Rapid Agitation Control With Ketamine in the Emergency Department: A Blinded, Randomized Controlled Trial

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Study objective: We hypothesized that the use of intramuscular ketamine would result in a clinically relevant shorter time to target sedation.

Methods: We conducted a randomized clinical trial comparing the rapidity of onset, level of sedation, and adverse effect profile of ketamine compared to a combination of midazolam and haloperidol for behavioral control of emergency department patients with severe psychomotor agitation. We included patients with severe psychomotor agitation measured by a Richmond Agitation Score (RASS) $\geq+3$. Patients in the ketamine group were treated with a 5 mg/kg intramuscular injection. Patients in the midazolam and haloperidol group were treated with a single intramuscular injection of 5 mg midazolam and 5 mg haloperidol. The primary outcome was the time, in minutes, from study medication administration to adequate sedation, defined as RASS $\leq$-1. Secondary outcomes included the need for rescue medications and serious adverse events.

Results: Between June 30, 2018, and March 13, 2020, we screened 308 patients and enrolled 80. The median time to sedation was 14.7 minutes for midazolam and haloperidol versus 5.8 minutes for ketamine (difference 8.8 minutes [95% confidence interval (CI) 3.0 to 14.5]). Adjusted Cox proportional model analysis favored the ketamine arm (hazard ratio 2.43, 95% CI 1.43 to 4.12). Five (12.5%) patients in the ketamine arm and 2 (5.0%) patients in the midazolam and haloperidol arm experienced serious adverse events (difference 7.5% [95% CI -4.8% to 19.8%]).

Conclusion: In ED patients with severe agitation, intramuscular ketamine provided significantly shorter time to adequate sedation than a combination of intramuscular midazolam and haloperidol. [Ann Emerg Med. 2021;■:1-8.]

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INTRODUCTION

Background

Emergency department (ED) patients with severe psychomotor agitation require rapid behavioral control for both patient and staff safety.[1] The administration of intramuscular sedatives allows safe assessment, stabilization, and monitoring[1-4] while maximizing patient and staff safety through the control of agitation and violent behavior.

While a recent systematic review has demonstrated the lack of a standard of care,[5] 2 main classes of medications—benzodiazepines and antipsychotics—are commonly used in EDs for the control of agitation. These methods are problematic; benzodiazepines are associated with increased risk of respiratory depression, oxygen desaturation, and unplanned airway interventions,[5] while antipsychotics are associated with dystonia, akathisia, parkinsonism, and neuroleptic malignant syndrome.[6]

Ketamine is a noncompetitive N-methyl-D-aspartic acid receptor antagonist and a highly dissociative sedative[7] that provides effective low-dose analgesia,[8,9] procedural sedation,[10,11] and general sedation.[12] Rapid dissociation,[13] favorable cardiovascular stability,[14,15] and preservation of respiratory drive, as evidenced by a low rate of cardiopulmonary adverse events,[11,12,16] suggest that ketamine may be an option for rapid, safe control of agitated and violent ED patients. Out-of-hospital[2,14,17-22] and ED-based[23,24] intramuscular ketamine has been shown to be rapidly effective for behavioral control in both retrospective and prospective series. The American College of Emergency Physicians highlighted the need for

Editor's Capsule Summary

What is already known on this topic

Rapid onset is desirable when administering drugs for acute agitation.

What question this study addressed

Which more rapidly achieves adequate sedation: ketamine 5 mg/kg IM or midazolam 5 mg plus haloperidol 5 mg IM?

What this study adds to our knowledge

In this randomized controlled trial of 80 adults, the median time to adequate sedation was significantly faster for ketamine versus midazolam/haloperidol (6 versus 15 minutes, respectively).

How this is relevant to clinical practice

Ketamine more rapidly calms acute agitation than midazolam/haloperidol.

"high-quality research…to establish the safety and efficacy of ketamine compared with other agents for the control of the acutely agitated patient in the ED."[25]

Importance

This study lends evidence toward the efficacy of ketamine as an option for rapid sedation of agitated patients presenting to the ED and contributes to a growing base of evidence for improved care for this vulnerable population.

Goals

We conducted a randomized clinical trial comparing the rapidity of onset, level of sedation, and adverse effect profile of ketamine compared to a combination of midazolam and haloperidol (a commonly used benzodiazepine plus antipsychotic combination) for behavioral control of ED patients with severe psychomotor agitation. We hypothesized that the use of intramuscular ketamine would result in a clinically relevant (3 minutes) shorter time to target sedation.

MATERIALS AND METHODS

Setting and Design

We conducted a parallel-arm 1:1 randomized trial at the ED of St. Paul's Hospital in Vancouver, Canada. This urban site receives more than 90,000 patients annually, many of whom have acute or chronic mental disorders or substance use disorders and are precariously housed or homeless. The study was approved by the Providence Health Care Research Ethics Board and registered prospectively at clinicaltrials.gov (NCT03375671) prior to patient enrollment. The trial protocol was published previously.[26]

Attending emergency physicians enrolled and treated all participants in this trial. Patients were screened for eligibility by trained research assistants between 8:00 AM and midnight, when study staff were available. Research assistants received standardized video and lecture training on trial protocols and assessments.

Patients

We included patients aged 19 to 60 years with severe psychomotor agitation measured by a Richmond Agitation Score (RASS) $\geq +3$. We excluded patients who had been previously enrolled, were in police custody, or had a known pregnancy or were breastfeeding as well as those with known hypersensitivity, intolerance or allergy to any study medication, or other specified comorbidities (Box 1 in Appendix E1, available online at www.annemergmed.com). All enrolling emergency physicians had undergone standardized training in study protocols,[26] and they assessed potential patients for trial eligibility during the triage process through direct notification of potentially eligible patients from the triage nurse. All potential patients were treated in a trauma bed with full cardiopulmonary monitoring and resuscitation capabilities. Research assistants provided verification of patient eligibility.

Informed Consent

A waiver of informed consent was granted by the University of British Columbia Providence Health Care Research Ethics Board for this study.[26] Details of this waiver can be found in Appendix E1.

Randomization and Blinding

The study biostatistician generated the treatment allocations before the start of the study using a randomized block design with varying block sizes (2, 4, 6, or 8). Each block contained equal numbers of participants for each arm. The randomization schedule was stored in a secure location with the study medications in a medication storage system (Omnicell) in the ED. The group allocation was concealed from study staff using a sealed, opaque envelope with a unique study identifier code on the exterior. A designated unblinded ED study nurse opened the next sequential envelope in the randomization system, obtained the appropriate study medications from the Omnicell, and administered them. This nurse was the only unblinded

individual involved with the study and was not involved with the collection of data or assessment of any study outcomes or other study procedures. Treatment allocation was concealed from all other study investigators, research assistants, and participants.[26]

Study Treatments

Patients in the ketamine group were treated with a 5 mg/kg intramuscular injection (split into multiple syringes; 50 mg/mL concentration, maximum of 4 mL per intramuscular site). Patients in the midazolam and haloperidol group were treated with a single intramuscular injection consisting of 5 mg midazolam and 5 mg haloperidol. Patients were placed on full cardiopulmonary monitoring for at least 30 minutes after medication administration. Physicians ordered the following standardized testing for all patients: complete blood count, electrolyte panel, serum toxicology (ethanol, acetaminophen, salicylate levels), and ECG. Research assistants did not observe medication administration; they began observation immediately after this occurred. They recorded the RASS continuously at 5-minute intervals until the primary endpoint or the 30-minute follow-up period was reached.

Research assistants prospectively recorded all potential adverse events until patients were discharged from the ED or hospital. All data were entered into a RedCap database (Vanderbilt University). Patients in both trial groups remained on cardiopulmonary monitoring for a standard 30 minutes after medication administration. There was no difference in monitoring between trial groups. Once the attending physician deemed a patient medically and behaviorally stable, the patient was transferred to a bed without cardiopulmonary monitoring and sequentially re-evaluated by the treating emergency physician and research assistants until either hospital admission or discharge.

Outcomes

The primary outcome was the time, in minutes, from study medication administration to adequate sedation, defined as RASS $\leq$-1. Patients who did not achieve adequate sedation were censored at the time of last observation or the end of the sedation assessment period of 30 minutes, whichever came first. The secondary outcomes were: 1) the need for rescue medications—defined as benzodiazepines, antipsychotics, or other sedative medications, and administered at the attending emergency physician's discretion—measured every 5 minutes until 30 minutes after study medication administration; 2) the occurrence of prespecified adverse events as defined by the Common Terminology Criteria for Adverse Events Version 4.0[26] and Tracking and Reporting Outcomes of Procedural Sedation criteria[27] (Appendix E1), and 3) the occurrence of neuroleptic malignant syndrome, defined by the International Consensus Diagnostic Criteria for Neuroleptic Malignant Syndrome,[28] within 72 hours through structured chart review, clinical records, and telephone follow-up. The principal investigator (DB) reviewed all safety data, and 2 independent emergency physicians not otherwise involved with the study reviewed any potential serious adverse events.

Sample Size

Previous research has demonstrated a mean time to sedation of 7 minutes for patients receiving benzodiazepines and antipsychotics.[5] The projected mean time of sedation for patients receiving ketamine in this study was anticipated to be 4 minutes (unpublished data), resulting in a mean reduction of 3 minutes and a hazard ratio (HR) of 1.75. However, to ensure adequate power, the sample size calculation assumed a lower mean reduction of 2.5 minutes (HR 1.56).[26] To achieve 80% power with an HR of 1.56 and an alpha of 0.05, we would require 83 patients per group, or 166 overall. Allowing for a 10% loss to follow-up (attrition), we planned for a final sample size of 184 (92 patients per group).[26]

Statistical Analysis

We conducted all analyses on an intention-to-treat basis. Demographic and baseline clinical characteristics were summarized using means and standard deviations or medians and interquartile ranges for continuous variables and using counts and percentages for categorical variables. The primary analysis used the Cox proportional hazard model with adjustment for age, gender, and baseline RASS (variables prespecified in the statistical analysis plan) to compare the time to sedation between the treatment arms. A patient who did not experience the primary outcome was censored at the earlier of 30 minutes or the time of last observed follow-up. A Kaplan–Meier cumulative incidence curve was used to summarize the time to adequate sedation. The proportion of patients who required rescue medications during the 30-minute observation period was reported for the 2 arms. Serious adverse events were summarized as counts and percentages. SAS (version 9.4) was used for statistical analysis. Statistical significance was set at $P<.05$, and all tests were 2-sided.

RESULTS

Between June 30, 2018, and March 13, 2020, we screened 308 patients and enrolled 80, randomized equally to 2 study arms. Two enrolled patients, both in the

ketamine arm, were lost to follow-up—1 patient who had no data collected beyond enrollment and 1 patient who had no data collected after the 5-minute outcome assessment. The first patient was excluded from the analyses, while the second patient had the primary outcome censored at 4 minutes. (The Consolidated Standards of Reporting Trials diagram can be found in Figure 1). The research ethics board halted the trial early due to a moratorium on in-person clinical research during the COVID-19 pandemic. Overall, 54 patients (68%) were men, the median age was 35 years, and 73% arrived by ambulance. A greater proportion of patients receiving ketamine were men and had RASS of +4 (Table 1).

The Kaplan–Meier cumulative incidence curves (Figure 2) showed that the time to adequate sedation was shorter in the ketamine arm. This observation was confirmed in the Cox proportional hazards model results both in unadjusted (HR 2.39, 95% CI 1.46 to 3.90) and adjusted (HR 2.43, 95% CI 1.43 to 4.12) analysis.

The median time to sedation was 14.7 minutes for midazolam and haloperidol versus 5.8 minutes for ketamine, for a difference of 8.8 minutes (95% CI 3.0 to 14.5). At each 5-minute time interval, a greater proportion of patients receiving ketamine achieved adequate sedation (Appendix E1). The distribution of RASS at each 5-minute time point was similar (Figure 3). The proportion of patients requiring rescue medications was similar (ketamine 13%, midazolam and haloperidol 15%) (Appendix E1). Five patients (12.5%) in the ketamine arm and 2 patients (5.0%) in the midazolam and haloperidol arm experienced a serious adverse event (difference 7.5% [95% CI -4.8% to 19.8%]) (Table 2). One patient who received ketamine experienced laryngospasm on 2 occasions within 15 minutes; both episodes resolved with minimal airway repositioning and supplemental oxygen. No patients required endotracheal intubation or ICU admission. Appendix E1 provides clinical vignettes for each serious adverse event.

LIMITATIONS

This trial was conducted in a single urban academic center where the staff were comfortable managing severely agitated patients, and not all ED systems may share this comfort.

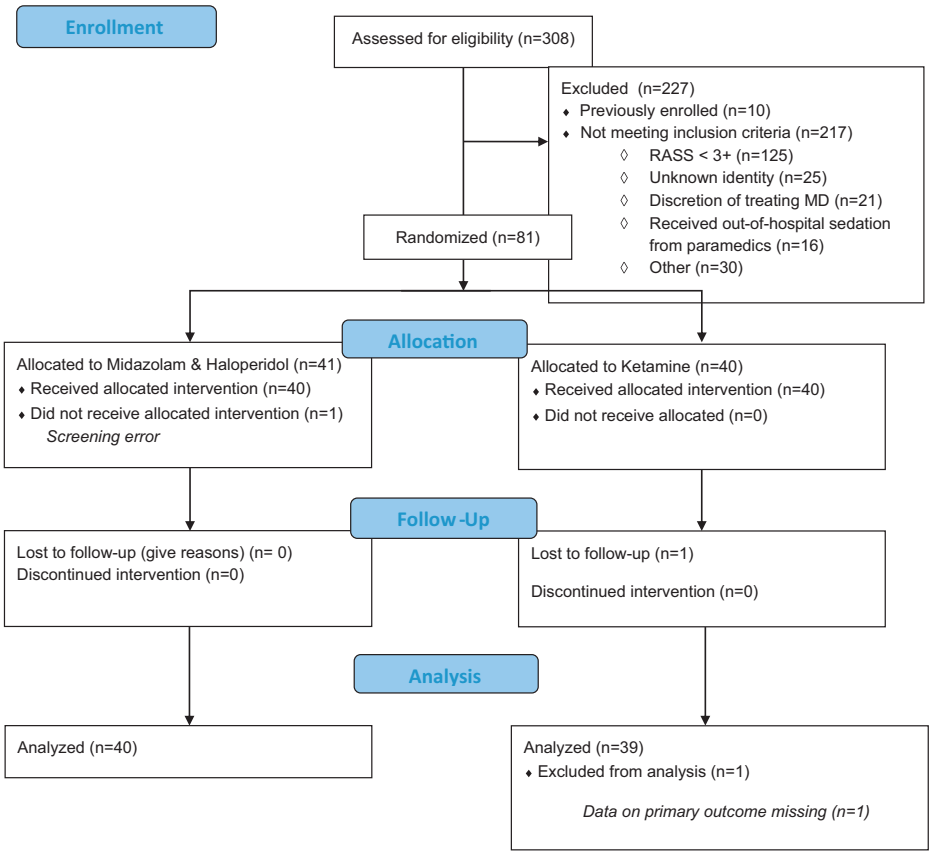

Figure 1. CONSORT 2010 Flow Diagram.

Table 1. Demographic characteristics of enrolled participants.

Variable	Midazolam & Haloperidol (n=40)	Ketamine (n=40)
Median age (years) [IQR]	37.5 [29.0–41.5]	33.5 [29.0–41.5]
Sex		
Male (%)	20 (50.0)	34 (85.0)
Female (%)	19 (47.5)	6 (15.0)
Transgender (%)	1 (2.5)	0 (0.0)
Arrival with paramedics (%)*	31 (77.5)	27 (69.2)
Arrival with police (%)	29 (72.5)	35 (87.5)
Initial RASS score*		
3+	22 (55.0)	14 (35.9)
4+	18 (45.0)	25 (64.1)
Median initial vital signs [IQR]		
Pulse rate (beats/min)	100.0 (92.0–112.0)	104.0 (90.0–120.0)
Respiratory rate (breaths/min)	20.0 (18.0–23.0)	20.0 (16.0–24.0)
Systolic blood pressure (mm Hg)	136.5 (129.0–148.0)	135.0 (125.0–153.0)
Diastolic blood pressure (mm Hg)	89.5 (78.0–99.0)	96.0 (77.0–107.0)
Oxygen saturation on room air	97.5 (96.0–100.0)	97.0 (96.0–99.0)
Temperature (°C)	37.0 (36.6–37.5)	37.2 (36.9–37.5)
Prior medical history†		
Hepatitis C	9 (23.7)	8 (20.5)
HIV	4 (10.5)	3 (7.7)
Illicit drug use	33 (86.8)	34 (87.2)
Alcohol use disorder	9 (23.7)	10 (25.6)
Schizophrenia/ schizoaffective	8 (21.1)	12 (30.8)
Bipolar disorder	8 (21.1)	9 (23.1)
Depression	6 (15.8)	7 (17.9)
Diabetes	1 (2.6)	0 (0.0)
Hypertension	0 (0.0)	1 (2.6)
Coronary artery disease	0 (0.0)	0 (0.0)
COPD	2 (5.3)	0 (0.0)

COPD, chronic obstructive pulmonary disease; IQR, interquartile range.
*n of missing=1
†n of missing=3

Importantly, we did not reach our targeted sample size due to COVID-19-mandated restrictions, and a larger trial would have provided greater precision in the estimate of the difference in sedation timing between the 2 arms and might have detected differences in serious adverse event rates.

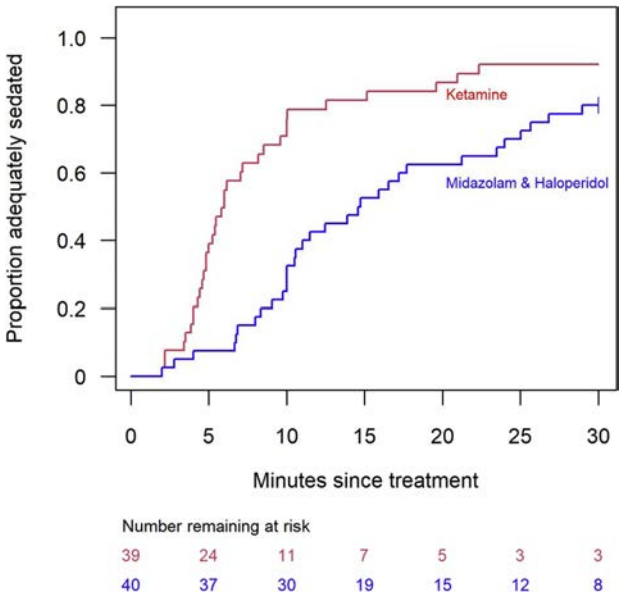

Figure 2. Kaplan–Meier cumulative incidence curve of the proportion of patients in each group achieving RASS ≤-1 at time after medication administration.

We compared 5 mg/kg ketamine to a combination of 5 mg midazolam plus 5 mg haloperidol, and a different comparator may have yielded different results. A greater proportion of patients receiving ketamine were men, although it is uncertain how this would affect results; a greater proportion of patients in the ketamine arm appeared to have a higher degree of agitation, but that should bias results toward the null. However, we adjusted for these imbalances using appropriate statistical methods. We did not monitor patients for level of sedation or rescue medication requirements beyond 30 minutes and cannot comment on discrepancies thereafter.

DISCUSSION

We conducted a randomized trial comparing intramuscular ketamine to a combination of intramuscular midazolam and haloperidol in ED patients with severe agitation. Baseline characteristics were similar, but we observed a statistically significant and clinically relevant shorter time to adequate sedation with ketamine. At every time interval, a greater proportion of patients receiving ketamine was adequately sedated. Similar proportions in each treatment arm required rescue medications. In both groups, adverse events were infrequent and quickly managed with no lasting sequelae. This assists clinicians by demonstrating that ketamine achieves faster sedation of severely agitated ED patients while maintaining a similar safety profile.

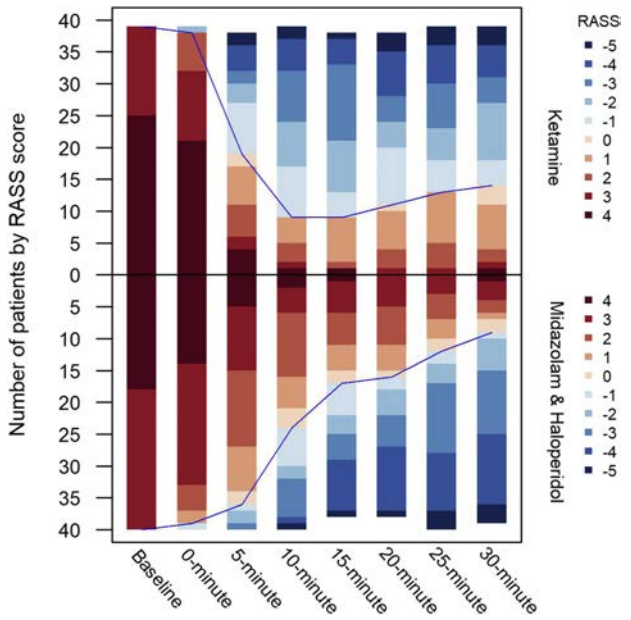

Figure 3. Relative distribution of RASS scores over time with solid lines indicating the -1 RASS thresholds for acceptable agitation.

Ketamine has demonstrated promise for rapid sedation of severely agitated patients in both out-of-hospital and ED settings,[21-24] but current findings are limited by small sample sizes and varying methodology. Hopper et al[23] conducted a retrospective records review of 32 ED presentations (27 patients) for acute agitation. Notably, 56% of cases had received other sedation medications prior to the administration of ketamine, and almost half of patients received ketamine intravenously. No data on time to sedation or potential ketamine-related serious adverse event were reported, making comparisons with our results challenging. Kowalski et al[29] described a case series of 5 adolescents with undifferentiated agitation receiving both intramuscular and intravenous ketamine in the ED but did not report accurate time to sedation or adverse events. Isbister[30] examined ketamine (median 300 mg intramuscularly) as rescue treatment for 49 patients with severe agitation refractory to 2 doses of 10 mg of droperidol; 3 patients (6%) experienced adverse events. No patients in this study required endotracheal intubation. Riddell et al[24] conducted a prospective observational cohort study comparing ketamine (n=24) to midazolam (n=17), lorazepam (n=33), or haloperidol (n=14), or in combination (n=10). The mean dose of ketamine and midazolam used in this study was less than in our trial (mean 2.97 mg/kg), and the time to sedation with ketamine was similar (6.57 minutes). Notably, 2 of 24 patients receiving ketamine required endotracheal intubation.

Table 2. Frequency of serious adverse events.

Serious Adverse Event	Haloperidol and Midazolam (n=40)	Ketamine (n=40)
Apnea	1 (2.5)	2 (5.0)
Supplemental oxygen required	1 (2.5)	1 (2.5)
Laryngospasm	0	1 (2.5)
Dystonia	0	1 (2.5)
Total	2 (5%)	5 (12.5%)

Heydari[31] randomized 90 patients to ketamine (4 mg/kg) or haloperidol (5 mg) alone and achieved a ketamine sedation time of 7.7 minutes. However, additional half doses of the study drug were commonly administered (ketamine group 64%; haloperidol group 51%). In our trial, patients did not receive a second dose of study medications, and the need for rescue sedation was similar between trial groups. While our sedation times appear roughly similar, Heydari[31] did not employ standardized adverse event or serious adverse event reporting. However, 9 patients (10%) required endotracheal intubation (6 ketamine; 3 haloperidol), and we cannot account for the substantial difference in patient safety profile compared to our results, except that we did not permit additional dosing.

Despite prior concerns regarding ketamine,[17,20] we were unable to observe a difference in serious adverse events between the trial groups. No patients in either trial arm required endotracheal intubation. Our results may give confidence to others managing severely agitated patients, although ketamine sedation in the out-of-hospital and psychiatric inpatient settings may require additional verification.

In conclusion, in ED patients with severe agitation, intramuscular ketamine provided significantly shorter time to adequate sedation than a combination of intramuscular midazolam and haloperidol. This study did not have sufficient power to assess potential differences in safety.

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monitoring, and successful completion of this study (Appendix E2, available online at www.annemergmed.com).

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Author contributions: DB, GA, BG, FXS, BM, SPB, and WGH conceived and designed the study. DB obtained funding and regulatory approval. DB, BG, and FXS were involved with the daily conduct of the study. DB, HQ, and HW conducted the statistical analysis. All authors were involved in the drafting and revision of this manuscript. DB takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria:(1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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