The Myths of Uncontrolled Emergence Reactions
and Consideration to Stop Mandatory, Protocolled Midazolam Coadministration With Ketamine

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ABSTRACT

Ketamine continues to demonstrate its utility and safety in the austere and prehospital environment, but myths persist regarding the frequency of behavioral disturbances and unpleasant reactions. These myths have led to protocollc midazolam co-administration. Properties of midazolam and other benzodiazepines have the potential to cause significant morbidity and potential mortality. Because of this risk, benzodiazepines should only be administered when the treating provider determines that the patient’s symptoms warrant it. We also present evidence that agitation and altered mental status (AMS) encountered with ketamine occurs during titration of lower pain control regimens and is much less likely to occur with higher doses. As such, in most prehospital situations, the treatment for this “incomplete dissociation” is more ketamine, not the addition of a potentially dangerous benzodiazepine.

KEYWORDS: ketamine; emergence; midazolam; Versed; dissociation

Introduction

Over the past two decades, ketamine has been used with increasing frequency on the battlefield. Its favorable cardiovascular profile, wide margin of safety, and lack of respiratory depressant side effects make it the drug of choice for battlefield analgesia and anesthesia. However, significant concern remains about ketamine’s potential to cause “emergence reactions.” These undesired psychiatric and behavioral side effects have resulted in prehospital and battlefield protocols, requiring co-administration of midazolam with ketamine.

Concerns over reactions to ketamine are perpetuated in many courses of instruction. These reactions are not unique to ketamine and can occur at any time, not just as ketamine is wearing off. We will review the literature associated with “emergence reactions,” introduce the concept of “incomplete dissociation,” and discuss why midazolam should be only be given in select situations.

Not only is the term “emergence reaction” poorly defined, but these behavioral sequelae can occur prior to complete dissociation with ketamine. Unfortunately, there is a paucity of literature discussing the incompletely dissociated ketamine patient. Additionally, midazolam is not a benign drug, as its cardiovascular and respiratory depressant effects are potentially disastrous in the acutely traumatized patient. Because of all of the above, midazolam should be administered at the discretion of the treating provider when truly needed, and not in a protocolled fashion.

There are two very important lessons for medical personnel that use ketamine in chaotic and austere situations. First, the empirical administration of midazolam with ketamine is not necessary and potentially dangerous. Second, sub-dissociative doses of ketamine may cause behavioral/psychiatric sequelae – most of which are not clinically important. It is the authors’ hope that the evidence presented here will serve as a framework to remove co-administration of midazolam with ketamine from protocolized treatment algorithms.

What Is an “Emergence Reaction,” and When Does It Occur?

This term is poorly defined. Classic emergence reactions occur as anesthesia is wearing off, but unwanted reactions can occur at any time. For the purposes of this paper, we will use the terms “psychiatric/behavioral sequelae.” Psychiatric/behavioral sequelae may occur at any time after administration of any medication that provides sedation, analgesia, and/or anesthesia, and is not specific to ketamine.

For prehospital providers, psychiatric or behavioral reactions to medications are of particular concern. In resource-limited environments, an agitated patient is hard to monitor. Agitation in an ambulance or aircraft puts both the patient and crew at increased risk of crashing. A loud or agitated patient also has the potential to betray tactical position. For the purposes of ketamine administration, we will define behavioral sequelae as any behavior that the treating medic perceives as (1) making care more difficult or (2) putting the patient, medic, or transport team at risk.

Emergence reactions have been described with terms that include unpleasant, giddy, disconnected, floating, agitation,
psychosis, euphoric, disorientation, and altered motor activity, among others. One pediatric study of 745 patients published in 2009 defined “delirium” as a child “who cried on awakening and did not settle easily.” A 2014 Cochrane review of sevoflurane emergence defined emergence delirium (ED) and emergence agitation (EA) under the umbrella of EA, and defined it as “restlessness”, may cause self-injury or may disrupt the dressing or surgical site of indwelling devices. Emergence has also been referred to as post-operative negative behavior (PONB), which includes emergence delirium, discomfort, temperature and pain. In one large pediatric study, where 91% of patients displayed PONB within 15 minutes of extubation, the authors concluded that it is nearly impossible to distinguish between emergence delirium and pain.9

While the definition of EA is unclear at best, the definitions of such reactions in the setting of ketamine are even murkier. In 2011, Green and Krauss found “ketamine-induced recovery reactions are too complex to simply classify as present or absent. Instead, they exhibit a dramatic spectrum of severity while exhibiting a wide and not necessarily proportionate range of patient agreeability. Vivid dreams or hallucinations need not always be feared or avoided.” Furthermore, trying to discern which reactions are clinically important is incredibly difficult, and can be summed up as “what counts as important is difficult to define.”10

Perhaps the largest misconception regarding emergence reactions is that they only occur as a medication is wearing off. This is not certainly the case, as these same reactions can occur during administration or shortly after. In the case of ketamine, we will refer to this as “incomplete dissociation.” A 2006 review of the use of ketamine for nonanesthesiologists noted that dissociation with ketamine is “either present or absent,” and that ketamine “is given as a single bolus . . . rather than as repeated small doses titrated to effect.”11 Increasing military experience with ketamine has taught us that this view of the dissociative state is incomplete.

Ketamine is frequently given in lower doses to control pain, often referred to as “analgesic dose” or “subdissociative” ketamine. However, some patients enter into a state of “incomplete dissociation” at a lower than expected dose, and there is a paucity of literature discussing this phenomenon. The signs and behavior observed in this state are difficult to distinguish from an emergence reaction. The 2011 American College of Surgeons (ACEP) Clinical Practice Guideline (CPG) acknowledges that “in smaller doses, ketamine exhibits analgesia and disorientation.” This definition is nearly identical to that of emergence reactions.12

In 2015, two papers addressed these phenomena directly. A review of four studies relating to low dose (subdissociative) ketamine use in the ED found that “it was difficult to conclude whether these events were related to dissociation or an emergence reaction.”2 The second study, a review of 500 cases, similarly concluded that “it is now apparent that mild dysphoric effects of LDK (low dose ketamine) occasionally occur with doses lower than what is traditionally considered the dissociative range.”13 This phenomenon was addressed by the military community directly when the Prolonged Field Care Working Group published recommendations regarding ketamine dosing. They similarly acknowledged that emergence reactions can occur in “the mid-range where they’re still awake but agitated and actively hallucinating,” while warning to “decide ahead of time if you’re going high or low, but don’t get stuck in the middle.”15

Are Abnormal Behavioral Reactions Unique to Ketamine?

No. Volatile gas anesthetics (VGA) and other medications are well-known to cause similar symptoms. An extensive literature review in 2015 noted emergence reactions with all general anesthetics, and reiterated the current lack of understanding of the phenomena.4 A 2014 Cochrane review was completed specifically to study which medications and strategies could reduce sevoflurane emergence agitation in children and several other studies over the past several years have evaluated strategies to combat VGA emergence phenomena in children.8,16–26 However, these studies generally reach the same conclusion – that emergence phenomena occur across the spectrum of analgesic, sedative, and anesthetic medications.

Perhaps surprisingly, even benzodiazepines can cause agitation and delirium in what is defined as a “benzodiazepine paradoxical reaction.” A case report demonstrated a 27-year-old woman undergoing MRI who became increasingly more agitated with repeated doses of midazolam intended for anxiety. Her agitation resolved with administration of propofol.27 A similar case report of a 4-year-old girl who received oral midazolam to facilitate closure of a facial laceration demonstrated the same phenomena, which resolved with flumazenil administration.28 In 2004, a review of 38 cases of paradoxical reactions to midazolam in adults was published, the majority of which resolved with the administration of either an alternative sedating medication or flumazenil.29 One anesthesia study of emergence reactions that did not involve ketamine found that “preoperative benzodiazepines is a significant risk factor for emergence delirium in the PACU. Use of benzodiazepines before surgery nearly doubled the risk of emergence delirium.”30

Interestingly, ketamine is sometimes used to treat emergence reactions from VGA, and has shown efficacy in limited published studies.4,13,28 In one recent study, children undergoing VGA sedation were pretreated with ketamine or midazolam. When comparing these two medications in their ability to prevent significant emergence reactions, ketamine significantly outperformed midazolam, with no incidence of emergence reactions.31 In another study of patients undergoing rhinoplasty, pretreatment with ketamine decreased the incidence of emergence agitation fivefold.32 Ketamine has similarly demonstrated success in patients with prior emergence reactions from propofol sedation.30 It is common practice in emergency departments and prehospital settings to treat severe agitation secondary to nearly any organic or inorganic cause with ketamine, as its general lack of respiratory depression and low side effect profile make it an ideal drug for this use.33–35

What Is the Danger in Coadministering Midazolam With Ketamine?

Cardiovascular collapse and respiratory depression. Ketamine is favored in remote and austere locations due to its favorable hemodynamic profile and its lack of respiratory depression. Its ability to provide everything from analgesia to complete dissociation without compromising respiratory drive makes it
an excellent choice in environments in which constant monitoring can be difficult. Benzodiazepines, specifically midazolam, on the other hand, are well known for their sometimes profound respiratory depression, a phenomenon that has been well documented for nearly forty years. As such, administering midazolam to prevent a potential reaction to ketamine negates the advantages of ketamine and makes its administration less safe.

A plethora of data exists regarding the risk of apnea when benzodiazepines are co-administered with ketamine. In a case series of 266 pediatric patients who were randomized to ketamine versus ketamine and midazolam, the risk of oxygen desaturation increased by 6% in the ketamine plus benzodiazepine group, with no difference in emergence events. Similarly, in a case series of 210 procedural sedations with ketamine as the primary agent, patients who received ketamine alone had no documented cases of apnea, while patients sedated with a benzodiazepine had a documented apnea or hypoxia rate of 12%. While there was a 19.5% rate of emergence phenomena in the ketamine only group, the reaction was most commonly described as a “vivid dream that was not disturbing.”

The same trends exist in military data. In 2014, a retrospective case series of nine patients who received ketamine for combat wounds was published. Four of the nine patients were also given midazolam. One of these four patients was given midazolam with each dose of ketamine and had an episode of apnea that resolved with mild painful stimuli. No episodes of behavioral changes or emergence of clinical or tactical concern was documented despite some individuals receiving up to 450mg of ketamine. During a prolonged evacuation scenario in Africa, a patient who initially received oral transmucosal fentanyl citrate (OTFC) then received midazolam prior to administration of ketamine. While in flight, the patient was noted to have decreased respiratory effort and oxygen saturations, necessitating the administration of flumazenil. No behavioral changes or safety concerns after midazolam reversal were documented. A second patient in this multiple-patient scenario was documented as having “delirium” after 100mg of ketamine was delivered intramuscular (IM) but was also documented as being compliant with placement of two peripheral IV lines without the need for further medication administration.

Conversely, a systematic review of ketamine use on the battlefield published in the *Journal of Trauma and Acute Care Surgery* confirmed the safety and efficacy of ketamine when used alone. Data from over 2000 causalities given ketamine from 2000 to 2019 demonstrated that the majority of side effects described after ketamine administration were “extreme movements and incoherent speech.” Despite nearly 20% of injured patients receiving ketamine towards the end of this study period, versus only 3.9% during the early portion, which is a significant increase due to updated guidance from the Committee of Tactical Combat Casualty Care in 2012, the incidence of adverse events did not increase.

**Are Psychiatric Reactions to Ketamine More Frequent and Severe in Adults?**

No. Concerns about the severity and frequency of reactions from ketamine are exaggerated. The authors have extensive experience with the administration of ketamine in numerous situations, at all dosing strategies, and from point of injury through surgery to postoperative care. Even when using the original ketamine (called CI-581), researchers in 1964 observed “frank emergence delirium was minimal. Most of our subjects described strange experiences like a feeling of floating.” When reactions did occur, they were easily treated “by coma-producing drugs.”

Several papers have been published on the frequency of reactions to ketamine, but the results are unreliable given the broad and inconsistent definition of emergence reaction. The British military first published a review of battlefield ketamine use in 1972. In 75 patients, without the addition of a benzodiazepine, “side effects were neither common or serious.” Over half of the side effects noted in this study were vivid dreams, with no serious reactions despite doses as large as 22mg/kg. A similar review of 70 cases of ketamine plus midazolam administration published in 2000 found that 7% of patients reported emergence reactions despite co-administration of a benzodiazepine. Similar studies have demonstrated that while “dreaming” is a common consequence of ketamine administration, these dreams are often described as pleasant or nondisturbing.

While much has changed over nearly 60 years of ketamine use, fear of ketamine-specific emergence reactions remains. A 2015 review of emergency department use of ketamine in adults concluded that “historically, the reluctance to use ketamine in adults was because of an increased rate of emergence reactions, but the severity of these reactions may have been overstated.” This fear is likely perpetuated by multiple studies that cite instances of emergence agitation that are of questionable clinical significance. One such study was published in *Annals of Emergency Medicine* in 2011. This study assessed the occurrence of “recovery agitation,” a phenomenon that was incompletely defined, and the ability of midazolam to reduce its occurrence. Recovery agitation was noted to be either present or absent, which was addressed as a study limitation as “minor transient restlessness or a soft moan may have been thus coded as positive.” In this study, midazolam reduced recovery agitation from 25% to 8%, with a number needed to treat of six. The supervising editor of this article discussed this further, noting that the number needed to treat is likely higher given the subjective nature of evaluating emergence agitation.

**Is Ketamine Safe Given to Patients With Preexisting Psychiatric Disease?**

Yes. Although “known or suspected schizophrenia” is listed as one of only two absolute contraindications to ketamine use in the ACEP 2011 CPG, this is likely more opinion than fact. More recent guidelines from this same body highlight ketamine’s “excellent safety profile”. A 2020 joint position statement from the American College of Emergency Physicians, American College of Surgeons, and multiple EMS governing bodies states that “ketamine does not appear to increase the incidence of psychosis” in patients with known schizophrenia. It further highlights ketamine’s unique and impressive safety profile in trauma patients in hemorrhagic shock or at significant risk of respiratory compromise.

A small case series of psychiatric patients from the psychiatry literature also highlights ketamine’s safety in this population. In this case series, the patients were so acutely agitated that,
without ketamine, intubation would have been required for the safety of crew and patient. Most had a primary diagnosis of exacerbation of schizophrenia, were transported via air safely on ketamine, and were followed for 72 hours after admission to inpatient psychiatric units. None had worsening psychiatric symptoms upon awakening from ketamine dissociation. A larger and more recent prehospital case series of 52 patients sedated with ketamine for excited delirium also found ketamine to be safe and effective.52

Most recently, a retrospective cohort study was published in 2019 comparing IM ketamine to an IM benzodiazepine for prehospital agitation in patients with known psychiatric disease.53 The authors found that there was no difference in psychosis, psychiatric evaluation, or admission to a behavioral health facility between the two groups. However, there was however a difference in hospitalization, with patients given IM benzodiazepines requiring medical admission 63% of the time versus only 3.8% of ketamine patients. This was due to significant airway compromise in the IM benzodiazepine group, with no instances of airway compromise in patients given ketamine.

Interestingly, patients on psychiatric medications may actually have higher rates of emergence reactions when benzodiazepines are administered. One large study of 1359 adults reported “preoperative medication by benzodiazepines is a significant risk factor for emergence delirium in the PACU. Use of benzodiazepines before surgery nearly doubled the risk of emergence delirium.”56

Does Ketamine Worsen Posttraumatic Stress Disorder (PTSD)?

No. Ketamine has been used safely in patients with both acute and chronic PTSD. Burned Servicemembers who underwent surgery at the USAISR and received ketamine had lower PTSD scores compared to those who did not receive ketamine. This occurred despite patients in the ketamine group having total body surface area percentages, injury severity scores, total intensive care unit days, and number of operative interventions twice that of the no-ketamine group.57 The results of a larger follow-up study from the same institution again demonstrated no increase in PTSD symptoms in the patients who received ketamine.58 A recent retrospective study from France of patients who received ketamine on the battlefield demonstrated that ketamine does not increase the risk of development of PTSD in this patient population.59 Furthermore, ketamine has even been used in patients with PTSD and known prior emergence reactions to general anesthesia. Two patients with PTSD and a history of emergence reactions were anesthetized with different regimens in an attempt to avoid recurrence of emergence agitation. The adult given midazolam and propofol had “severe emergence delirium” and the elderly female given ketamine and had no side effects.60

Not only is ketamine safe in this patient population, but there is an increasing popularity in the psychiatry community regarding the potential benefits of ketamine in patients with severe, refractory PTSD. PTSD has been linked to 3,4-methylendoxymethamphetamine (MDMA) receptor overactivity making ketamine, a medication that works directly to inhibit MDMA receptors, a logical choice.61 Early human studies show this theory to be promising. In one study, patients with “moderate to severe PTSD symptom levels” were enrolled in a randomized, double-blind, crossover trial of ketamine 0.5mg/kg compared with midazolam 0.045mg/kg over 40 minutes to treat PTSD. Dissociative symptoms were observed but not described in the results, however “no emergence of significant psychotic or manic symptoms was observed.” The patients were followed for 7 days after medication administration and the authors concluded that a single dose of ketamine significantly reduced PTSD symptoms.62 In 2012, three experienced military certified registered nurse anesthetists with a combined 14 deployments to Iraq and Afghanistan voiced a strong preference for ketamine total intravenous anesthesia (TIVA) with military personnel who had or were at risk for PTSD/traumatic brain injury (TBI) to reduce risk of emergence reactions.63

Which Strategy for Midazolam Administration With Ketamine Is Recommended?

The “PRN strategy” should be used. Midazolam should only be given if the patient is hemodynamically stable, no longer bleeding, and continued ketamine administration is no longer required for the medical care of the patient. In a 2008 extensive literature review, three strategies were presented.11 These included “predisassociation strategy” (sedative agent before ketamine administration), “preemergence strategy” (sedative agent shortly before emergence) and “PRN strategy.” We agree with the authors of this paper who recommended the PRN strategy due to decreased risk of respiratory depression and shorter recovery time.11 Other recent literature supports the PRN strategy as well. In a case series of 52 agitated patients controlled with ketamine in the prehospital environment, half received midazolam prior to hospital arrival for prevention of emergence. In this series, 12% of patients who received preemergence midazolam experienced “significant” respiratory depression (one required bag-valve mask use and two required intubation). No cases of respiratory depression were noted in the ketamine-only group. Although a protocol violation, many medics often did not administer midazolam “due to the excellent sedation routinely achieved by ketamine alone.” The authors concluded that “this suggests that further sedation with a benzodiazepine could potentially be delayed until hospital arrival.”65

The PRN strategy is effective and prehospital medics have demonstrated an ability to execute this strategy safely. In a case series discussing the British protocol, simultaneous administration of midazolam and ketamine is specifically avoided due to the risk of respiratory compromise.66 Midazolam is administered only when “aggression or agitation” was noted during recovery from ketamine. In a report of 32 patients who received prehospital ketamine in Britain, no cases of respiratory compromise were documented in the 12 patients who received midazolam following this protocol.67 In 2013, the Journal of Special Operations Medicine published a review of the use of ketamine to facilitate evacuation in trauma patients. Midazolam was only given with ketamine during transport if the provider judged its administration to be safe. Specifically, “the dose of midazolam was at the request of the emergency department at the primary Role III hospital to help mitigate the possible emergence phenomenon the patient may experience if extubated.”68 In this series, the medics transporting the patients demonstrated a higher comfort level with ketamine than the emergency physicians receiving the patients.

Israeli protocols during prolonged transport promote a similar strategy. In one case series from Israel, 11 severely injured and
agitated multi-trauma patients were given ketamine +/- midazolam at the providers’ discretion. In all 11 cases, ketamine alone was successful, with all patients avoiding intubation or the use of restraints. As such, their current protocol calls for ketamine first and midazolam only if judged to be necessary. Likewise, the Australians are employing a similar approach based on data from a randomized controlled trial in 2012.57

Summary

Ketamine is a safe and effective drug for use in the prehospital, combat, and prolonged field care stages of care. Ketamine possesses a wide margin of safety with both the cardiovascular and respiratory systems. Midazolam is an effective drug for treating agitation associated with incomplete dissociation and emergence. However, midazolam should only be administered after the treating medical provider has performed a careful risk/benefit analysis of both the medical and tactical situation. Strict protocols requiring midazolam administration to prevent agitation are not recommended.

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Author Contributions

BD, JS, MC conceived the study concept. HH, BD, AF compiled the evidence and literature review. HH and BD wrote the manuscript. BD, JS, MC, and HH approved the final manuscript.

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