unit; MV: mechanical ventilation

[a]Regions: Northeast [Maine, Massachusetts, Rhode Island, Connecticut, New Hampshire, Vermont, New York, Pennsylvania, New Jersey, Delaware, Maryland]; Southeast [West Virginia, Virginia, Kentucky, Tennessee, North Carolina, South Carolina, Georgia, Alabama,

Mississippi, Arkansas, Louisiana, Florida]; Midwest [Ohio, Indiana, Michigan, Illinois, Missouri, Wisconsin, Minnesota, Iowa, Kansas, Nebraska, South Dakota, North Dakota]; Southwest [Texas, Oklahoma, New Mexico, Arizona]; West [Colorado, Wyoming, Montana, Idaho, Washington, Oregon, Utah, Nevada, California, Alaska, Hawaii]

Table S4: Institutional Pain, Sedation and Agitation, and Delirium Assessment Tools (n=25)

Institutional Practices	n (%)
Institutional scale for pain assessment	
CPOT	15 (60)
NRPS	10 (40)
BPS	5 (20)
NVPS	3 (12)
MOPAT	1 (4)
CNPI	1 (4)
DVPRS	1 (4)
PAINAD	1 (4)
Wong-baker	1(4)
Other	1 (4)
None	3 (12)
Institutional scale for sedation assessment	
RASS	22 (88)
SAS	3 (12)
Institutional screening tool for delirium assessment	
CAM-ICU	24 (96)
ICU-DSC	0 (0)
None	1 (4)

Abbreviations: CPOT: critical care pain observation tool; NRPS: numerical rating scale 1-10; BPS: behavioral pain scale; NVPS: nonverbal pain scale; MOPAT: multidimensional objective pain assessment; CNPI: checklist of nonverbal pain indicators; DVPRS: defense and veterans pain rating scale; PAINAD: pain assessment in advanced dementia scale; RASS: Richmond Agitation and Sedation Scale; SAS: Riker Sedation Agitation Scale; CAM-ICU: confusion assessment method for the ICU; ICU-DSC: intensive care unit delirium screening checklist

Table S5: Additional Baseline Demographics (n=390)

Demographics	n (%)
Co-morbidities[a]	
Kidney disease (acute or chronic)	56 (14.4)
Thyroid disorder	32 (8.2)
Seizure	30 (7.7)
Heart failure	30 (7.7)
Tachyarrhythmia	28 (7.2)
Hepatic failure/cirrhosis	20 (5.1)
Head injury	19 (4.9)
Stroke	14 (3.6)
Intracranial mass/Increased ICP	13 (3.3)
Glaucoma/increased ocular pressure	3 (0.8)
None	153 (39.2)
Psychiatric illness	
Depression	46 (11.8)
Bipolar	13 (3.3)
Schizophrenia	9 (2.3)
Other psychiatric illness	37 (9.5)
Substance abuse	
Alcohol	44 (11.3)
Opioids	35 (9.0)
Marijuana/Synthetic cannabinoids	24 (6.2)
Cocaine	15 (3.8)
Benzodiazepines	8 (2.1)
Amphetamines	2 (0.5)
Other	5 (1.3)
Medication Allergies, Intolerances, or Known Clinical Failure	
Benzodiazepines	7 (1.8)
Propofol	8 (2.1)
Dexmedetomidine	6 (1.5)
Haloperidol	5 (1.3)
Atypical antipsychotics	5 (1.3)
None	365 (93.6)
Consult Service Recommending Ketamine	
Yes	70 (18.0)
Unknown	28 (7.2)
Type of Consult Service	
Acute pain	42 (60.0)
Anesthesia	8 (11.4)
Cardiovascular/thoracic surgery	2 (2.9)
Critical care-pulmonology	3 (4.3)
Critical care-surgery	1 (1.4)
Neurocritical care	5 (7.1)
Pharmacy	7 (10.0)
Trauma surgery	2 (2.9)

Presented as n (%); Abbreviations: ICP: Intracranial pressure

[a]Only comorbidities that would potentially effect ketamine use were collected.

Table S6: Primary Admitting Diagnosis

Diagnosis	n (%)
Trauma	93 (23.8)
Respiratory failure	
Non-asthma	69 (17.7)
Asthma	17 (4.4)
Post-operative care	
Non-cardiac surgery (elective)	27 (6.9)
Cardiac surgery	10 (2.6)
Non-cardiac surgery (emergent)	8 (2.1)
Shock	
Septic	33 (8.5)
Cardiogenic	4 (1.0)
Hemorrhagic (non-intracranial)	2 (0.5)
Other	2 (0.5)
Cardiac emergency[a]	24 (6.2)
Gastrointestinal[b]	12 (3.1)
Seizure	10 (2.6)
Toxic ingestion	10 (2.6)
Acute pain	9 (2.3)
Encephalopathy	7 (1.8)
Stroke-Hemorrhagic	7 (1.8)
Burn	6 (1.5)
Infection, non-sepsis	6 (1.5)
Oncologic emergency	6 (1.5)
Hepatic failure/Biliary disease	4 (1.0)
Solid organ transplant	4 (1.0)
Sickle cell disease	3 (0.8)
Renal failure	2 (0.5)
Stroke-Ischemic	2 (0.5)
Endocrine emergency	1 (0.3)
Other	12 (3.1)

Presented as n (%).

[a] Cardiac emergency, including aortic dissection/aneurysm, arrhythmia, cardiac arrest, heart failure/pulmonary edema, hypertensive emergency, and myocardial infarction

[b] Gastrointestinal, including bleeding (non-shock), perforation, pneumatosis, obstruction, pancreatitis

Table S7: Baseline Analgesic, Sedative, and Antipsychotic Use (n=351)

Analgesics, Sedatives, and Antipsychotics	n (%)
IV or PO PRN Opioids	
Fentanyl	121 (34.5)
Hydromorphone	64 (18.2)
Oxycodone	35 (10.0)
Morphine	32 (9.1)
Hydrocodone	22 (6.3)
Methadone	3 (0.9)
Meperidine	2 (0.6)
Tramadol	1 (0.3)
IV or PO PRN Sedatives	
Midazolam	82 (23.4)
Lorazepam	42 (12.0)
Diazepam	11 (3.1)
Clonazepam	6 (1.7)
Propofol	6 (1.7)
Alprazolam	2 (0.6)
Diphenhydramine	1 (0.3)
IV or PO PRN Antipsychotics	
Haloperidol	16 (4.6)
Atypical antipsychotics	11 (3.1)
IV or PO PRN Medications, None	110 (31.3)
IV, PO or Transdermal ATC Opioids	
Fentanyl (IV or transdermal)	29 (8.3)
Hydromorphone	23 (6.6)
Oxycodone	22 (6.3)
Methadone	7 (2.0)
Morphine	6 (1.7)
Hydrocodone	1 (0.3)
IV or PO ATC Sedatives	
Midazolam	23 (6.6)
Lorazepam	12 (3.4)
Diazepam	7 (2.0)
Clonazepam	4 (1.1)
Alprazolam	2 (0.6)
Zolpidem	1 (0.3)
IV or PO ATC Antipsychotics	
Atypical antipsychotics	19 (5.4)
Haloperidol	6 (1.7)
IV or PO ATC Medications, None	245 (69.8)
Continuous Infusion Opioids	
Fentanyl	182 (51.9)
Hydromorphone	17 (4.8)
Morphine	7 (2.0)
Continuous Infusion Sedatives	
Propofol	129 (36.8)
Dexmedetomidine	94 (26.8)
Midazolam	72 (20.5)

Lorazepam	3 (0.9)
Continuous Infusion Medications, None	86 (24.5)
Adjunctive Non-opioid Analgesics and Sedatives	
No adjunctive agents	182 (51.9)
Acetaminophen	138 (39.3)
Gabapentin	38 (10.8)
Lidocaine	16 (4.6)
Non-steroidal anti-inflammatory drugs	15 (4.3)
Methocarbamol	10 (2.8)
Pregabalin	8 (2.3)
Cyclobenzaprine	6 (1.7)
Baclofen	4 (1.1)
Tizanidine	2 (0.6)
Amitriptylline	1 (0.3)
Bupivacaine, liposomal	1 (0.3)
Buspirone	1 (0.3)
Carbamazepine	1 (0.3)
Clonidine	1 (0.3)
Memantine	1 (0.3)
Valproate	1 (0.3)

Abbreviations: IV: Intravenous; PO: By mouth; PRN: As needed; ATC: Scheduled around the clock

Table S8. Continuous Infusion Ketamine Daily Doses, Minimum/Maximum Doses, and Volume Infused

Day	First 24 hours	25-48 hours	Day 3	Day 4	Day 5	Day 6	Day 7
n	382	224	133	78	59	41	31
Cumulative Daily Dose: mg	517.5 (187.4-1206.3)	555.3 (233.3-1674.0)	616.0 (196.8-1772.6)	857.5 (440.5-2326.6)	816.0 (391.6-1771.7)	950.4 (583.2-1773.6)	1152.0 (695.2-2106.3)
Daily Dose: mg/kg/hr	0.3 (0.2-0.8)	0.4 (0.2-0.9)	0.4 (0.2-0.9)	0.5 (0.3-1)	0.5 (0.3-0.9)	0.6 (0.3-1)	0.6 (0.4-1)
Daily Dose: mg/hr	27.4 (12.2-63.5)	29.5 (15.1-75.0)	33.0 (16.5-83.3)	39.6 (22.8-111.0)	39.6 (21.2-99.0)	45.9 (29.1-105.6)	48.9 (32.1-95.6)
Minimum Daily Dose: mg/kg/hr	0.2 (0.1-0.4)	0.3 (0.1-0.6)	0.3 (0.2-0.9)	0.3 (0.2-0.9)	0.4 (0.2-0.7)	0.4 (0.3-0.7)	0.5 (0.2-0.6)
Minimum Daily Dose: mg/hr	16.5 (7.1-32.8)	22.6 (9.7-54.5)	28.2 (11.6-63.3)	33 .0 (17.1-73.4)	32.6 (17.3-69.9)	39.7 (23.1-81.6)	34.0 (16.2-56.2)
Maximum Daily Dose: mg/kg/hr	0.5 (0.2-1)	0.4 (0.2-1)	0.5 (0.2-1)	0.6 (0.3-1.2)	0.5 (0.3-1)	0.6 (0.4-1.5)	0.7 (0.4-1.2)
Maximum Daily Dose: mg/hr	34.1 (17.6-81.2)	33 .0 (17.9-80.4)	37.6 (18.6-92.3)	48.7 (28.4-119.6)	40.2 (24.2-112.2)	48.8 (30.6-126.5)	62.3 (38.9-106.4)
Volume infused: ml	276.5 (104.0-721.5)	321.2 (117.8-892.0)	306.6 (110.3-886.3)	495.5 (212.5-938.7)	475.2 (216.6-852.6)	425.0 (243.6-822.1)	583.2 (330.9-1011.6)

Presented as median (IQR)

Table S9: Hemodynamic Changes and Cardiac Abnormalities Associated with Continuous Infusion Ketamine

Cardiovascular Effect	Baseline	4 hour	5-24 hour	25-48 hour	p-value
Hypertension (n=221)		53 (24.0%)	83 (37.6%)	89 (40.3%)	<0.001
Hypotension (n=221)		52 (23.5%)	69 (31.2%)	54 (24.4%)	0.053
Tachycardia (n=221)		43 (19.5%)	56 (25.3%)	50 (22.6%)	0.142
Bradycardia (n-221)		5 (2.3%)	10 (4.5%)	7 (3.2%)	0.232
A-fib/flutter (n=390)	18 (4.6%)	10 (2.6%)	11 (2.8%)	9 (2.3%)	0.013
Ventricular tachycardia (n=390)	7 (1.8%)	7 (1.8%)	8 (2.1%)	4 (1.0%)	0.463
Ventricular fibrillation (n=390)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.392
Myocardial infarction (n=390)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	N/A
Heart block (n=390)	3 (0.8%)	3 (0.8%)	1 (0.3%)	2 (0.5%)	0.392

Presented as total n (%) during the listed time frame

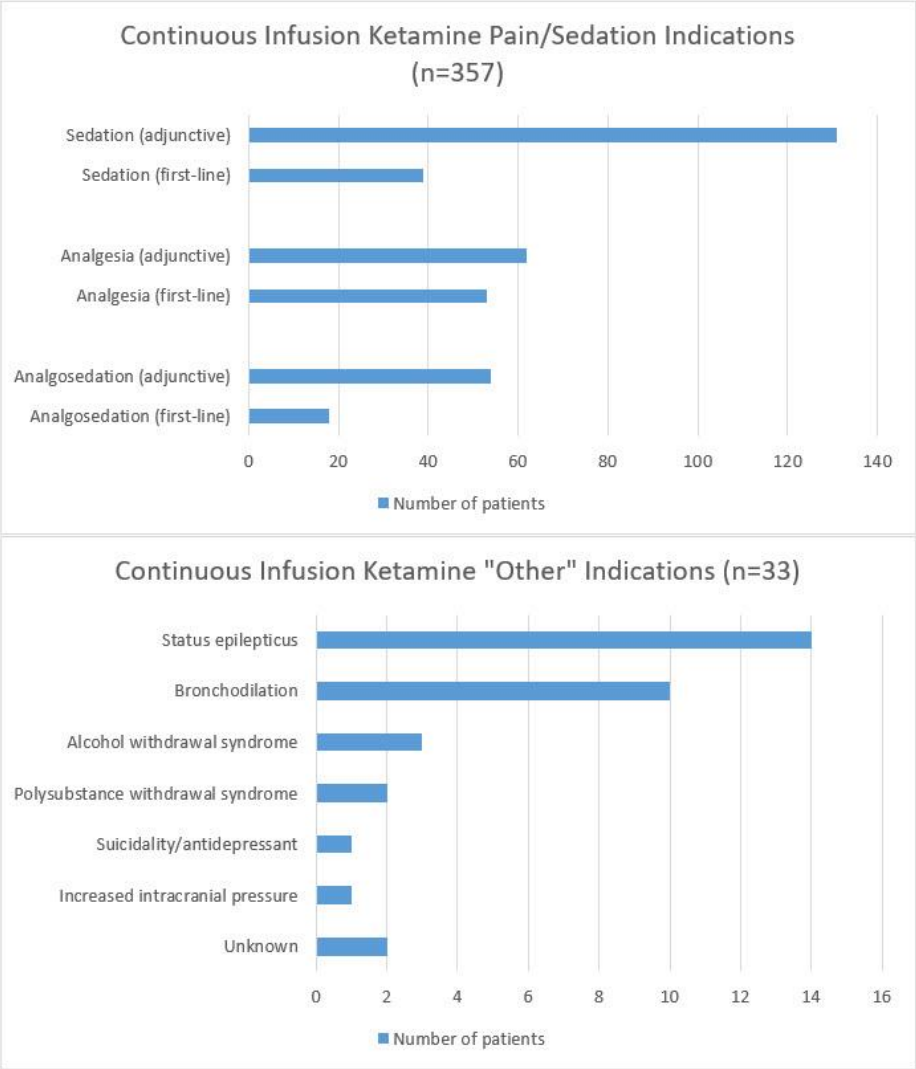

Figure 1. Schematic representation of the indications for continuous infusion ketamine. The top figure shows the number of patients receiving adjunctive or first-line ketamine for sedation, analgesia, or analgosedation. The bottom figure shows the number of patients receiving ketamine for other indications. Sedation was defined as the use of ketamine for the sole purpose of providing sedation in patients with uncontrolled agitation. Analgesia was defined as the use of ketamine for the sole purpose of providing analgesia and typically started at lower doses below 0.5 mg/kg/hr. Analgosedation was defined as the use of ketamine for both its analgesic and sedative effects or when it was unclear if it was solely being used for analgesia versus sedation.

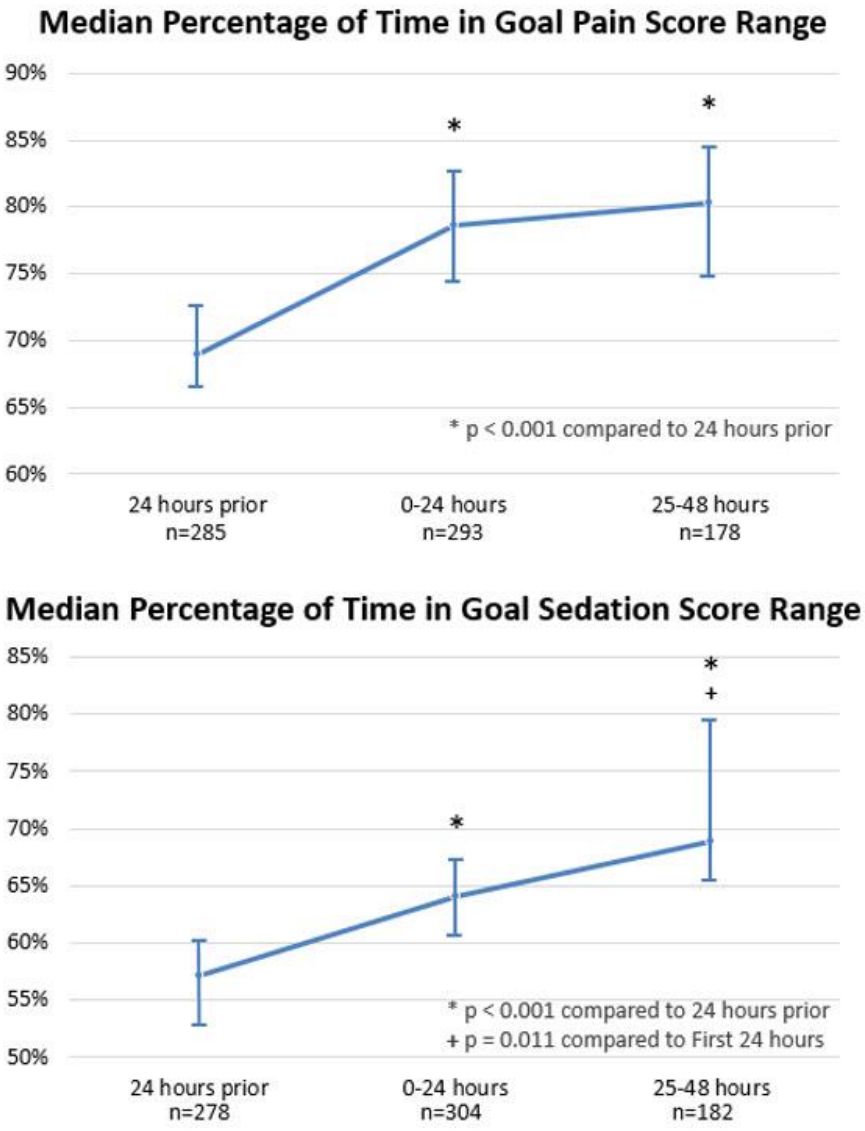

Figure 2. Schematic representation of time spent in goal pain and sedation score range with the use of continuous infusion (CI) ketamine. The top figure shows the median [IQR] percentage of time spent in goal pain score range in the 24 hours prior to CI ketamine compared to the 0-24 hours and the 25-48 hours after. The bottom figure shows the median [IQR] percentage of time spent in goal sedation score range in the 24 hours prior to CI ketamine compared to the 0-24 hours and the 25-48 hours after.

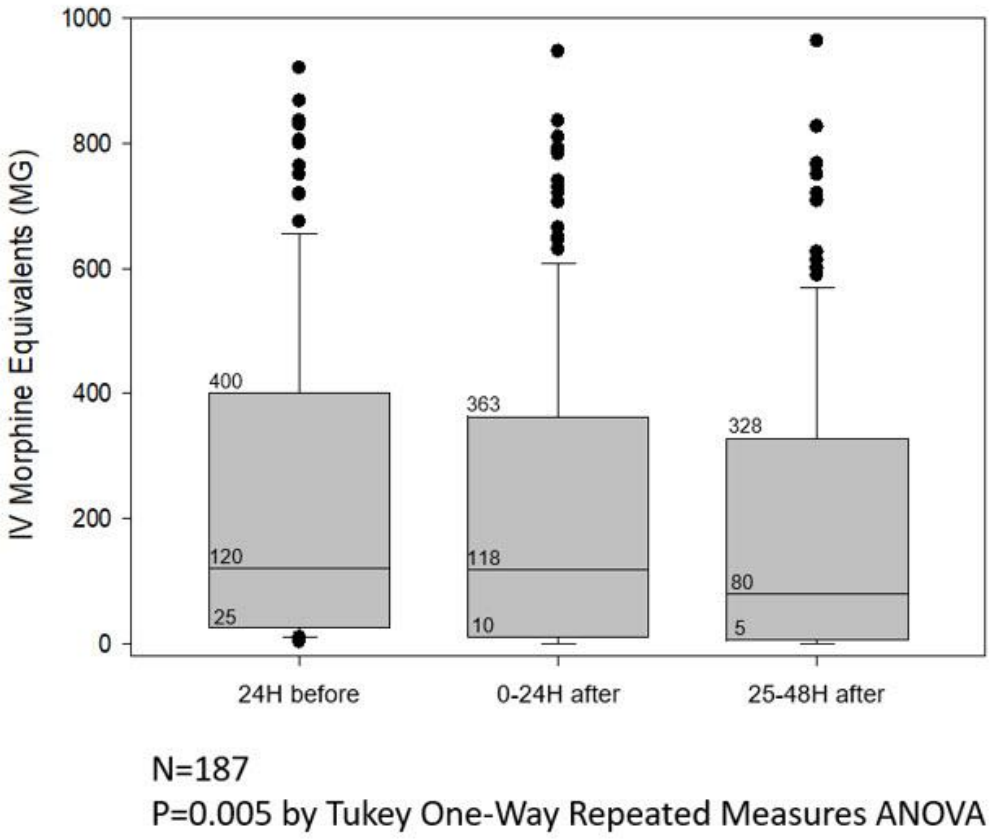

Figure 3. Schematic representation of the effect of continuous infusion (CI) ketamine on analgesic requirements. The figure shows the median [IQR] intravenous morphine equivalents in mg during the 24 hours prior to CI ketamine compared to the 0-24 hours and the 25-48 hours after.

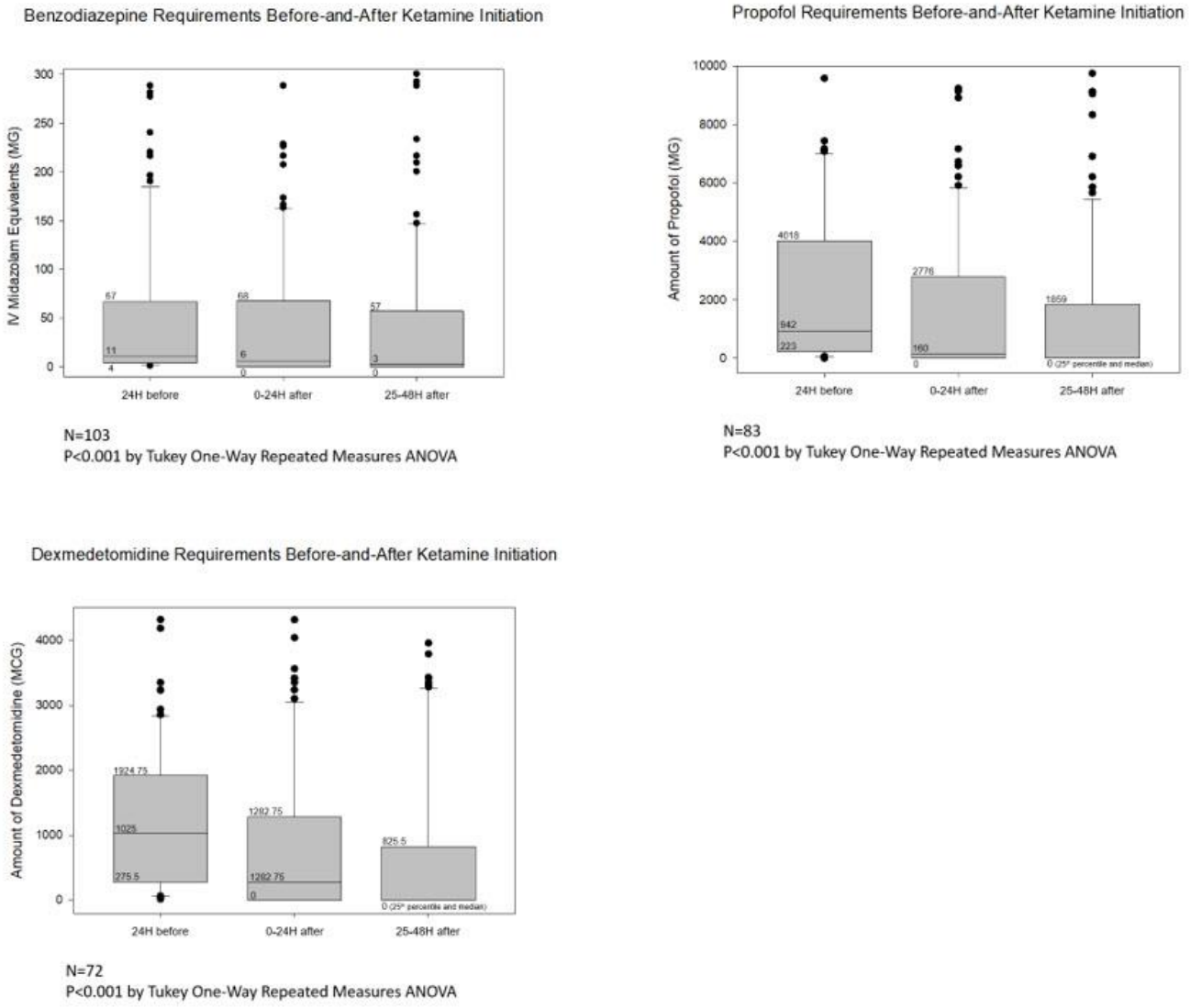

Figure 4. Schematic representation of the effect of continuous infusion (CI) ketamine on sedative requirements. The top figure shows the median [IQR] intravenous midazolam equivalents in mg during the 24 hours prior to CI ketamine compared to the 0-24 hours and the 25-48 hours after. The middle figure shows the median [IQR] propofol equivalents in mg during the 24 hours prior to CI ketamine compared to the 0-24 hours and the 25-48 hours after. The bottom figure shows the median [IQR] dexmedetomidine equivalents in mcg during the 24 hours prior to CI ketamine compared to the 0-24 hours and the 25-48 hours after.

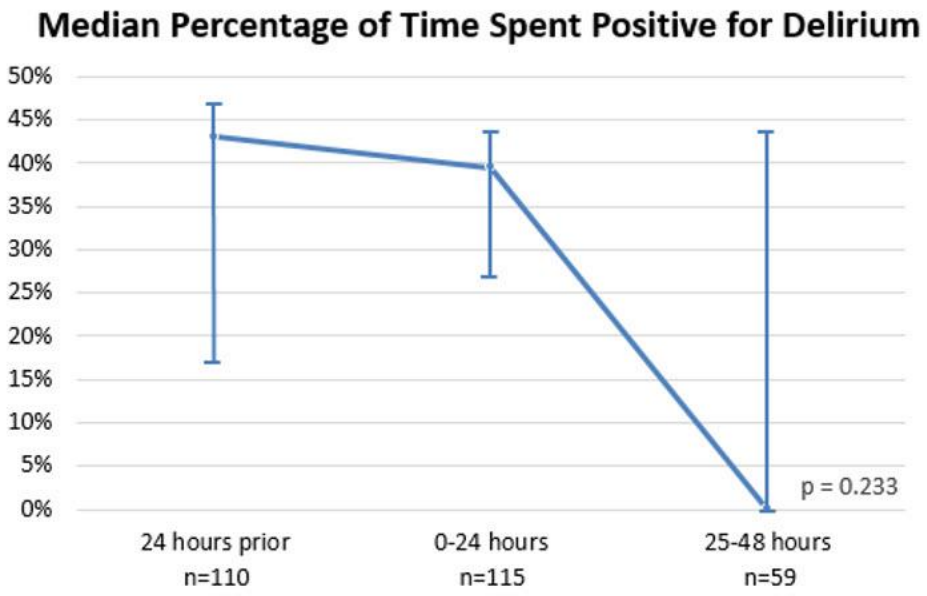

Figure 5. Schematic representation of time spent in positive for delirium with the use of continuous infusion (CI) ketamine. The figure shows the median [IQR] percentage of time spent positive for delirium in the 24 hours prior to CI ketamine compared to the 0-24 hours and the 25-48 hours after.