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Analgesia and Sedation Requirements in Mechanically-Ventilated Trauma Patients with Acute, Pre-Injury Use of Cocaine and/or Amphetamines

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Abstract

Background—The purpose of this study was to determine if mechanically-ventilated trauma patients with a positive urine drug screen (UDS) for cocaine and/or amphetamines have different opioid analgesic and sedative requirements compared to similar patients with a negative drug screen for these stimulants.

Methods—This retrospective, single-center cohort study at a tertiary care, academic medical center and level 1 trauma center in the United States, included patients admitted to an adult intensive care unit (ICU) with a diagnosis of trauma between 2009 and 2013, aged 16 years and older with a UDS documented within 24 hours of admission, and mechanically ventilated for greater than 24 hours. The primary endpoint was the daily dose of opioid received during mechanical ventilation, expressed as morphine equivalents, for patients presenting with a positive UDS for cocaine and/or amphetamines as compared to patients with a negative UDS for these stimulants. Secondary endpoints included the daily benzodiazepine dose and median infusion rates of propofol and dexmedetomidine received during mechanical ventilation, duration of mechanical ventilation, ICU and hospital length of stay and in-hospital mortality. Analgesic and sedative goals were similar for the duration of the study period and both intermittent and continuous infusions of opioids and sedatives were administered to achieve these targets, though a standardized approach was not employed. A multivariate logistic regression analysis and a propensity-adjusted model evaluated patient characteristics predictive of a higher median opioid requirement.

Results—One-hundred and fifty patients were included in the final analysis. In univariate analysis, opioid and sedative requirements were similar for patients presenting with a positive UDS for cocaine and/or amphetamines as compared to patients with a negative UDS for these stimulants. In the multivariate regression analysis, increasing age and Abbreviated Injury Scale – head and neck were associated with decreased daily opioid requirements, (OR 0.95, 95% CI 0.93–0.97) and (OR 0.71, 95% CI 0.65–0.77), respectively, while pre-injury stimulant use was not predictive of opioid requirements (OR 0.88, 95% CI 0.40–1.90). In a propensity-score adjusted model, pre-injury stimulant was similarly not predictive of opioid requirements during mechanical ventilation (OR 0.97, 95% CI 0.44–2.11).

Conclusions—For trauma patients presenting with acute, pre-injury use of cocaine and/or amphetamines, analgesic and sedative requirements are variable and may not be greater than those patients presenting with a stimulant-negative UDS to achieve desirable pain control and depth of sedation, though this observation should be interpreted cautiously in light of the wide confidence interval observed in the propensity-score adjusted model. Although unexpected, these findings indicate that empirically increasing analgesic and sedative doses based on positive UDS results for these stimulants may not be necessary.

Introduction

Patients with drug use disorders are at increased risk of motor vehicle collisions and other traumatic injuries.(1–4) Following traumatic injury, patients co-intoxicated with alcohol and other drugs are more likely to experience complications, including need for mechanical ventilation and pneumonia.(5) Sedation management for these patients is particularly challenging and often strategically focused on avoiding withdrawal syndromes and mitigating severe agitation to reduce the risk of self-extubation.(6)

Medical patients with a history of alcohol and drug abuse require mechanical ventilation more frequently, have longer duration of mechanical ventilation and longer intensive care unit (ICU) length of stay.(7,8) In one small, retrospective study, mechanically-ventilated medical ICU patients with a history of alcohol and drug use disorders required five-fold greater opioid equivalents and 2.5-fold greater benzodiazepine equivalents to achieve target sedation levels similar to patients without drug use disorders.(9)

The existing literature in both the medical and trauma populations has primarily focused on the consequences of alcohol use disorders, both acute intoxication and chronic use, and co-intoxication with alcohol and other illicit substances. Studies directly examining the pre-injury use of stimulants, such as cocaine and amphetamines, and post-injury analgesia and sedation requirements in the trauma population are lacking. According to the Substance Abuse and Mental Health Services Administration, the prevalence of cocaine use in adolescents and adults has declined modestly from 2007 to 2012.(10) However, both prescription and nonmedical use of amphetamines is rising in adolescents and adults, and particularly amongst college students.(11–15) Additionally, driving under the influence of illicit drugs is increasing and is most prevalent amongst young adults 18–25 years old,(10) highlighting a significant public health problem and the need for targeted therapies for these patients when traumatically injured.

The purpose of this study is to determine if the analgesic and sedative requirements of mechanically-ventilated trauma patients who have a urine drug screen (UDS) positive for cocaine and/or amphetamines are different from those who do not use these stimulants.

Methods

The study protocol was reviewed and approved by the Institutional Review Board at Duke University Hospital with a waiver of informed consent. This retrospective cohort study identified patients from the Duke University Hospital Trauma Registry admitted between January 1, 2009, and June 15, 2013. Inclusion criteria were age 16 years and older, an admitting diagnosis of trauma, admission to an adult ICU, a urine drug screen (UDS) documented within 24 hours of admission, and the need for mechanical ventilation for 24 hours or more. Trauma patients aged 16 years or older were included in this study since 16 and 17 year old trauma patients are admitted and treated in an adult ICU at our institution. Patients were excluded if they were pregnant, received targeted temperature management, received continuous neuromuscular blockade or did not receive any opioid analgesic or sedative due to declaration of brain death or withdrawal of care. Patients with long-acting

opioids documented as a home medication were also excluded as they are expected to require higher analgesic doses due to tolerance and would confound the primary outcome. Long-acting opioids included fentanyl transdermal patch, hydromorphone extended-release, methadone, morphine extended-release, oxycodone extended-release, and oxymorphone extended-release.

Institutional policy mandates that a UDS is obtained for all level 1 and level 2 trauma patients, and is optional for level 3 trauma admissions. For the purposes of this study, stimulant use was defined as having a positive UDS for cocaine and/or amphetamines. All patients with a UDS positive for stimulants, regardless of other positive results, and who met the study criteria were included in the stimulant-positive arm. The stimulant-negative group consisted of anyone meeting study eligibility that did not have a positive result for a stimulant, regardless of positive results for other agents. Because a larger sample of stimulant-negative patients was available in the registry, patients were organized chronologically by admission date and every fifth patient was evaluated for enrollment eligibility to provide an even distribution of patients admitted during the study period.

The primary endpoint was the median daily dose of opioid analgesia required during mechanical ventilation, expressed in morphine equivalents. Secondary endpoints were the median daily dose and infusion rate of propofol; the median daily dose and infusion rate of dexmedetomidine; the median benzodiazepine daily dose, expressed in lorazepam equivalents; duration of mechanical ventilation; ICU length of stay; hospital length of stay; and in-hospital mortality. Duration of mechanical ventilation was defined as the duration of endotracheal intubation until first extubation or tracheostomy. This endpoint was truncated at time of tracheostomy because sedative duration may be reduced for patients following removal of the endotracheal tube and placement of the tracheostomy.(16)

During the study period, both pain and depth of sedation were assessed every 4 hours or within 30–60 minutes following intervention. The Numeric Rating Scale (NRS) was utilized for those patients who could self-report pain. For patients unable to self-report pain, Face, Legs, Activity, Cry, Consolability (FLACC)(17); Wong-Baker Faces or Pain Assessment in Advanced Dementia (PAINAD)(18) were utilized at different points during the study period. Depth of sedation was evaluated utilizing the Richmond Agitation Sedation Scale (RASS).

During the study period, a formal sedation protocol was not in place. Analgesic endpoints were defined by nursing policy (goal NRS < 4). Initial analgesic orders were placed at the discretion of the provider and opioid infusions were initiated and titrated by provider order only based on pain assessment and intermittent opioid administration pursuant to nursing policy. Fentanyl and hydromorphone were the most commonly used intravenous opioids. RASS goal was specified in the administration instructions within the individual order for propofol and dexmedetomidine (default RASS goal –2) and titrated by bedside nurses. Benzodiazepine infusions were initiated and titrated by provider order only in response to RASS assessment and intermittent benzodiazepine use. The Surgical ICU is a semi-closed unit staffed by an attending physician (anesthesiology intensivist or trauma surgeon, 24 hours/day coverage), anesthesiology and/or surgical critical care fellows, anesthesiology and/or general surgery residents, advanced practice providers and allied health staff

including a pharmacist, dietitian, respiratory therapist(s) and physical therapist(s). Multidisciplinary rounds occur three times each day with routine evaluation of analgesic and sedative goals and requirements. Providers and nursing were aware of UDS results at the time of treatment.

Statistical Analysis

Based on the knowledge of patient availability, the study initially sought to collect information on approximately 50 patients in the stimulant-positive group. For the primary analysis, assuming 30% opioid dosage variability, a total sample size of 159 subjects (1:2) was needed to detect a difference of 15% in daily opiate dose with 80% power at a significance level 0.05. In the absence of previously reported studies in a similar patient population, these values were selected by the authors as being clinically meaningful. The Wilcoxon rank sum test was used for continuous, non-parametric data and Fisher's Exact test was used for categorical data, where appropriate. Data is reported without correction for false-discovery rate.

A multivariate logistic regression with backward variable selection ($p < 0.4$) was used to predict increased opioid requirements, defined as greater than the median of 1.24 mg/kg/day. Variables evaluated in the regression analysis were age, gender, Injury Severity Score (ISS), mechanism of injury – gunshot wound, a UDS positive for stimulants, a UDS positive for cannabinoids, and positive blood alcohol level, Glasgow Coma Scale (GCS) score, Abbreviated Injury Scale (AIS) – head and neck score, AIS – spine score and traumatic brain injury (TBI). In addition, a propensity score adjusted model (adjusted for all of the above variables) was used to determine the significance of a UDS positive for stimulants on opioid requirements, expressed as morphine equivalents greater than the median of the cohort. First, a logistic regression was used to obtain probability predicted scores (propensity) of the above variables to predict a UDS positive for stimulants. In a separate logistic regression, a propensity score-adjusted model in which the propensity score was used as a co-variate to examine if a UDS positive for stimulants predicted opioid requirements equivalent to greater than the median of the cohort. Model assumptions were examined and goodness of fit determined. Full details of the statistical model are available in the Supplementary Material. All analyses were conducted using JMP Version 11 and SAS 9.4 (SAS Corporation, Cary, North Carolina).

Results

This study enrolled 150 patients, 49 patients with a UDS positive for cocaine and/or amphetamines and 101 patients with a UDS negative for these substances. (Figure 1) Enrolled patients were equally distributed in each group over time thus were subject to similar sedation strategies. Baseline characteristics are reported in Table 1. In the stimulant-positive group, 10 patients (20.4%) were positive for amphetamines, 39 patients (79.6%) were positive for cocaine and 2 patients (4.1%) were positive for both substances on the UDS. Of note, 2 of the 10 amphetamine-positive patients (20%) had amphetamine/dextroamphetamine documented as a home medication: one was admitted due to a fall following an overdose of opioids and benzodiazepines, and the second following a motor

vehicle collision while intoxicated with alcohol. The nature of stimulant use was evaluated by review of provider and social work progress notes documenting patient and family reported pre-injury use. Binge use was noted in 7 patients (14.2%), chronic ingestion for 23 patients (46.9%) and 19 patients (38.8%) denied use or had an unknown history of use.

An opioid was administered to 148 patients (98.7%) in the cohort. Two patients that did not receive an opioid were stimulant-positive on admission met inclusion criteria and were successfully extubated, thus were included in the analysis. The use of a fentanyl infusion, a hydromorphone infusion or the sequential administration of a fentanyl and hydromorphone infusion were as follows: 57.1% vs 64.4%, $p=0.47$; 14.3% vs 5%, $p=0.06$; and 18.4% vs 19.8%, $p=1.0$; respectively. Oxycodone and methadone utilization in the stimulant-positive as compared to the stimulant-negative arm were 6.1% vs 8.9%, $p=0.75$ and 4.1% vs 1%, $p=0.25$, respectively. The median number of intravenous opioid bolus doses per day of mechanical ventilation was 2.82 (IQR 0.94–4.99) in the stimulant-positive arm and 3.07 (IQR 1.5–5.48) in the stimulant negative arm ($p=0.36$). The primary endpoint, median daily opioid requirements, expressed as morphine equivalents, is reported in Table 2. Different pain scales were utilized during the study period and are not comparable, thus this data was not recorded.

Sedative administration and assessments are reported in Table 2. Propofol was the most commonly utilized sedative, followed by benzodiazepines and dexmedetomidine. For patients receiving a benzodiazepine infusion, midazolam infusions were used most commonly (18.4% vs 23.8%, $p=0.53$), followed by lorazepam infusions (6.1% vs 10.9%, $p=0.55$) or the sequential use of a midazolam and lorazepam infusion (4.1% vs 5.9%, $p=1.0$).

To further characterize the medication requirements for these patients, administration of adjunctive sedative and analgesic medications was also collected. (Table 3) For all 9 patients who received ketamine, ketamine was initiated in the setting of multimodal analgesia for uncontrolled pain despite traditional intravenous opioid therapy and initiated between days 1 and 3 of intubation. All had lidocaine transdermal patches placed, 8 received acetaminophen, 3 received non-steroidal anti-inflammatory drugs, 4 received adjuncts for neuropathic pain and 2 patients had epidural analgesia. One patient in the stimulant-positive arm had documentation that ketamine was initiated specifically because of a history of polysubstance abuse. The number of visits to the operating room during mechanical ventilation was a median of one in each group. Clinical outcomes, including duration of mechanical ventilation, ICU length of stay, hospital length of stay, and in-hospital mortality are reported in Table 4.

Self-extubation was reported for one patient in each arm (2.04% vs 0.99%, $p=0.55$) and extubation requiring reintubation within the following 24 hours was not different between groups (6.12% vs 5.94%, $p=1.0$). The proportion of patients who received a tracheostomy and the time to tracheostomy were 22.5% vs 27.7%, $p=0.55$ and 5.33 vs 6.84 days, $p=0.46$, respectively. Two patients (18.1%) in the stimulant-positive arm and 6 patients (21.4%) in the stimulant-negative arm received an early tracheostomy (days 2 or 3) due to facial fractures or spinal cord injury. The median ISS for patients who received a tracheostomy

was 25 (IQR 22–34) vs 24.5 (IQR 14.8–37.3), $p=0.46$ and the majority presented with TBI (72.7% vs 57.1%, $p=0.47$) with a median GCS in each group of 7.

Predictors of opioid requirements, defined as greater than the median of 1.24 mg/kg/day of morphine equivalents, were evaluated using a multivariate logistic regression analysis with backward variable selection. In the final model, increasing age and AIS – head and neck were associated with decreased daily opioid requirements: OR 0.95 (95% CI 0.93–0.97) and OR 0.71 (95% CI 0.58–0.87), respectively, and pre-injury stimulant use was not predictive of opioid requirements (OR 0.88, 95% CI 0.40–1.90).

In a second multivariate analysis of a propensity score-adjusted model, the same predictors as those used in the above logistic regression were used to first predict stimulant use. The predicted scores from this model were then used to adjust the stimulant use, and predict opioid requirements. In this propensity-score adjusted model, opioid requirements were not significantly affected by pre-injury stimulant use (OR 0.97, 95% CI 0.44–2.11). In a third logistic model adjusted by quintiles of propensity scores, stimulant use was not a significant predictor of opioid requirements (OR 0.89, 95% CI 0.41–1.94).

A *post-hoc* analysis of patients presenting with TBI was performed to determine additional factors influencing the primary and secondary outcomes of the cohort. Baseline characteristics, opioid and propofol requirements in this subgroup are reported in Table 5.

Discussion

Unexpectedly, the results of this study demonstrate that mechanically-ventilated patients with a positive UDS for cocaine and/or amphetamines have widely variable daily opioid or sedative requirements that may not be different than patients with a negative UDS for these agents, when normalized for body weight. Co-intoxication with alcohol and cannabinoids was common in this cohort, though did not appear to affect requirements. Depth of sedation and clinical outcomes did not differ between groups. Stimulant-positive patients presenting with TBI spent less time within the target RASS range and may have required intervention for elevated ICP more often, suggesting a more complicated neurological course.

Data examining the effect of drug use disorders and analgesic and sedative requirements during mechanical ventilation in the trauma or surgical patient populations is limited. de Wit, et.al. retrospectively examined sedative requirements in mechanically-ventilated medical patients (n=70) with a history of general substance use, including alcohol (31%), cocaine (7%), and other drugs within the past year, as identified by Diagnostic and Statistical Manual of Mental Disorders criteria.(9) These patients with a history of a drug use disorder received more daily morphine equivalents (0.5 vs 0.1 mg/kg/day, $p=0.03$) and lorazepam equivalents (0.5 vs 0.2 mg/kg/day, $p=0.004$), while no difference was noted in propofol requirements, depth of sedation and duration of mechanical ventilation. Not surprisingly, patient demographics in this study by de Wit, et.al. differed from our study population in several respects: they were older, had a history of alcohol or cocaine within the previous year rather than acute use of cocaine and/or amphetamines, only a small proportion of patients had a history of stimulant use specifically, and benzodiazepine administration

was more common. Additionally, the patients in our study received higher quantities of morphine equivalents than patients in this trial, which might be expected for a trauma cohort as compared to a medical one; however, the five-fold difference in opioid requirements was not reproduced in our study. We also did not appreciate any differences in administration of adjunctive analgesics or sedative requirements.

Importantly, this study does not distinguish between drug users and abusers. Abuse may occur when a patient experiences adverse socioeconomic or health consequences that are related to the use of a substance and it often leads to dependence and/or addiction.(19) However, this study is likely a more pragmatic approach since the ability to distinguish between the two is often not possible in trauma patients on presentation or early in their hospital course. In this study, two patients had a stimulant documented as a home medication. This finding may be conservative given that a large portion of trauma patients had unknown or incomplete past medical histories.

Although pre-injury binge use of stimulants was less common, chronic stimulant use was documented for nearly one-half of stimulant-positive patients and nearly 40% of patients had unknown use or denied illicit substance use despite a positive UDS. Primary symptoms of stimulant withdrawal include agitation, depressed mood, fatigue and discomfort. Though not observed in this study, it is possible that patients with chronic substance abuse may require higher doses of sedatives to mitigate this withdrawal syndrome. One potential explanation for this lack of difference may be due to the findings revealed in the subgroup analysis of patients with TBI. Although severity of injury scores at presentation and mean RASS were not statistically different, clinically, the stimulant-positive patients with TBI required intervention for elevated ICP more frequently and appeared to be more deeply sedated despite similar medication use. Less sedation may have been needed due to the evolution of the disease process and a more complicated neurological course for the stimulant-positive patients, and subsequently may have influenced the lack of difference in sedation requirements observed in the larger cohort. These statements are made with caution due to the small sample size of the TBI subgroup.

One interesting finding in this study was the trend toward a greater use of ketamine in the stimulant-positive group. Ketamine administration may reduce peri-operative opioid requirements and sensitize opioid receptors, thus offers an attractive adjunctive agent in trauma and surgical patient population.(20–23) Although our findings may reflect an institutional practice amongst the anesthesiology intensivists at our institution, the role of ketamine and other adjunctive analgesics for patients with a history of stimulant use warrants further exploration.

This study has several limitations. First, this was a retrospective study which, amongst other implications, suggests the potential for treatment bias if a clinician was aware of the drug screen results prior to drug selection and titration. There is also the potential for differing sedation practices from 2009 through 2013, with consensus guidelines for pain, agitation, and delirium recommending propofol and dexmedetomidine as first-line sedatives, while minimizing benzodiazepine use.(24) Yet, it is unlikely that these guidelines had a large impact on the results since they were only made available at the latter end of the study

period. A cultural transition toward targeting lighter levels of sedation may have occurred in the study period in light of emerging literature; however this is difficult to characterize retrospectively and included patients were equally distributed over time so we expect patients were sedated similarly. Drug shortages may have also impacted drug selection during this time period. For example, dexmedetomidine may have been used during a propofol shortage. Finally, registry data from 2006–2010 at our institution indicates that approximately 30% of patients receive a UDS at the time of admission following traumatic injury, and that women and patients age 45 years old or greater are less likely to receive a UDS.(25) Although similar to previously published reports(26), this biased screening process may have limited our sample size.

As a strength of its design, this study included patients in the stimulant-positive group based on positive results for cocaine and/or amphetamines and into the stimulant-negative group based on negative results for these agents, regardless of other positive results. Therefore, co-intoxications were common in this study. Although this could have altered results, it is likely encountered in practice since co-intoxication is common in this patient population.(27) This study is a realistic representation of sedation practice in this patient population over a period of time and offers us guidance on optimal sedation management of these patients.

In summary, achieving desirable pain control and depth of sedation may not require higher doses of analgesic and sedative medications for trauma patients presenting with acute intoxication of cocaine and/or amphetamines as compared to their stimulant-negative counterparts. These findings should be interpreted cautiously in light of the wide confidence interval observed in the propensity-score adjusted model. The findings, although unexpected, indicate that empirically increasing analgesic and sedative doses based on positive UDS results for these stimulants is may not be necessary. Utilizing a multi-modal approach in the management of pain and agitation in this patient population, and particularly the role of ketamine, warrant further exploration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Subject Selection

Table 1Baseline Characteristics^a

	Stimulant-Positive (n=49)	Stimulant-Negative (n=101)	p
Age, years	39.4 (28.2–51.7)	43.4 (25.8–63.9)	0.25
Gender, male	39 (79.6)	76 (75.3)	0.68
Weight, kg	75.5 (71–96.5)	80.6 (70–96.9)	0.51
Past Medical History			
Anxiety	8 (16.3)	3 (3)	0.006
Depression	9 (18.4)	8 (7.9)	0.1
Bipolar/Schizophrenia	2 (4.1)	1 (1)	0.25
Dementia	0	1 (1)	1
None	24 (49)	69 (68.3)	0.03
Unknown	7 (14.3)	20 (19.8)	0.5
Mechanism of Injury			
Motor Vehicle Collision	22 (44.9)	53 (52.5)	0.49
Gunshot Wound	12 (24.5)	6 (5.9)	0.002
Fall	5 (10.2)	14 (13.9)	0.61
Vehicle-Pedestrian	6 (12.2)	11 (10.9)	0.79
Blunt Assault	1 (2)	9 (8.9)	0.17
Penetrating Assault	1 (2)	1 (1)	0.55
Shotgun Wound	0	1 (1)	1.00
Other	2 (4.1)	6 (5.9)	1.00
Injury Severity Score	22 (13–29)	19 (13–27)	0.41
Abbreviated Injury Score			
Head/Neck	0 (0–3)	3 (0–4)	0.03
Thorax	2 (0–3)	2 (0–3)	0.81
Abdomen	0 (0–2)	0 (0–2)	0.27
Spine	2 (0–3)	0 (0–2)	0.002
Extremities	2 (0–3)	1 (0–2)	0.11
Glasgow Coma Scale	12 (3–15)	8 (3–15)	0.25
Traumatic Brain Injury	18 (36.7)	50 (49.5)	0.16
Co-Ingestion			
Canniboid	23 (46.9)	25 (24.8)	0.009
Alcohol	23 (46.9)	30 (29.7)	0.046
Blood Alcohol Concentration, mg/dL ^b	157 (68–220)	130.5 (87.3–211)	0.63

^a data are reported as n (%) or median (interquartile range);

b_i for patients with alcohol co-ingestion

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Table 2Analgesic and Sedative Medication Requirements^a

	Stimulant-Positive (n=49)	Stimulant-Negative (n=101)	p
Opioid requirements ^b			
Infusion	44 (89.8)	90 (89.1)	1.0
Morphine equivalents (mg)	337.5 (137.5–573.3)	337.5 (121.7–600)	0.96
Morphine equivalents (mg/kg/day)	1.36 (0.85–2.4)	1.16 (0.56–1.96)	0.20
Propofol			
Infusion	33 (67.4)	92 (91.1)	0.0007
mg	6428.16 (3206–12276)	7553.4 (3221.8–13911.3)	0.744
mg/kg/day	29.64 (9.21–58.2)	29.41 (9.7–51.3)	0.42
mcg/kg/min	37.95 (27.15–56.4)	37.03 (24.2–46.7)	0.26
Dexmedetomidine			
Infusion	17 (34.7)	39 (38.6)	0.72
mcg	1020.84 (322.1–2119.25)	988.2 (256–3102.1)	0.79
mcg/kg/day	2.81 (1.4–14.8)	2.63 (1.43–6.4)	0.92
mcg/kg/h	0.5 (0.37–0.9)	0.53 (0.3–0.7)	0.67
Benzodiazepine utilization			
Administered ^c	28 (57.1)	61 (60.4)	0.72
Infusion	14 (28.6)	41 (40.6)	0.15
Lorazepam equivalents (mg)	21 (2.25–100.3)	15 (4–95.75)	0.95
Lorazepam equivalents (mg/kg/day)	0.1 (0.02–0.3)	0.07 (0.01–0.2)	0.53
Sedation Assessment			
Time within RASS ^d –2 to +1	71.4% (52.05–94.9%)	75.4% (53.5–87.9%)	0.25
Average RASS	–2.2 (–2.45 to –1.75)	–1.99 (–2.44 to –1.66)	0.13

^a data are reported as median (IQR), except as noted;

^b n=2 stimulant-positive patients did not receive opioid, but received sedatives. All patients were included in this analysis;

^c Bolus and/or infusion;

^d Richmond Agitation Sedation Scale

Conversion factors: For conversion of midazolam to lorazepam, 1 mg midazolam = 0.5 mg lorazepam. For conversion of opioids to morphine equivalents, 10 mg morphine = 1.5 mg hydromorphone = 0.1 mg fentanyl(24)

Table 3Adjunctive Analgesic and Sedative Use^a

	Stimulant-Positive (n=49)	Stimulant-Negative (n=101)	p
Acetaminophen	35 (71.4)	76 (75.3)	0.07
NSAID	6 (12.2)	14 (13.9)	1.00
Neuropathic pain adjuvant	6 (12.2)	5 (5)	0.18
Lidocaine transdermal patch	9 (18.4)	13 (12.9)	0.46
Ketamine	6 (12.2)	3 (3)	0.06
Epidural	6 (12.2)	6 (5.9)	0.21
Antipsychotic	3 (6.1)	10 (9.9)	0.55

^adata are reported as n (%)

Table 4Clinical Outcomes^a

	<i>Stimulant-Positive (n=49)</i>	<i>Stimulant-Negative (n=101)</i>	p
Duration of mechanical ventilation, days	2.97 (1.69–5.15)	3.35 (2.05–6.79)	0.14
ICU length of stay, days	7 (4–14)	9 (5–14.5)	0.34
Hospital length of stay, days	18 (9–36.5)	16 (9.5–27)	0.37
In-hospital mortality	3 (6.1)	15 (14.9)	0.18

^a data are reported as n (%) or median (IQR)

Table 5Traumatic Brain Injury Subgroup Analysis^a

	Stimulant-Positive (n=18)	Stimulant-Negative (n=50)	p
Glasgow Coma Scale	4.5 (3–7.25)	3 (3–10.5)	0.95
Injury Severity Score	25.5 (21.5–35.75)	22 (13.75–27.5)	0.08
Abbreviated Injury Score – Head and Neck	3.5 (2.75–5)	3 (3–4)	0.79
Morphine equivalents, mg/kg/day	1.07 (0.4–1.8)	0.87 (0.35–1.6)	0.74
Propofol			
Mg/kg/day	21.03 (6.9–26.8)	23.19 (3.03–47.5)	0.63
Mcg/kg/min	23.82 (16.7–49)	32.2 (18.44–44.2)	0.64
Sedation Assessment			
Time within RASS ^b –2 to +1	50.1% (7.95–70.85%)	77.4% (55.8–91%)	0.01
Average RASS	–2.26 (–4.6 to –1.65)	–2.08 (–2.5 to –1.5)	0.17
Intracranial Pressure Management			
Monitoring	10 (55.6)	28 (56)	1.0
Hyperosmolar therapy	4 (22.2)	7 (14)	0.28
Decompressive craniectomy	4 (22.2)	2 (4)	0.04

^a data are reported as n (%) or median (IQR);

^b Richmond Agitation-Sedation Scale