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ORIGINAL RESEARCH

Ketamine Versus Haloperidol/Lorazepam/Diphenhydramine Combination Treatment for Management of Acute Agitation in the Emergency Department

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Purpose: Appropriate use and timing of agents for chemical management of patient agitation is critical for the safety of patients and providers. Ketamine may have a preferable safety profile in acutely agitated patients, especially those with an unknown medication history given that it does not carry the same cardiovascular and respiratory risks as other sedative agents currently used in practice. This study aimed to evaluate subsequent chemical sedation requirements and the incidence of adverse events following the use of ketamine for agitation as compared to combination antipsychotic/sedative use in the ED.

Methods: This was a retrospective, single-center, observational cohort study of 102 adult patients who received chemical sedation for agitation/aggression/combative behavior from January 2018 to December 2023 at the Mount Sinai Medical Center Emergency Department. Patients who received at least one dose of ketamine (n = 51) were compared to patients who received at least one dose of the B52 combination (diphenhydramine (Benadryl) 25 mg, haloperidol (Haldol) 5 mg, and lorazepam (Ativan) 2 mg) (n = 51) for management of aggression. The primary endpoint was restricted mean survival time (RMST) to next sedative given. Secondary endpoints included the number of additional sedatives needed, adverse events, and length of stay.

Results: The use of ketamine was associated with patients requiring additional sedation both more often and sooner than patients who received the B52 combination (RMST to next sedative: 2.1 hours ketamine vs 4 hours B52; $p = 0.032$, median additional doses: 3 doses ketamine group vs 0 doses B52 group; $p < 0.00$).

Conclusion: In agitated patients within the ED, the administration of ketamine demonstrated inadequate duration of sedation and increased need for supplemental sedative use compared to B52.

Keywords: sedation, aggression, rapid tranquilization, B52, ketamine

Introduction

Agitated patients pose a safety risk to themselves and to healthcare staff as aggressive behavior can turn into physical violence. This risk must be weighed against the risk of using pharmacologic agents to manage agitation that can be overly sedating and sleep-inducing which prevents full clinical assessment and can prolong length of stay. Appropriate use and timing of agents for chemical sedation is critical for the safety of patients and providers. The ideal agent to treat agitation would be one that is effective, fast-acting, easy to dose and administer without adverse effects. One measure of efficacy for these agents is resolution of agitated behavior without the need for additional sedative use.

Current American College of Emergency Physicians (ACEP) guidelines recommend the use of benzodiazepines for common causes of agitation including alcohol withdrawal, seizures, and intoxication.[1] A combination of diphenhydramine (Benadryl), haloperidol (Haldol), and lorazepam (Ativan) is commonly used as a first agent for treatment of agitation in the emergency department (ED).[2,3] The combination of diphenhydramine (Benadryl), haloperidol (Haldol), and lorazepam (Ativan) will be abbreviated to B52.

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Pharmacologic rationale for the B52 combination is as follows. Haloperidol blocks dopamine receptors, which may relieve agitation resulting from dopaminergic imbalances, lorazepam enhances GABA inhibitory action to relieve anxiety and cause sedation, and diphenhydramine provides sedation and reduction of dystonia from haloperidol. Although effective, this combination can cause adverse events including profound sedation leading to unconsciousness.[1,2]

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that can provide sedation and analgesia. Ketamine is an alternative agent reserved for patients who need rapid resolution of severe agitation, intubation, or those whose aggression is resistant to other sedatives.[3,4] In addition to NMDA, ketamine has affinity for other CNS receptors that can cause dysphoria, nausea, hallucinations, and changes in blood pressure and heart rate. Ketamine can cause hypersalivation and airway complications that may require intubation. Ketamine has a fast onset of action and can provide deep procedural sedation but is associated with the risk of blood pressure lability, and variable recovery periods, which can be concerning side effects in the agitated patient.[5,6] The potential for abuse and psychological side effects including hallucinations, and emergence reactions may worsen agitation in patients with schizophrenia and other comorbid psychiatric disorders especially when given as a bolus dose.[7]

Providers may choose to use ketamine in agitated patients with unknown medication history given that it has a fast onset of action, between 2 and 10 minutes intramuscularly (IM) and less than 2 minutes intravenously (IV). In comparison, the combination of haloperidol, lorazepam, and diphenhydramine has a variable onset of action between 5 and 30 minutes.[2] Additionally, ketamine does not carry the same risk of over-sedation and drug interactions as other sedative agents currently used in practice. The joint position statement (ACEP, ACS-COT, NASEMSO, NAEMSP, NAEMT) released in 2020 on the use of ketamine in the acute trauma patient calls for 3–5 mg/kg IM dosage and 1–2 mg/kg IV dosage in acute agitation and/or excited delirium.[8]

While ketamine use in the emergency department for agitation has increased, there is a scarcity of studies evaluating the duration of its efficacy and impact on the need for subsequent sedatives.[5] Previous studies have reported on the endpoint of adequate sedation with the use of ketamine for agitation, therefore opening discussion to the need for evaluating duration of sedation and the overall impact on subsequent chemical sedation requirements.[9,10] This study's purpose was to evaluate the efficacy and safety associated with ketamine in patients presenting to the ED with acute agitation.

Materials and Methods

Study Design

This was a retrospective, single-center, observational cohort study approved on October 25, 2023 by the Mount Sinai Medical Center institutional review board (FWA00000176). This research was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The need to obtain informed patient consent was waived with institutional review board approval.

Data collection was conducted by reviewing the electronic medical records (EMRs) of patients who received chemical sedation for agitation/aggression/combative behavior from January 2018 to December 2023 at Mount Sinai Medical Center Emergency Department.

Initial search of the medical records identified 563 patients who received a dose of the B52 combination and 1138 patients who received a dose of ketamine while in the ED. Of these 1138 ketamine patients, 51 had a documented indication of agitation/aggression. Identification of qualifying patients was done by evaluation of medication order and provider notes mentioning aggressive behavior, agitation, and combativeness that required medical sedation and the confirmation of specific agents used. To match group sizes, we then randomly selected 51 of the 563 patients who received a B52 using the RAND() function in Excel. We then performed a detailed chart review on these 102 patients. Patients were excluded if ketamine was used for procedural sedation or pain. B52 patients were required to have been given all 3 agents within a 15-minute timeframe as noted by the medication administration report (MAR). Patients were excluded from the B52 group if they reached ketamine during the ED visit.

Treatment

Patients who received ketamine by any route for the management of agitation in the ED were compared to patients who received diphenhydramine (Benadryl), haloperidol (Haldol), and lorazepam (Ativan) (B52).

Assessment

The primary endpoint was the administration of subsequent sedative agents/antipsychotics for agitation within 3 hours of receiving ketamine or B52 because of inadequate sedation. Adequate sedation was assessed by provider notes and the number of doses needed to calm the patient. ED length of stay, incidence of hypoxia/intubation, hypo/hypertension, intubation due to respiratory distress, and other adverse effects were evaluated for safety.

Statistical Analysis

Baseline patient characteristics were compared by Kruskal–Wallis ANOVA or Pearson's Chi Square (Table 1). The primary endpoint was assessed through a Kaplan Meier Survival Analysis using Restricted Mean Survival Time (RMST) to next sedative agent used for agitation. Kaplan-Meier with RMST was also used to compare length of stay. Cox Regression analysis was used as multivariate survival analysis for baseline differences in age and ethnicity. Incidence of adverse events was assessed with Wald Z test or Pearson's chi-squared test, and the percentage of patients requiring additional sedatives in the following 3 hours was evaluated with Pearson's chi-squared test. Subsets of cannabinoid-positive patients and those who received ketamine as the first agent were compared between groups by Wald Z test for independent proportions. Significance level was set at $p < 0.05$.

Table 1 Baseline Characteristics of Patients

	Ketamine (N = 51)	**B52 (N = 51)**	**p-value**
Age, median (IQR)	45 (33–54)	39 (31–47)	0.04*
BMI (kg/m^2)	26	26	0.80
First sedative used, No. (%)	18 (35%)	48 (94%)	< 0.000*
Sex, No. (%)			0.64
Male	40 (78%)	38 (75%)	
Female	11 (22%)	13 (25%)	
Ethnicity, No. (%)			0.26
White or Caucasian	26 (51%)	29 (57%)	
Hispanic	26 (51%)	10 (20%)	0.004*
African American	9 (18%)	15 (29%)	
Multiracial	10 (20%)	5 (15%)	
Other	6 (12%)	2 (4%)	
Toxicology Screen			
Ethanol level > 80 mg/dL, No. (%)	8 (16%)	13 (25%)	0.16
+ for benzodiazepines No. (%)	7 (14%)	2 (4%)	0.08
+ for cannabinoids, No. (%)	15 (29%)	24 (47%)	0.07
+ for any screened substance, No. (%)	22 (43%)	27 (53%)	0.39

Notes: *Statistically significant; illicit substances tested: amphetamine/methamphetamine, benzodiazepines, cocaine, cannabinoids, opiates, phencyclidine, barbiturates.

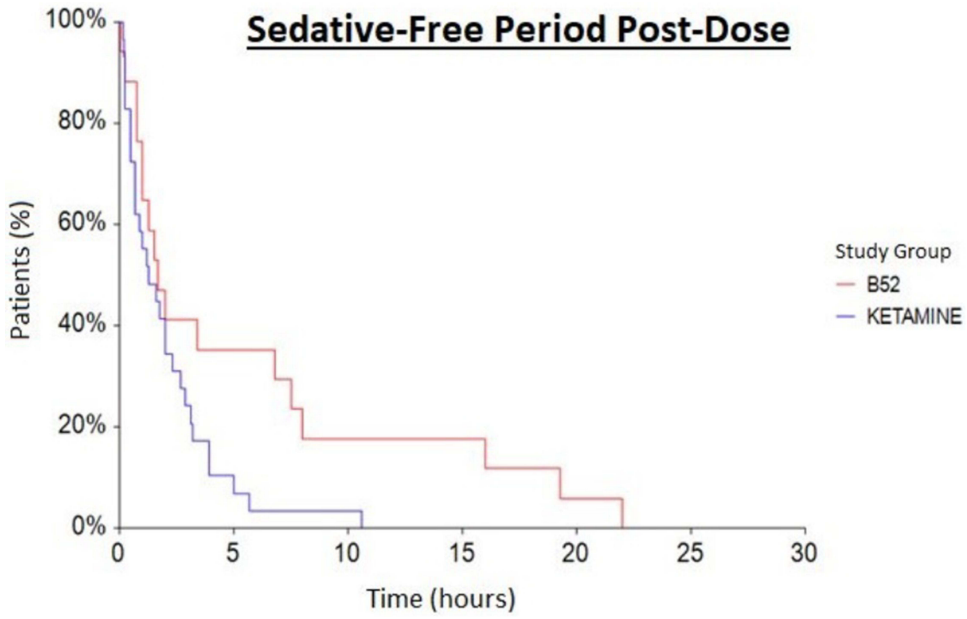

Figure 1 Kaplan-Meier Analysis of time until additional sedative agent needed.

Results

The RMST (mean time to receiving another sedative agent) between the groups was significantly different (Figure 1). Time to next sedative dose was 4 hours in the B52 group and 2.1 hours in the ketamine group (p = 0.03). The time until a patient in the ketamine group needed additional sedation was much less than a patient in the B52 group. The percentage of patients in the ketamine group that needed additional pharmacologic sedation within 3 hours was higher than the B52 group (p = 0.01). Primary and secondary endpoints are summarized in Tables 2 and 3.

In the small subset of patients who received ketamine first, prior to another other sedative for agitation, 10 out of 16 patients (62.5%) required additional sedatives compared to 17 patients out of the 47 who received B52 first (36%) (p=0.03). These patients included those with reported haloperidol allergy, those known to providers to have sub-optimal responses to other agents, and suspected drug overdoses.

For patients whose toxicology report tested positive for cannabis, in the ketamine group, all 15 of them (100%) required additional sedatives compared to 43% of the overall ketamine group. Of the B52 patients, 8 of 24 (33%) patients positive for cannabis needed additional sedation within the next 24 hours, which matches the overall group prevalence (31%). Down-regulation of cannabinoid receptors in patients with chronic cannabis use may result in decreased efficacy of ketamine for sedation, given the reported role of endogenous cannabinoid (CB1) receptors in ketamine action.[11]

Table 2 Primary Endpoints

	Ketamine (N = 51)	**B52 (N = 51)**	**p-value**
Dose, average	IV: 1.4 mg/kg	Haloperidol 5 mg, Lorazepam 2 mg, Diphenhydramine 25 mg	N/A
	IM: 2.5 mg/kg		
Efficacy Outcomes			
Additional sedative in 3 hours	22 (43%)	10 (20%)	p = 0.01
Time to next sedative, RMST	2.1 hours	4 hours	p = 0.03
Number of additional doses, median	3	0	p < 0.00
Adequate Sedation, No. (%)	30 (59%)	43 (84%)	p = 0.06

Table 3 Secondary Endpoints

	Ketamine (N = 51)	B52 (N = 51)	p-value
Length of stay (mean, h)	10.3	10.7	p = 0.88
Change in blood pressure > 20 mmHg	13 (25%)	10 (20%)	p = 1
Change in heart rate > 20 bpm	14 (27%)	10 (20%)	p = 1
Intubation post-dose	2 (4%)	0 (0%)	p = 0.5
Increase in O2 requirements	10 (20%)	2 (4%)	p = 0.2
Noted AE attributed to drug	11 (20%)	5 (10%)	p = 0.1

No difference in length of stay or any safety parameters including change in blood pressure, heart rate, or oxygenation was identified. The incidence of other adverse effects, including intubation, emesis, and loss of consciousness attributed to the given drug regimen was 22% in the ketamine patients compared to 10% in the B52 patients (p=0.1). The relative risk ratio between ketamine and B52 accounting for baseline differences in age and ethnicity was 1.42 (95% CI [1.01–1.99] p = 0.043). This multivariate analysis showed that patients receiving ketamine were 1.42-fold more likely to need another sedative sooner than patients receiving B52 (Table 4).

To adjust for the fact that most patients did not receive ketamine as initial treatment, multivariate analysis was performed on the subset of patients who did receive ketamine or B52 first (Tables 5 and 6). In this subgroup analysis,

Table 4 Cox Regression Analysis (N = 102)

Independent Variable	Risk Ratio (95% Confidence Interval)	p-value
Age (years)	1.01 (0.99–1.03)	0.35
Study Group (Ketamine vs B52)	1.42 (1.01–1.99)	0.04
Ethnic group (non-Hispanic vs Hispanic)	0.74 (0.47–1.18)	0.20
Ethnic group (unknown vs Hispanic)	1.16 (0.58–2.32)	0.68

Table 5 Subgroup Analysis (N = 63)

Study Group	First Sedative		Total
	B52	Ketamine	
B52	47	0	47
Ketamine	0	16	16

Table 6 Cox Regression Subgroup Analysis (N = 63)

Independent Variable	Risk Ratio (95% Confidence Interval)	p-value
Age (years)	1.03 (0.99–1.07)	0.09
Study Group (Ketamine vs B52)	1.68 (1.06–2.68)	0.03
Ethnic group (non-Hispanic vs Hispanic)	0.73 (0.41–1.31)	0.30
Ethnic group (unknown vs Hispanic)	1.21 (0.53–2.77)	0.65

patients who were first treated with ketamine were 1.68 times more likely to receive additional sedation in the next 1.4 hours than patients who received B52 first (risk ratio of 1.68 (95% CI [1.06–2.68] p = 0.03).

Discussion

Given the difference in time to the next sedative, it can be said that ketamine either provided insufficient relief, or the relief wore off faster necessitating re-treatment. Forty percent of B52 patients made it to 5 hours post-dose without needing an additional sedative as compared to around 10% of ketamine patients. The number of additional sedative doses and the average agitation-free period (as determined by time to the next sedative used) also differed between the two groups suggesting inadequate agitation resolution in the ketamine group.

Addressing aggression and agitation properly is time-consuming and labor-intensive and the attention needed by these patients may detract from the team's ability to care for other patients. Although not statistically significant due to sample size, patients that received ketamine had higher incidence of adverse events including hypertension, tachycardia, over-sedation, and aspiration leading to intubation. Recently ketamine has emerged as a groundbreaking therapy for multiple behavioral health conditions including autism spectrum disorder and attention deficit hyperactivity disorder. Ketamine's ability to enhance synaptic plasticity and activation of the brain's glutamate system make it a promising agent for these conditions. Of note, there were two neurodivergent patients included in the study who received ketamine with provider-noted suboptimal agitation response. Variability in patient response might have been attributed to specific ketamine doses, underlying psychological conditions, and concomitant medication use. Future studies in larger cohorts of patients are needed to assess the efficacy of ketamine in neurodivergent patients.

The 2023 ACEP agitation guidelines make no specific recommendation of ketamine dosage for agitation within the emergency department. Previous literature has described a ketamine dosage of 4–6 mg/kg IM for severe agitation with one meta-analysis showing a mean dose of 4.9 mg/kg.[12] This is a higher dosage range than the 2020 joint position statement recommendation of 3–5 mg/kg IM for acute trauma patients. Higher doses of ketamine (>5 mg/kg) are associated with increased risk of adverse effects including hypoventilation, hyper-salivation, and hypoxia. O'Brien et al investigated dosing ketamine intramuscularly for the management of agitation and found that reduced doses of 2 mg/kg provided adequate sedation in 13 of 15 (87%) patients without subsequent intubation.[13] This study was limited by sample size, lack of control, and the use of ketamine as a rescue agent, where 11 of 15 patients had received other sedatives first.

In this study, doses were given intramuscularly in 18 patients in the ketamine group with an average IM dose of 2.5 mg/kg. This IM dose was below the previously studied range of 4 to 6 mg/kg with only three patients dosed between 4 and 6 mg/kg IM. Despite documentation that these three patients achieved adequate sedation without adverse events, one of them still received additional sedatives. Low IM dosing may be partially responsible for insufficient sedation warranting the need for additional agents. Notably, none of the patients dosed intramuscularly required intubation.

Doses were given intravenously (IV) in 33 patients who received ketamine with a mean IV dose of 1.4 mg/kg. This average matches ACEP guideline recommended IV agitation dosage between 1.0 and 2.0 mg/kg.[1] However, 7 out of 33 IV doses were less than 1.0 mg/kg which represents underdosing in 21% of patients who received IV regimens. An opportunity exists to provide education and dosing protocols to aid ketamine dosage standardization. Future prospective studies with larger sample sizes, controls, and increased documentation are needed for ketamine agitation dosing recommendations.

Concerns for side effects, such as emesis requiring intubation as observed in two patients may discourage providers from using ketamine as a first-line agent. However, one of these cases was related to an overdose of diphenhydramine in attempted suicide. Both cases have an unclear causality with ketamine. Providers also more frequently documented that patients remained agitated after receiving ketamine than after receiving B52 (84% vs 59%, p = 0.064).

Study Limitations

Patients in this study rarely received ketamine initially for agitation, many of the patients in the ketamine group had often already failed other treatment modalities. Additionally, the variable dosing of ketamine in this study may have affected the primary outcomes. The average IM dose of 2.5 mg/kg falls below the recommended agitation dosing with several patients in the IV group also being under-dosed per guidelines recommendations. The consensus statement by ACEP states that doses between 0.5 and 0.9 mg/kg administered IV are not effective in sedation and can increase the risk of

delirium or hallucination.[8] Therefore, it is possible that the underdosed patients did not receive a satisfactory trial of ketamine. Attempting to answer this question with another subgroup analysis would result in further reduced sample size and may be misleading.

The limitations of a single center, non-randomized, small sample size, and retrospective design yield potentially non-generalizable results. The use of randomization in a future study would greatly benefit the analysis given that the use of ketamine may have been used mostly for difficult/refractory cases. Additionally, comparison to individual components of the B52 formulation as well as alternative antipsychotic/benzodiazepine combinations may facilitate generalization to other regimens utilized in other institutions. In this study, due to resource limitations, abstraction was performed by non-blinded study investigators which provides the risk of abstraction bias. Ideal future design would rely on blinded abstractors with a formal coding manual and interrater reliability assessment.

Conclusion

In acutely agitated ED patients, there is insufficient evidence to support the use of ketamine as first-line monotherapy in place of the B52 combination. Prospective, multicenter, randomized controlled trials can provide further insight into the role of ketamine in the ED for the management of agitation and aggression. Reserving ketamine for use in patients who have suspected contraindications to other treatments (allergies, illicit substance use, drug overdose) may be a reasonable approach for addressing hard to treat agitation. The short half-life of ketamine may make it insufficient for the management of agitation without additional agents. Providers using ketamine should be mindful of ketamine's fast offset that may warrant the need for additional agents in the event of returned agitation or emergence reactions.[14] Future use of ketamine for agitation within the ED should address the creation of order sets and clinical decision support that provides dosing and supplemental sedative options. A standardized workflow that includes monitoring at set intervals for patient re-evaluation and allows providers to have a pre-defined alternative sedative to use in ketamine-refractory agitation may improve patient and staff safety.

Disclosure

The author(s) report no conflicts of interest in this work.

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