A Novel Agent for Management of Agitated Delirium
A Case Series of Ketamine Utilization in the Pediatric Emergency Department

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Abstract: Control of the agitated patient in the emergency department is challenging. Many options exist for chemical sedation, but most have suboptimal pharmacodynamic action, and many have undesirable adverse effects. There are reports of ketamine administration for control of agitation prehospital and in traumatically injured patients. Ketamine is a noncompetitive N-methyl-D-aspartic acid receptor antagonist, making it an effective dissociative agent. We present 5 cases of ketamine administration to manage agitated adolescent patients with underlying psychiatric disease and/or drug intoxication. Ketamine, as a dissociative agent, may be an alternative pharmacological consideration for the control of agitation in patients with undifferentiated agitation delirium.

Key Words: ketamine, excited delirium, sedation, agitation

Management of an agitated patient within an emergency department (ED) can be a chaotic and harrowing undertaking. Undifferentiated agitation, if not addressed promptly, can progress to excitable delirium and rapidly become a fatal condition. The physiologic state involving delirium, hyperthermia, and acidosis has been defined as excited delirium syndrome.1 This condition, ultimately, can lead to metabolic derangements and lethal cardiac dysrhythmias.1 Therefore, it is essential to recognize excitable delirium syndrome early in its course and intervene to interrupt the downward spiral of hypermetabolic activity and acidosis. Excited delirium should be a concern when evaluating a patient with delirium and an excited mental state, even if other physical findings are lacking.2

In the delirious state, teenaged and adult patients can be unruly and pose a threat to themselves, medical staff, and property. Current recommendations for the management of delirium describe minimizing physical restraint. Increased muscle activity, involved in struggling, can add to the existing metabolic derangement of rhabdomyolysis and acidosis. Chemical sedation should be initiated as early as possible to quell the hyperadrenergic state and to allow for goal-directed medical care.2

Most commonly, benzodiazepine or antipsychotic medications are administered in the ED to achieve sedation. These drugs are associated with adverse effects such as respiratory depression, cardiac dysrhythmia, dystonic reaction, or seizures. Some patients may not respond to escalating doses or may exhibit paradoxical increased agitation.3 Intramuscular (IM) administration of traditional sedating agents may have a long time to onset of action, and this may place the patient and staff in danger for a longer period than is desired or necessary. Unpredictable onset with the IM route can lead to repeated doses or “stacking” and a detrimental effect on the patient.

Ketamine is a dissociative agent often used in procedural sedation and general anesthesia.4 The drug is a noncompetitive N-methyl-D-aspartic acid receptor (NMDAR) antagonist, making it an effective dissociative agent.5 Intramuscular administration is well tolerated and reasonable for patients without immediate intravascular (IV) access. Recent reports have suggested that ketamine may have utility in the prehospital setting among agitated and traumatically injured patients.6,7 Ketamine has only infrequently been reported to be used for control of agitation in the ED8 and was not mentioned in a recent review article discussing pharmacological control of agitated delirium in the pediatric ED.9

We report 5 cases of teenagers initially presenting with undifferentiated agitation but who were ultimately identified as representing drug intoxication and psychiatric disease. These cases were successfully managed using ketamine to control the patients’ manic state. We searched the medical literature through PubMed using the keywords “ketamine,” “agitation,” “delirium,” “excited delirium,” and “emergency department.” We also searched the abstracts from the North American Congress of Clinical Toxicology for 2012, 2013, and 2014. We did not recover a previous case series describing the use of ketamine for management of acute agitation due to psychiatric disease or intoxication in the pediatric ED setting.

CASES

Case 1
A 16-year-old adolescent boy, estimated to weigh a muscular 100 kg, with a history of depression and oppositional defiant disorder presented to an ED with his parents after expressing suicidal intent. His medications included escitalopram without any known drug allergies. He refused to answer questions or participate in a medical examination. After approximately 15 minutes, he expressed his intent to leave the ED and started to walk out. Medical staff used soft voices and negotiation techniques to convince him to stay, but all attempts were unsuccessful.

When confronted by hospital security officers, he verbally threatened staff and became violent. Subsequently, security restrained him by the arms and legs in a supine position on the floor. He continued to struggle and tried to bite hospital staff while shouting profanity. The decision was made to use pharmacological sedation for the protection of the patient and staff. His parents denied any family history of abnormal heart rhythm or known sudden cardiac death. He was administered 200 mg of IM ketamine hydrochloride into the deltoid muscle. Within 5 minutes, he was sedate enough to cease physical restraint, and he was placed onto a bed.

Vital signs were obtained; temperature was 37.2°C, heart rate was 80 per minute, respiratory rate was 14 per minute, blood pressure was 120/70 mm Hg, and hemoglobin oxygen saturation via transcutaneous pulse oximetry was 96%. A complete physical

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examination was performed and revealed no evidence of head trauma. There was presence of mild nystagmus, normal thyroid shape and texture, normal deep tendon reflex function, and dry skin with capillary refill less than 3 seconds. Intravenous access was obtained, an electrocardiogram demonstrated normal sinus rhythm with normal QRS and QTc intervals, and serum electrolytes were normal.

Approximately 20 minutes after ketamine administration, with signs of resolving sedation, he was administered lorazepam of 2 mg IV and haloperidol of 2.5 mg IM. A urine drug immunoassay detected tetrahydrocannabinol metabolites; ethanol was undetectable in the blood. He remained sedate throughout his ED stay, experienced no observable adverse effects related to the respiratory or cardiovascular systems, and was transferred for inpatient psychiatric care.

Case 2
An 18-year-old, 68-kg, woman with a known history of schizophrenia and chronic abdominal pain was transported by ambulance to an ED for evaluation after exhibiting paranoid and erratic behavior at her home. She was believed to be noncompliant with her prescribed olanzapine and stopped attending her outpatient psychology appointments. There were no family concerns of illicit drug use or drug overdose. She had an unkempt appearance, appeared restless, and initially seemed to give little attention to her surroundings or caregivers.

Vital signs included a temperature of 37.4°C, heart rate of 96 per minute, respiratory rate of 16 per minute, blood pressure of 100/50 mm Hg, and oxygen saturation of 100% in room air. Her pupils were midposition and reactive, there was no palpable goiter, her heart and lungs were normal to auscultation, her abdomen was soft, and cranial nerves were intact, with normal deep tendon reflex function and strength in all extremities as well as dry skin with normal perfusion. Her distrust of the medical staff seemed to escalate, and she began to pace around her examination room. Suddenly, she physically attacked her mother causing both of them to fall to the floor. Security guards restrained her, and staff attempted to verbally calm her. She was prescribed olanzapine, 10 mg by mouth, but she spit it at a nurse. Then, while attempting to escape the ED, she assaulted staff members with her fingernails. Again, she was physically restrained by security officers and placed into leather 4-point extremity restraints, but she continued to struggle. Intramuscular ketamine was administered at 100 mg, injected into her left thigh. Her struggling ceased, and she became compliant within 10 minutes, at which time all physical restraints were removed.

Once she was calm, IV access was placed in the upper extremity. A complete blood count and a comprehensive metabolic chemistry panel were obtained but unremarkable except for a mild normocytic anemia. In addition, she had a negative pregnancy test, and a urine immunoassay for common drugs of abuse was negative. An electrocardiogram displayed a normal sinus rhythm with a QTc interval of 0.45 milliseconds. She was subsequently given three 1-mg doses of lorazepam IV to maintain mild sedation, and a urine drug immunoassay was negative for benzodiazepines and tetrahydrocannabinol metabolites but negative for cocaine and amphetamines. An electrocardiogram demonstrated a sinus tachycardia with normal QRS and QT intervals. A blood pressure of 150/90 mm Hg was finally obtained.

Approximately 45 minutes after ketamine administration, his sedation diminished, and he was given another 2.5-mg dose of IV lorazepam. He was hospitalized and received several more doses of lorazepam overnight to address sympathomimetic symptoms and agitation. The next day, his vital signs normalized, and his attention, behavior, and cognition returned to baseline. He admitted to use of a substance known as “bath salts.” Subsequent urine analysis by liquid chromatography mass spectroscopy by a national reference laboratory confirmed the presence of methylendioxypyrvalerone.

Case 3
A 16-year-old adolescent boy of approximately 80 kg presented to the ED with his family for evaluation of erratic behavior. Per his family, he was previously healthy except for seasonal allergies and a concern for recreational alcohol, tobacco, and marijuana abuse. His sister heard him shouting profanities and found him breaking his personal belongings. She and their mother were unable to calm him and became frightened, calling emergency medical services for help.

When medics arrived, his blood dextrose concentration was 110 mg/dL, and the emergency medical technician reported having to physically restrain him during the transport to the hospital. Several over-the-counter pharmaceuticals including antihistamines and prescription pain medications were available within the household, but none was unaccounted. He had no febrile prostration, no cough, and no known history of recent head trauma.

Upon arrival to the ED, he was agitated and would not cooperate for an examination. His oral temperature was 37.7°C, heart rate was 110 beats per minute (BPM), respiratory rate was 20 breaths per minute, and hemoglobin oxygen saturation via transcutaneous pulse oximetry was 98%; he would not cooperate with blood pressure measurement. He would regard family members and healthcare staff and would answer simple questions appropriately but was inattentive and was suspected to be having hallucinations. His pupils were 5 mm, symmetric and reactive to 4 mm, and he was mildly diaphoretic. The remainder of his physical examination was unremarkable.

An IV line was placed in his upper extremity while he sat on the hospital bed. He was administered lorazepam of 2.5 mg IV. Abruptly, after lorazepam administration, he exhibited violent behavior necessitating physical restraint by staff members. The IV line became dislodged during the struggle. He was administered ketamine of 200 mg IM and became passive within 6 minutes. Another IV line was inserted, and a complete blood count and serum electrolyte panel were obtained but were unremarkable. A computed tomography (CT) scan of the brain was normal. Ethanol was undetectable in the blood, and a urine drug immunoassay was positive for benzodiazepines and tetrahydrocannabinol metabolites but negative for cocaine and amphetamines. An electrocardiogram demonstrated a sinus tachycardia with normal QRS and QT intervals. A blood pressure of 150/90 mm Hg was finally obtained.

A previously healthy 15-year-old adolescent boy, weighing approximately 70 kg, presented to the ED with agitation, aggressive behavior. He admitted to ingesting “four tabs of acid” approximately 2 hours before his visit. There was no history of substance abuse per his family.

Initial vital signs included a temperature of 96.4°F, heart rate of 84 BPM, respiratory rate of 18 breaths per minute, blood pressure of 107/74 mm Hg, and oxygen saturation of 100% in room air. Upon physical examination, he appeared in mild distress, exhibiting some anxiety. He laughed inappropriately and refused to answer questions. The pupils were 8 mm and reactive bilaterally. A cardiovascular examination demonstrated a regular rate with intermittent elevation in heart rate and blood pressure to 130 BPM and 150 systolic, respectively.

During the medical evaluation, the patient was aggressive, swearing at staff, pulling his IV, and attempting to get out of...
TABLE 1. Characteristics of Alternative Agents for Control of Undifferentiated Delirium

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
<th>Onset/Duration of Action</th>
<th>Indications</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>Adults: 5 mg IM/IV</td>
<td>Onset: 30–45 min</td>
<td>All forms of agitation</td>
<td>EPSs, QTc prolongation, NMS, hypotension, cholinergic blockade</td>
</tr>
<tr>
<td>Children: 6–12 y, 1–3 mg; &gt;12 y, 2.5–5 mg</td>
<td>Duration: 4–24 h</td>
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<tr>
<td>Lorazepam</td>
<td>Adults: 2–4 mg IM/IV</td>
<td>Onset: IV, 15–20 min; IM, 30–45 min</td>
<td>All forms of agitation</td>
<td>Respiratory depression, ataxia, hypotension</td>
</tr>
<tr>
<td>Children: 0.05–0.1 mg/kg</td>
<td>Duration: 8–10 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Adults: 5–10 mg IV</td>
<td>Onset: IV 1–5 min</td>
<td>All forms of agitation</td>
<td>Respiratory depression, ataxia, hypotension</td>
</tr>
<tr>
<td>Children: not indicated for agitation</td>
<td>Duration: 15–60 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>Adults: 5 mg IM/IV</td>
<td>Onset: IV, 1 min; IM, 3–5 min</td>
<td>All forms of agitation</td>
<td>Respiratory depression, ataxia, hypotension</td>
</tr>
<tr>
<td>Children: 0.1–0.2 mg/kg</td>
<td>Duration: 30–120 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>Adults/children: 1.5–2 mg/kg IV, 4–5 mg/kg IM</td>
<td>Onset: IV, 15 min; IM, 30 min</td>
<td>Acute agitation</td>
<td>Emergence phenomenon, potential increased IOP, hypertension, tachycardia, salivation, vomiting, laryngospasm</td>
</tr>
<tr>
<td></td>
<td>The duration listed is for dissociation; full recovery takes longer</td>
<td></td>
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</tr>
</tbody>
</table>

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EPSs indicates extrapyramidal symptoms; NMS, Neuromalignant Syndrome.

Case 5

A 14-year-old adolescent boy with severe autism, mental impairment, impulse control disorder, self-injurious behavior, hypotonia, and seizure disorder was transferred from his residence at an inpatient treatment facility. He presented to the ED for evaluation of aggressive behavior with new facial contusions over his zygoma and temporal-mandibular area. His home medications included lorazepam as needed, quetiapine, and clonidine.

The patient’s history was significant for a recent intensive care unit admission due to a grade II liver laceration approximately 4 weeks prior. At that time, the boy had thrown his body against a metal cafeteria table after an increase in self-injurious behavior. During the previous hospitalization, lasting 48 hours, the boy required physical and chemical restraint. During the first 30 hours of admission, in addition to 4-point restraints, he received 3 doses of haloperidol, 7 doses of lorazepam, and 4 doses of morphine. He was finally cleared and discharged to his home facility.

Physical examination during the most recent hospitalization revealed multiple, large contusions on his face, head, and torso, as well as a diffuse inflamed, excoriated rash. The patient’s aggressive behavior prevented further physical examination or vital sign assessment. Both his parents and the staff from the facility who knew him were concerned about his change in behavior and felt that it was similar to that which occurred with his recent liver laceration. The primary team, caring for the patient, believed a further diagnostic work-up was necessary to exclude more serious injuries, but he required sedation. This was discussed with the parents and the facility staff, and all were in agreement.

Two security guards assisted in restraining the boy while ketamine at 4 mg/kg was administered IM. He struggled against the physical restraint briefly for several minutes and then relaxed. An IV was placed, and laboratory studies were sent. Vital signs were obtained, which were normal, and physical examination was completed without additional findings. The boy was transported to radiology for a CT of the brain and facial bones without incident. All studies were normal except for a pharyngeal swab, which was positive for group A streptococcus. He awoke from sedation without consequence and was subsequently discharged to his facility.

DISCUSSION

Gamma-aminobutyric acid agonists, such as benzodiazepines, may be effective sedating agents for delirious patients (Table 1). However, sedative-hypnotic agents have several disadvantages, which may limit their use when rapid containment of violent agitation is desired. Intramuscular administration is difficult to titrate, and stacking of doses may contribute to respiratory depression necessitating endotracheal intubation. Paradoxical excitation to benzodiazepine administration has been described.8 Furthermore, subsets of prehospital patients have demonstrated a failure to respond to benzodiazepines, necessitating a second-line agent.9,10

Antipsychotic drugs, such as haloperidol, are also therapeutic considerations and among the most common choices in the ED for an agitated patient (Table 1).11 However, the butyrophenone antipsychotics have a long onset of action time, may lower the seizure threshold, may reduce the body’s ability to dissipate heat, and may produce dystonia. They have also been associated with an increase in the QT interval with subsequent torsades de pointes.12,13 Ketamine does not exhibit these untoward effects.
and has received consensus support as a dissociative medication to break the downward cycle of metabolic derangement.2

Ketamine is recognized worldwide as an effective surgical adjunct.9 As a dissociative anesthetic, it has been widely used in procedural sedation in EDs for at least 20 years.15 Most recently, in the American College of Emergency Physician’s clinical policy for procedural sedation, ketamine has gained a level A recommendation for pediatrics and a level C recommendation for adults as an agent for procedural sedation.16 In addition, the drug is relatively safe as a class B medication in pregnancy.17

Ketamine is a noncompetitive NMDAR antagonist. The NMDAR is a glutamate receptor, which, when stimulated, results in neuroexcitability, plasticity, stimulation, and increased alertness. N-methyl-D-aspartic acid receptor antagonism, with administration of ketamine, causes a decrease in central nervous system stimulation and produces sedation. Dissociation occurs between the cortical and limbic systems of the brain. This ultimately results in a decreased perception of environmental stimulation. In higher doses, ketamine demonstrates analgesic effects by binding to mu and sigma receptors.

The initial IV and IM dissociative doses are 1 to 2 and 4 to 5 mg/kg, respectively. At this time, there are no clear recommendations on applying ideal or actual body weight for dosing calculations in obese individuals. With IM administration, there is a bioavailability of approximately 93%. The drug is lipophilic with a volume of distribution of 1 to 3 L/kg. There is rapid distribution to highly perfused tissues including the brain.19 As a result, onset of dissociation is quick, approximately 30 seconds in IV administration or 3 to 4 minutes with IM administration. Ketamine has an alpha elimination half-life of several minutes and a beta elimination half-life of approximately 3 hours19 and undergoes hepatic metabolism via hydroxylation and N-demethylation producing an active metabolite, norketamine.18 The metabolite demonstrates one third of the potency of the prodrug. Finally, approximately 90% is renally eliminated as metabolites, whereas 3% to 4% is excreted unchanged.18

Ketamine has qualities that make it an attractive consideration in the management of an agitated patient for both the safety of the patient, as well as healthcare providers. From time of administration, there is a rapid onset to peak effect. Ketamine does not require titration; instead, the provider must achieve a dissociation for pediatrics and a level C recommendation for adults as an agent for procedural sedation.16 In addition, the drug is relatively safe as a class B medication in pregnancy.17

Ketamine has multiple routes of administration including IV, IM, intranasal, oral, and rectal.15 Intranasal administration has reportedly been effective for pediatric procedural sedation.23 This route is often overlooked in a crisis situation and may reduce risk to the provider through inadvertent injury and disease transmission via needle stick from a delirious patient.

Unlike the typical antipsychotics, ketamine has no associated dysrhythmia other than tachycardia. Symptomimetic effects including tachycardia and hypertension are thought to be secondary to inhibition of catecholamine reuptake.24 Although elevated blood pressure is a concern, it is usually transient and returns to baseline within 15 minutes after administration.18 An increase in myocardial oxygen demand has been attributed to ketamine, but achieving rapid sedation of a patient is likely to reduce metabolic rate in the setting of violent agitation.

Recently, there has been an increased acceptance for use of ketamine among patients at risk for intracranial injury. Increased intracranial pressure was previously considered a relative contraindication, but ketamine likely does not cause a significant increase and may even be favorable to maintain cerebral perfusion pressure.25 If agitation is suspected from a traumatic head injury, ketamine is now a fair alternative to other agents.

In the past, there has been a concern for increasing intracranial pressure with ketamine use. Drayna et al26 demonstrated a lack of significant elevation among 25 pediatric patients aged 7 to 17 years who received less than 4 mg/kg of ketamine for procedural sedation. Most recently, Wadia et al27 reported transient IOP elevation of 5 mm Hg or greater with ketamine administration of 0.5 mg/kg per minute in children aged 8 to 18 years. The subjects in both studies had non–ocular-related complaints, and therefore, the findings are of unknown clinical significance. At this time, it would be wise to strongly consider alternatives to ketamine for use in the setting of ocular trauma until further studies elucidate this question.

Airway concerns are rarely clinically significant when ketamine is used for pediatric procedural sedation and typically respond to simple repositioning. The most dreaded airway complication of ketamine utilization is laryngospasm. This is a rare occurrence, with 1 source citing 0.02% of cases requiring intubation.2 A case series of 1022 ketamine administrations for pediatric procedural sedation by Green et al1 reported complications including laryngospasm (4), apnea (2), and respiratory depression (1), none of which required intubation. One case of laryngospasm after prehospital ketamine administration was successfully managed with positive pressure ventilation.28 During ketamine use to control violent agitation, we feel that the use of rapid sequence paralysis and endotracheal intubation to treat rare instances of refractory laryngospasm would be an acceptable treatment approach.

NMDAR is likely to have a physiochemical role in psychosis and schizophrenia. Caution has been advised when administering ketamine to patients with known schizophrenia25 as there is concern that ketamine may exacerbate schizophrenic symptoms. We do not advocate ketamine as a treatment for schizophrenia, but in the undifferentiated agitation and delirium that is a life-threatening emergency within the ED, ketamine has several clear benefits to allow situational control and the subsequent administration of goal-directed therapy.

CONCLUSIONS We report 5 cases of the use of ketamine for “chemical restraint” of agitated patients, aged 14 to 18 years, within an ED setting. In three of the cases, clinicians felt that initial therapies with benzodiazepine or butyrophenone drugs had been suboptimal, and in each of the 5 cases, the clinicians were satisfied with the ketamine result. Rapid control of extreme agitation is paramount as excited delirium is a precarious condition that places patients and providers at risk.

Appropriate medications for chemical sedation include benzodiazepines, antipsychotics, and dissociative agents.22 The early use of sedating or dissociative medications could be lifesaving in cases of excited delirium.2 Ketamine, as a dissociative agent, may be an alternative consideration for the control of agitation in patients with undifferentiated excited delirium.

REFERENCES

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