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Original Contribution

A prospective study of ketamine as primary therapy for prehospital profound agitation

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ABSTRACT

Objective: We investigated the effectiveness of ketamine as a primary therapy for prehospital profound agitation.
Methods: This was a prospective observational study of patients receiving 5 mg/kg of intramuscular ketamine for profound agitation, defined as a score of +4 on the Altered Mental Status Scale (AMSS), a validated ordinal scale of agitation from −4 (unresponsive) to +4 (most agitated). The primary outcome was time to adequate sedation (AMSS < +1). Secondary outcomes included need for additional sedatives, intubation frequency, complications associated with ketamine, and mortality.
Results: Forty-nine patients were enrolled. Median age was 29 years (range 18–66); 76% (37/49) were male. Median time to adequate sedation was 4.2 min (95% CI: 2.5–5.9, range 1–25 min) and 90% (44/49) had adequate sedation prehospital. Seven patients (14%) received a second sedative prehospital. Intubation occurred in 57% (28/49) of patients. Mechanical ventilation lasted <24 h in 82% (23/28) of patients, and <48 h in 96% (27/28) of patients. A single physician intubated 36% (10/28) of the patients. Complications related to ketamine included hypersalivation (n = 9, 18%), vomiting (n = 3, 6%), and emergence reaction (n = 2, 4%). One patient died from complications of septic shock on hospital day 29, likely unrelated to ketamine.
Conclusions: In patients with prehospital profound agitation, ketamine provides rapid effective sedation when used as a primary therapy. Intubation was common but accompanied by a short duration of mechanical ventilation and appears to have been subject to individual physician practice variation.

1. Introduction

1.1. Background

Agitation is a common problem for prehospital providers [1]. Agitation exists on a spectrum from those patients who respond to verbal de-escalation techniques [2] to profound agitation requiring immediate sedation for the safety of the patient and their caregivers [3]. Profound agitation may culminate in excited delirium syndrome (ExDS), a condition associated with significant morbidity and mortality where patients experience metabolic acidosis and hyperadrenergic autonomic dysfunction that may result in death [4,5].

Profound agitation, including ExDS, is best managed with rapid chemical sedation to decrease endogenous heat and acid production and to facilitate additional evaluation and care [6]. Though the optimal drug for parenteral chemical sedation of agitated patients in the prehospital environment is not yet known, multiple options have been proposed including droperidol [7], haloperidol [7,8], and benzodiazepines such as midazolam [8,9]. Recently the use of ketamine for agitation in the prehospital environment has gained favor [3,10-12].

We recently completed a trial of ketamine versus haloperidol for severe agitation. In that trial we used the Altered Mental Status Scale (AMSS), a validated [13,14], ordinal scale of agitation from −4 (unresponsive) to +4 (combative, most agitated possible) to define severe agitation as an AMSS score of +2 or +3, and profound agitation as an AMSS score of +4 [15]. That prior study included only patients with an AMSS score of +2 or +3, and demonstrated that ketamine effectively sedated patients with severe agitation (AMSS +2 or +3) typically within 5 min. Patients with profound agitation (AMSS +4) were specifically excluded from that comparative trial for purposes of patient and provider safety. Based on over a decade of experience successfully treating profound agitation with ketamine, our institution at the time deemed it unethical and unsafe to withhold ketamine from these patients for their safety as well as the safety of EMS. Although these profoundly agitated patients were excluded from that trial, prospective data were still collected on them for quality assurance purposes, which we now report in the present study.

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1.2. Importance

Profound agitation may be a precursor to ExDS and its significant metabolic disturbances [16]. Though the final common pathway for death in ExDS is not known, expert consensus suggests it involves a combination of acidosis, hyperthermia, and sympathomimetic surge [4]. Volunteer law enforcement studies on "use of force" encounters demonstrate these conditions, if left unchecked, worsen over time [17]. Therefore, if ketamine can rapidly sedate these patients it may curb or prevent the complications of ExDS. To our knowledge no study has prospectively assessed the effectiveness of ketamine as a primary therapy for profound agitation in the prehospital environment.

1.3. Goals of this investigation

The aim of the current study was to prospectively assess the effectiveness of ketamine 5 mg/kg intramuscular (IM) for profound agitation (AMSS +4) in the prehospital environment, by analyzing data collected on profoundly agitated patients during our comparative trial. Time to adequate sedation was the primary outcome. Secondary outcomes included additional sedatives required prehospital, complications associated with ketamine, intubation frequency, ECG and laboratory data, and hospital length of stay.

2. Methods

2.1. Study design

This was an IRB approved Waiver of Consent [18] observational study of patients receiving ketamine for profound agitation (AMSS +4) within the EMS primary service area subsequently transported to the study hospital's Emergency Department (ED) during our comparative trial on severe agitation (AMSS +2 or +3) [15]. The comparative trial was originally designed as a blinded, randomized trial, and registered at ClincalTrials.gov under identifier number NCT02103881. For feasibility reasons the comparative trial was later redesigned as a before and after open label trial and withdrawn from ClinicalTrials.gov.

2.2. Study setting and population

This study was conducted from October 2014 to November 2015 at an urban Level 1 trauma center safety-net hospital (in conjunction with its hospital-based EMS agency) with >110,000 annual ED visits. Data were collected during the period our comparative trial took place. The participating EMS agency is 1 of 5 agencies within the EMS system. This EMS agency responds to over 75,000 calls annually, serving an urban and suburban population of over 1,000,000 covering >200 mile^2. All ambulances are staffed with two EMT-paramedics at all times. Mean scene time for the agency is 17.9 min; mean transport time is 12.2 min. Approximately 500 patients per year receive chemical sedation for agitation (severe or profound combined) within the EMS agency. The EMS agency regularly transports patients to the study hospital as well as 10 other hospitals; only patients transported to the study hospital were included for analysis.

All paramedics within the EMS agency were trained in the Altered Mental Status Scale (AMSS), a validated [14] agitation scale regularly used in research at our institution [15,19] (Table 1). The AMSS was chosen as an agitation measurement tool not only because of our familiarity with it, but because it was developed on intoxicated, agitated, ED patients [13] and has been used in agitation studies in both the United States [15,19] and Australia [14,20]. Because the AMSS provides information on both the degree of agitation and the depth of sedation, it can be used to determine time to adequate sedation. Training was completed both via an online video and at in-person training sessions led by the primary investigator. All paramedics were required to pass a quiz containing example patients for all nine points on the AMSS; a correct AMSS score needed to be assigned for all nine cases. The study hospital's ED was staffed 24 h a day, 7 days a week, 365 days a year with research associates (RAs) trained in an identical manner in the AMSS. Research associates consisted of undergraduate and medical students reporting to research coordinators. In addition, RAs were proctored by senior RAs for their initial cases, and intermittently took refresher quizzes designed to keep scoring standardized.

Profound agitation was defined by two criteria, both of which were required for enrollment. This first criterion was based upon our EMS agency's standard operating procedure for behavioral emergencies, and is defined as "a patient with active physical violence to himself/herself or others evident, and usual chemical or physical restraints may not be appropriate or safely used." [3] The second criterion for inclusion was an AMSS score of +4. All patients in our EMS agency with profound agitation receiving ketamine who were transported to the study hospital's ED were included, regardless of the etiology of agitation. Exclusion criteria included obviously gravid women and persons who appeared to be or were known to be <18 years of age.

2.3. Study protocol

All patients with profound agitation (AMSS +4) received ketamine dosed at 5 mg/kg IM with dose calculation made by paramedic-estimated weight in the field if the weight was unknown. AMSS scores were recorded by medics on a standard data collection form at time = 0 and every 5 min thereafter until adequate sedation was achieved. Paramedics calculated total time to adequate sedation in minutes (primary outcome) by using a hand held stopwatch. Time to adequate sedation was defined as the time from ketamine administration, until the patient achieved an AMSS score < +1.

Immediately upon ED arrival, paramedics transferred both the stopwatch and data collection form to RAs. In the circumstance where adequate sedation was not reached prehospital, RAs continued recording AMSS scores every 5 min or until adequate sedation was reached.

2.4. Measurements

In addition to time to adequate sedation and AMSS scores, RAs also prospectively assessed, in conjunction with the treating physician, for

Table 1
The Altered Mental Status Scale.

Score	Responsiveness	Speech	Facial expression	Eyes
+4	Combative, very violent, or out of control	Loud outbursts	Agitated	Normal
+3	Very anxious, agitated, mild physical element of violence	Loud outbursts	Agitated	Normal
+2	Anxious, agitated	Loud outbursts	Normal	Normal
+1	Anxious, restless	Normal	Normal	Normal
0	Responds readily to name in normal tone	Normal	Normal	Clear, no ptosis
−1	Lethargic response to name	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (<half eye)
−2	Responds only if name is called loudly	Slurring or prominent slowing	Marked relaxation (slacked jaw)	Glazed and marked ptosis (>half eye)
−3	Responds only after mild prodding	Few recognizable words	Marked relaxation (slacked jaw)	Glazed and marked ptosis (>half eye)
−4	Does not respond to mild prodding or shaking	Few recognizable words	Marked relaxation (slacked jaw)	Glazed and marked ptosis (>half eye)