Adjunct Ketamine Use in the Management of Severe Ethanol Withdrawal

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Objectives: Ketamine offers a plausible mechanism with favorable kinetics in treatment of severe ethanol withdrawal. The purpose of this study is to determine if a treatment guideline using an adjunctive ketamine infusion improves outcomes in patients suffering from severe ethanol withdrawal.

Design: Retrospective observational cohort study.

Setting: Academic tertiary care hospital.

Patients: Patients admitted to the ICU and diagnosed with delirium tremens by *Diagnostic and Statistical Manual of Mental Disorders V* criteria.

Interventions: Pre and post guideline, all patients were treated in a symptom-triggered fashion with benzodiazepines and/or phenobarbital. Postguideline, standard symptom-triggered dosing continued as preguideline, plus, the patient was initiated on an IV ketamine infusion at 0.15–0.3 mg/kg/hr continuously until delirium resolved. Based upon withdrawal severity and degree of agitation, a ketamine bolus (0.3 mg/kg) was provided prior to continuous infusion in some patients.

Measurements and Main Results: A total of 63 patients were included (29 preguideline; 34 postguideline). Patients treated with ketamine were less likely to be intubated (odds ratio, 0.14; $p < 0.01$; 95% CI, 0.04–0.49) and had a decreased ICU stay by 2.83 days (95% CI, −5.58 to −0.089; $p = 0.043$). For ICU days outcome, correlation coefficients were significant for alcohol level and total benzodiazepine dosing. For hospital days outcome, correlation coefficients were significant for patient age, aspartate aminotransferase, and alanine aminotransferase level. Regression revealed the use of ketamine was associated with a nonsignificant decrease in hospital stay by 3.66 days (95% CI, −8.40 to 1.08; $p = 0.13$).

Conclusions: Mechanistically, adjunctive therapy with ketamine may attenuate the demonstrated neuroexcitatory contribution of N-methyl-D-aspartate receptor stimulation in severe ethanol withdrawal, reduce the need for excessive gamma-aminobutyric acid agonist mediated–sedation, and limit associated morbidity. A ketamine infusion in patients with delirium tremens was associated with reduced gamma-aminobutyric acid agonist requirements, shorter ICU length of stay, lower likelihood of intubation, and a trend toward a shorter hospitalization. (*Crit Care Med* 2018; 46:e768–e771)

Key Words: delirium tremens; ethanol withdrawal; intensive care unit; ketamine

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Nearly 10% of hospital admissions are complicated by ethanol withdrawal, and approximately a third of those develop severe withdrawal (1). Severe withdrawal prolongs hospital length of stay and adds significant cost (1, 2). Efforts to advance the management of these critically ill patients can potentially improve both medical care and cost efficiency.

Historically, treatment of ethanol withdrawal has focused on the administration of gamma-aminobutyric acid (GABA) agonists such as barbiturates and benzodiazepines (3). Although most patients suffering from mild-to-moderate withdrawal have good outcomes with these agents, a subset of patients progress to severe withdrawal (i.e., delirium tremens) despite therapy. This subset of patients frequently requires ICU-level care, large doses of GABA agonists, prolonged hospitalization, and occasional mechanical ventilation. These interventions are associated with the highest rates of hospital-associated

morbidity and healthcare cost and are largely associated with prolonged sedation and delirium following large doses of long-acting GABA agonists (2, 3).

Ketamine offers a logical pharmacologic mechanism with favorable kinetics to potentially minimize these risks in the most severe cases of ethanol withdrawal. First, like ethanol, ketamine is an N-methyl-D-aspartate receptor antagonist and treats ethanol withdrawal at a receptor infrequently addressed by traditional therapy (4). Second, a ketamine infusion does not require mechanical ventilation (5). Finally, due to its short half-life, ketamine therapy does not result in protracted sedation or delirium as is often seen following treatment with longer acting GABA agonists (4).

The purpose of this study is to determine if a treatment guideline using an adjunctive ketamine infusion improves outcomes in patients suffering from severe ethanol withdrawal.

METHODS

This is a retrospective observational cohort study of patients identified from the medical toxicology patient database admitted to the ICU at the University of Pittsburgh Medical Center, Presbyterian Campus for treatment of severe ethanol withdrawal from January 2008 to March 2011 (preguideline) and April 2011 to January 2015 (postguideline). Patients were included in the study if admitted to the ICU, diagnosed with delirium tremens (DT), and had complete medical records available for review. The diagnosis of DT was made by board-certified medical toxicologists or critical care physicians according to *Diagnostic and Statistical Manual of Mental Disorders* criteria (6). This study was approved by the Investigational Review Board.

For all eligible patients, basic demographic and clinical information were recorded. This included admission diagnosis, admission laboratory data, pharmacologic therapy, hospital and ICU length of stay, and need for intubation. In addition, adverse drug events were collected systematically through evaluation of all notes in a patient's medical record. During the study period (pre- and postguideline), all patients were treated in a symptom-triggered fashion under the direction of medical toxicology, critical care, and/or clinical pharmacy. In general, diazepam is the preferred agent used in the management of ethanol withdrawal at our institution. However, diazepam was not exclusively used. For the sake of comparison, all GABA agonist dosing was converted to diazepam equivalents: diazepam 10 mg equals to lorazepam 1.5 mg equals to midazolam 1 mg equals to phenobarbital 3.3 mg (7). Dosing of benzodiazepines was based on a Withdrawal Assessment Scale (WAS) score greater than 10 or bedside physician clinical evaluation. The decision to intubate was determined by the individual bedside clinician. Once intubated, patients were often treated with a combination of benzodiazepines, propofol, and/or dexmedetomidine.

Postguideline, as soon as the diagnosis of DT was recognized, the patient was initiated on an IV ketamine infusion at 0.15–0.3 mg/kg/hr continuously until delirium resolved as an adjunct to standard symptom-triggered GABA agonist dosing as described above. Based upon clinical judgement, a ketamine bolus (0.3 mg/kg) was provided in some cases prior to starting the continuous infusion. Ketamine, as a bolus, was only provided once at the initiation of therapy if provided at all. As in the previous cases, need for intubation was determined by the bedside clinician.

STATISTICS

Patient-specific factors were analyzed using descriptive statistics. Pearson correlation coefficients were determined for association between all factors and the outcomes of interest (ICU days, hospital days, and need for intubation). Based on the number of patients in the study, an a priori cutoff of 0.2 was used as a significant correlation coefficient. This corresponds to a $p = 0.10$. Factors with significant correlation coefficients were included in a multivariable linear regression analysis for the outcomes of ICU days and hospital days and in a multivariable logistic regression for intubation need. A p value equals to 0.05 was used as a cutoff for statistical significance. t test and chi-square analysis were used to determine unadjusted differences between groups. All data were analyzed using STATA 14 (StataCorp College Station, TX).

RESULTS

A total of 63 patients were included in the analysis. This included 29 patients preguideline and 35 postguideline. Except for gender and admission ethanol level, pre- and postguideline characteristics were similar (**Table 1**). The primary admission diagnosis was ethanol withdrawal in 41.4% (12/29) and 29.4% (10/35) of patients pre- and postguideline, respectively. However, despite varying admission diagnoses, all patients would have been admitted to the ICU for treatment of DT.

Correlation coefficients for ICU days were significant for ethanol level and total GABA agonist dosing. Regression revealed the use of ketamine was associated with a significant decrease in ICU stay of 2.83 days (95% CI, –5.58 to –0.089 d; $p = 0.043$) and, although statistically insignificant, was associated with a trend toward a decreased hospital stay of 3.66 days (95% CI, –8.40 to 1.08 d; $p = 0.13$). Ketamine use also was associated with a decreased likelihood of intubation when compared with preguideline treatment (odds ratio, 0.14; $p < 0.01$; 95% CI, 0.04–0.49). The observed effects on duration of ICU treatment, need for intubation, and trend toward decreased hospital length of stay were not statistically attributable to any other recorded variable.

Using Student t test, **Table 2** summarizes outcomes in patients based on ketamine use. Ketamine patients received far fewer benzodiazepines but did have a nonsignificant increase in dexmedetomidine which was infrequently used in both groups. Furthermore, intubated patients on ketamine received fewer benzodiazepines and days on propofol while a nonstatistical increase in propofol use was noted for the patients in the nonketamine group.

TABLE 1. Clinical Characteristics

Clinical Characteristics	No Ketamine (*n* = 29)	Ketamine (*n* = 34)
Mean age (SD)	53.3 (12.2)	47.0 (9.6)
Men, *n* (%)	28 (96.6)	23 (67.7)
History of complicated withdrawal: delirium tremens or seizure, *n* (%)	8 (27.6)	7 (20.6)
Primary ICU admit diagnosis, *n* (%)		
Withdrawal	12 (41.4)	10 (29.4)
Toxicology	1 (3.5)	6 (17.6)
Trauma	5 (17.2)	8 (23.5)
Gastrointestinal	2 (6.9)	4 (11.8)
Elective surgery	7 (24.1)	1 (3.0)
Cardiac	1 (3.5)	3 (8.8)
Other	1 (3.5)	2 (5.9)
Mean corpuscular volume (SD)	96.2 (5.4)	96.3 (6.6)
Median serum aspartate aminotransferase (IQR)	85 (43–122)	69 (43–156)
Median serum alanine aminotransferase (IQR)	53 (30–88)	48 (29–80)
Median serum ethanol (IQR)	19 (0–224)	0 (0–43)

IQR = interquartile range.

TABLE 2. Outcomes in Patients With Severe Ethanol Withdrawal Who Receive No Ketamine Versus Ketamine

Outcomes	No Ketamine (*n* = 29)	Ketamine (*n* = 34)	*p*
Mean ICU days	11.2	5.7	< 0.001
Mean hospital days	16.6	12.5	0.03
Mean benzodiazepine dose in DE, mg	2,525.1	1,508.5	0.02
Dexmedetomidine use, *n*	3	9	0.1
Mean dexmedetomidine time, d	2.33	1.77	0.4
Intubations, *n*	22	10	< 0.001
Mean benzodiazepine dose in DE equivalents, mg	3,016.1	833.6	0.01
Propofol use, *n*	20	9	0.9
Mean propofol time, d	4.57	2.4	0.03

DE = diazepam equivalents.

Only one documented adverse event occurred from ketamine use, which was over sedation requiring a dosing adjustment. No rescue medications were provided as a documented side effect from ketamine. These findings are consistent with a case series including part of our cohort which documented a paucity of adverse events (8), and another study using similar ketamine dosing as a sedative for agitated psychiatric patients also documenting no adverse events (9). Mean ketamine infusions were low and comparable with doses used in the pain literature which are well below doses typically used for general anesthesia (10). Therefore, the ketamine doses used are not expected to cause the adverse effect profile documented with larger doses used in the anesthesia literature (10, 11).

A detailed review of ketamine dosing and benzodiazepine use in the ketamine group is provided in **Table 3**. More than half of patients (55.9%) received a ketamine bolus. The median duration of ketamine was 47 hours with an overall mean infusion dose of 0.19 mg/kg/hr. Benzodiazepine dosing did increase after ketamine was initiated, but ketamine is started at the onset of DT's when withdrawal symptoms and agitation are worsening.

DISCUSSION

The addition of ketamine to symptom-triggered GABA agonist dosing resulted in significant reductions in duration of ICU treatment and mechanical ventilation in patients with severe ethanol withdrawal. GABA agonists remain the most widely accepted management strategy for withdrawal. Even though ketamine is only Food and Drug Administration approved for use as an anesthetic, it is investigational for use in the treatment of ethanol withdrawal. However, ketamine, by nature of its pharmacokinetics and pharmacodynamics, appears to offer a logical adjunctive therapy in the management of severe ethanol withdrawal (3, 12). We suggest that additional therapy with a short acting, continuously infused NMDA antagonist, like ketamine, may safely attenuate the demonstrated neuroexcitatory contribution of NMDA stimulation in severe ethanol withdrawal, reduce the need for excessive GABA agonist–mediated sedation, and limit associated morbidity (4). As early as 1972, the benefit of using ketamine in DT was recognized (13). Although much higher dosing was implemented, the authors recognized no disadvantages to ketamine use including respiratory depression or loss of gag or cough reflexes.

Based upon clinical characteristics of patients in this study as well as the demonstrated tolerance to large doses of GABA agonists, this population is expected to have protracted and complicated courses (14). Patients demonstrating such significant resistance to benzodiazepine therapy frequently require sedation with more potent GABA agonists often leading to the need for mechanical ventilation (3). We theorize the decreased intubation rate was the result of augmenting large GABA agonist doses with ketamine, which is unlikely to cause respiratory depression or oversedation at the dosage used in this study.

More research is required to explain the shorter ICU stay and trend toward shorter hospital stay in the ketamine cohort. Although long hospitalizations for patients suffering from severe withdrawal is multifactorial, we suspect, in part, large doses of long-acting GABA agonists required to safely sedate patients will

TABLE 3. Details of Ketamine Treatment

Ketamine Dosing	Ketamine ($n = 34$)
Ketamine loading dose, *n* (%)	19 (55.9)
Initial infusion dose, mg/kg/hr, mean (SD)	0.24 (0.10)
Infusion dose during therapy, mg/kg/hr, mean (SD)	0.19 (0.10)
Duration of ketamine treatment, hr, median (IQR)	47.0 (35.0–71.0)
Total ketamine dose, mg, median (IQR)	825.4 (440.0–1,456.0)
Benzodiazepine dose in DE pre ketamine initiation, mg, median (IQR)	333.4 (106.6–626.6)
Benzodiazepine dose in DE since ketamine initiation, mg, median (IQR)	450.0 (295.0–700.0)
Total benzodiazepine dose in DE, mg, median (IQR)	892.5 (453.3–1,646.6)

DE = diazepam equivalents, IQR = interquartile range.

have persistent clinical effects beyond the time course required to treat withdrawal (1). Prolonged effects of GABA agonists may lead to iatrogenic delirium after severe withdrawal has resolved. Ketamine use reduced benzodiazepine dosing in a statistically significant manner and potentially diminished requirements sufficiently to minimize posttreatment delirium and length of ICU stay.

There are several limitations of this study. Most notably, this study was not randomized, and treatments were not standardized. Although ketamine dosing was standardized within a finite range, occasionally, based on the bedside clinician's decision, a ketamine bolus was provided as well. However, since these patients were managed by the same medical toxicologists, intensivists, and pharmacists, consistent patient care is expected. In using the WAS as determining the initiation of treatment, we cannot exclude subtle differences in scoring by practitioners treatment initiated prior to toxicology or critical care involvement. Furthermore, patients were originally admitted to the ICU for various reasons. Even though, all patients with DT are admitted to the ICU in our institution, the variations in primary admission diagnosis may have altered outcomes. Plus, data were collected over a relatively long-time frame that may alter outcomes as well. However, since Gold et al (3) published their landmark study in 2007, our management of the most severely ill ethanol withdrawal patients has not deviated significantly with the exception of ketamine administration. Finally, because no standardized comparison exists in patients suffering from ethanol withdrawal, we cannot exclude subtle differences in our cohorts. Furthermore, we did not control for other sedating medications administered as part of their ICU care. We did have a difference in gender that may skew our data, but all other demographic and biomarkers were similar in each group. Furthermore, gender has not been linked to more severe withdrawal (15).

CONCLUSIONS

Ketamine, an NMDA antagonist, offers an adjunct to traditional GABA agonist treatment of severe ethanol withdrawal. A ketamine infusion in patients with DT was associated with reduced GABA agonist administration, fewer intubations, and shorter ICU length of stay in a pragmatic retrospective evaluation of a limited sample of patients. Follow-up, prospective studies are required to determine the true utility of ketamine in severe ethanol withdrawal.

REFERENCES

1. Foy A, Kay J, Taylor A: The course of alcohol withdrawal in a general hospital. *QJM* 1997; 90:253–261
2. Genther DJ, Gourin CG: The effect of alcohol abuse and alcohol withdrawal on short-term outcomes and cost of care after head and neck cancer surgery. *Laryngoscope* 2012; 122:1739–1747
3. Gold JA, Rimal B, Nolan A, et al: A strategy of escalating doses of benzodiazepines and phenobarbital administration reduces the need for mechanical ventilation in delirium tremens. *Crit Care Med* 2007; 35:724–730
4. Reich DL, Silvay G: Ketamine: An update on the first twenty-five years of clinical experience. *Can J Anaesth* 1989; 36:186–197
5. Miner JR, Moore JC, Austad EJ, et al: Randomized, double-blinded, clinical trial of propofol, 1:1 propofol/ketamine, and 4:1 propofol/ketamine for deep procedural sedation in the emergency department. *Ann Emerg Med* 2015; 65:479–488.e2
6. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. DSM-5. Washington, DC, American Psychiatric Publishing, 2013
7. Miller NS, Gold MS: Management of withdrawal syndromes and relapse prevention in drug and alcohol dependence. *Am Fam Physician* 1998; 58:139–146
8. Wong A, Benedict NJ, Armahizer MJ, et al: Evaluation of adjunctive ketamine to benzodiazepines for management of alcohol withdrawal syndrome. *Ann Pharmacother* 2015; 49:14–19
9. Parsch CS, Boonstra A, Teubner D, et al: Ketamine reduces the need for intubation in patients with acute severe mental illness and agitation requiring transport to definitive care. *Emerg Med Australas* 2017; 29:291–296
10. Peltoniemi MA, Hagelberg NM, Olkkola KT, et al: Ketamine: A review of clinical pharmacokinetics and pharmacodynamics in anesthesia and pain therapy. *Clin Pharmacokinet* 2016; 55:1059–1077
11. Kwok RF, Lim J, Chan MTV, et al. Does ketamine have preemptive effects in women undergoing abdominal hysterectomy procedures. *Anesth Analg* 2000; 80:1419–1422
12. Whittington MA, Lambert JD, Little HJ: Increased NMDA receptor and calcium channel activity underlying ethanol withdrawal hyperexcitability. *Alcohol Alcohol* 1995; 30:105–114
13. Condi M, Sallerin T, Devaux C: [Use of ketamine in the treatment of delirium tremens and medical delirium]. *Anesth Analg (Paris)* 1972; 29:377–394
14. Marik P, Mohedin B: Alcohol-related admissions to an inner city hospital intensive care unit. *Alcohol Alcohol* 1996; 31:393–396
15. Goodson CM, Clark BJ, Douglas IS: Predictors of severe alcohol withdrawal syndrome: A systematic review and meta-analysis. *Alcohol Clin Exp Res* 2014; 38:2664–2677