CAN WE FINALLY DISPENSE WITH KETAMINE’S MANY MYTHS?

Joshua Hurwitz, MD

Department of Emergency Medicine, PeaceHealth Southwest Medical Center, Vancouver, Washington
Corresponding Address: Joshua Hurwitz, MD, Emergency Medicine Associates, P.O. Box 1600, Vancouver, WA 98668

INTRODUCTION

I had the opportunity to respond to questions submitted to me by my institution’s peer review committee regarding my care of an agitated, violent patient who received ketamine to control violent behavior and permit evaluation. This was an interesting and complex case. The patient was taken to the emergency department (ED) by paramedics after he jumped from a bridge approximately 30 feet into a river. He presented with mild hypothermia and moderate hypertension and was initially cooperative with the evaluations, including radiological testing and blood draws. After returning from the radiology department (where computed tomography scans proved negative for serious injury), this large, muscular patient leaped from his bed, threatened violence to multiple staff members, exited his room suddenly to attack a staff member, and was tackled to the ground.

Verbal de-escalation failed to calm the patient. It took no fewer than 6 staff members struggling mightily on the floor of the ED hallway to physically restrain this patient before adequate sedation could be obtained and the patient safely returned to his room for additional care. Immediate effective sedation was paramount.

Questions from the peer review committee were addressed as follows.

1. Did you know that ketamine can have adverse effects on hypertensive patients, patients with possible head injury, or patients with psychotic episodes?

HYPERTENSION

In the case under discussion, the patient’s systolic blood pressure climbed from 186 to 220 mm Hg after administration of ketamine. Regarding hypertension, it is well known that ketamine, a phencyclidine derivative, has sympathomimetic effects and results in increases in both heart rate and blood pressure. The literature on complications from ketamine-induced hypertension resulting in end organ dysfunction is sparse. A database search produced one recent case report of a patient with pulmonary edema possibly resulting from hypertension after the administration of ketamine (1). A previous case report purporting to associate ketamine with pulmonary edema may be confounded by concomitant barbiturate withdrawal (2). Conversely, one small study showed no clinically meaningful effect of ketamine-induced hypertension (3). A 2015 study of 27 patients receiving ketamine to treat agitation showed an average increase in systolic blood pressure of 17 ± 25 mm Hg (4).

The 2011 Clinical Practice Guideline for Emergency Department Ketamine Dissociative Sedation does not
mention hypertension among its absolute or relative contraindications (5). A study involving 70 adult patients with baseline blood pressures up to 218/109 found no clinically important effects of ketamine with regard to hypertension. The authors report that “[a]ll changes in blood pressure and heart rate were transient, and did not necessitate intervention” (6).

I have used ketamine in a variety of clinical scenarios and have found the increase in blood pressure associated with this medication to be moderate at worst and without end organ dysfunction. Some authors feel it is contraindicated in uncontrolled hypertension. While I respect the hemodynamic effects of this medicine and generally try to avoid it in patients with highly elevated blood pressure in the ED, I do not hesitate to use it when other agents are comparatively suboptimal. The argument could be made that I might have better managed this patient’s postketamine hypertension with more aggressive antihypertensive therapy. I happened to choose labetalol and hydralazine, and these interventions appeared to have the intended effect.

I would be eager to review the available literature ascribing harmful blood pressure effects to ketamine if quality data has skipped my attention. If good evidence exists, it would benefit myself and the ED as a whole to craft evidence-based parameters around the safe use of ketamine in hypertensive patients, with cutoff blood pressure values beyond which it should not be used. In the absence of such literature, I would advise continued use of it in the setting of hypertension as directed by clinician judgement.

**HEAD TRAUMA**

The contraindication to ketamine in the setting of head trauma has been thoroughly debunked in modern literature. Data from the 1970s showing increases in intracranial pressure in patients with nontraumatic brain lesions were extrapolated to head trauma, resulting in the belief that ketamine will cause clinically adverse effects in the traumatized brain. These case reports and small case-control studies involved atraumatic patients with obstructed cerebrospinal fluid pathways (e.g., hydrocephalus, tumors, etc.) (7). Calculations made recently using data from those early studies show that, in patients with normal cerebrospinal fluid flow, cerebral perfusion pressure actually improves with ketamine (8). Recent data refute the claim that ketamine increases intracranial pressure in head trauma (9).

Indeed, evidence is emerging that ketamine may in fact lower intracranial pressure and was demonstrated in a recent large trial to be equivalent to etomidate during rapid sequence induction for intubation of severely injured trauma patients (8,10–12). Ketamine was shown in another trial to have no adverse effect on cerebral hemodynamics (13). The Annals of Emergency Medicine removed head injury as a contraindication to ketamine in its 2011 Clinical Practice Guideline (5).

Ketamine can safely be used in cases of head trauma.

**PSYCHOSIS**

Regarding psychotic patients, while there is a contraindication to the use of ketamine in patients with a diagnosis of schizophrenia, there is no such contraindication to patients with acute psychosis generally. In fact, in reviewing the literature on the subject I was unable to find any study or case report describing detrimental long-term neuropsychiatric effects of dissociative sedation using ketamine in patients with schizophrenia or psychotic patients in general. Studies appear limited to subdissociative (i.e., “semiawake”) dosing, and these tend to demonstrate a brief, self-limited exacerbation or production of psychotic symptoms in both schizophrenic and normal volunteers, and the dose-response profile appears equivalent (14,15).

I avoid using ketamine in patients known to have schizophrenia, but have found it useful and without untoward effects in acutely agitated psychotic patients. The Annals of Emergency Medicine’s 2011 Clinical Practice Guideline advises caution when using ketamine in undifferentiated psychosis based on the Lahti et al. article cited above, and I do take care to weigh the risks and benefits of this agent when selecting it for use in the agitated patient (15). However, in the severely agitated, frankly violent patient requiring immediate sedation to prevent harm to themselves or others, it is superior to other alternatives, as will be discussed below. In fact, ketamine as an intervention to chemically restrain the acutely agitated patient has ascended to first-line treatment for many clinicians (16,17).

2. Did you consider other sedatives in this hypertensive, combative patient with the potential for head injury given the mechanism of injury?

This was a case of an extremely violent patient requiring immediate sedation to prevent harm to staff and the patient himself. In my experience, common alternative parenteral agents, such as haloperidol, olanzapine, ziprasidone, and the various benzodiazepines, act too slowly to be of optimal benefit when a violent patient cannot be redirected and, in my estimation, is likely to require intubation because of agitation. Time to onset and dose requirements of agents such as lorazepam and midazolam are too variable and require patience and titration to achieve a satisfactory effect while avoiding the dangerous respiratory sequelae of high-dose benzodiazepines.
Olanzapine can only be used via intramuscular or oral routes, and time to onset is too slow in the violent patient. Ziprasidone requires cumbersome mixing and can also only be given intramuscularly or orally. Haloperidol may be used intravenously, but with an attendant risk of QT prolongation. In general, I prefer to avoid large doses of haloperidol in severely agitated patients because latent QT prolongation or comorbid effects of cocaine or other drugs can trigger torsade-de-pointes and result in cardiac arrest. In addition, haloperidol must often be titrated to effect because of its narrow therapeutic window.

Another drawback to haloperidol is its extrapyramidal effects. Haloperidol alone can produce dystonia, complicating or preventing appropriate sedation. In practice, extrapyramidal symptoms are routinely averted with the coadministration of diphenhydramine (18). The “B52” (Benadryl 25–50 mg, haloperidol 5 mg, and lorazepam 2 mg intramuscularly) is a common cocktail used to effect behavioral control in acutely agitated patients, and one that I use regularly in appropriately selected patients. A variation of this cocktail includes olanzapine 10 mg and lorazepam 1 to 2 mg. Indications for the use of this cocktail in my practice include patients with whom verbal de-escalation has failed and who require sedation because of uncontrolled agitation, often as a means to permit physical restraint. Most of these patients are not frankly violent, though they may threaten violence, and time may be taken to monitor the patient for effectiveness of the intervention and titrate further dosing as needed.

The case in question involved an extraordinarily violent patient who, in my estimation, would not tolerate physical restraint without a high risk of injury to himself or others and required paralysis and intubation to permit safe care and further diagnostic studies. Rapid sedation was critical. A single agent capable of chemically restraining the patient within a couple of minutes was essential. I chose ketamine because it is safe to use in this circumstance, generally requires a single dose to be effective, and has a faster onset than most alternatives. The published literature bears this out, demonstrating ketamine’s favorable time to onset as compared to other agents. Cole et al. in particular showed ketamine’s time to adequate sedation (intramuscularly) was 5 min compared to 17 min for haloperidol (16).

Other medications used for this purpose have been described. Droperidol was for years considered by many to be the ideal agent, but unfortunately it is no longer readily available. Propofol’s effects on respiratory drive are too variable to be considered safe in this setting. The same is true of etomidate. Dexmedetomidine may be a viable alternative agent, but a literature basis demonstrating its safety in the setting of violent agitation has not been published.

I will allow that research on the safety of ketamine for rapid sedation of the violent, acutely agitated patient is in its formative stages. Studies such as that of Isbister et al., who reported on sedation by ketamine as a rescue agent after failure of other measures, primarily droperidol, lend credence to the position that ketamine’s role in the sedation of acutely agitated patients is justified (19). Yet there are no prospective randomized, controlled trials establishing ketamine’s superiority in this setting. The 2017 American College of Emergency Physicians Clinical Policy regarding management of acutely agitated patients states that “ketamine is one option for immediate sedation of the severely agitated patient who may be violent or aggressive,” but notes that the best literature on the subject is derived largely from prehospital studies rather than those performed in EDs. The Clinical Policy goes on to mention ketamine’s well-known adverse effects, primarily vomiting, laryngospasm, emergence reaction, and hypersalivation (20). While I respect these effects, it seems prudent to use ketamine in light of them when resources allow for close monitoring and, if needed, paralysis, intubation, and continued sedation. In the case at hand, the plan included these latter measures at the outset of the intervention.

I acknowledge the literature’s limitations and look forward to a multicenter randomized, controlled trial evaluating ketamine in comparison to the alternative agents mentioned above. In the absence of such studies, practitioners must rely on available data, expert opinion, and anecdotal experience to guide practice. Such is the case with a number of interventions in the emergency department; parallels can be made to the use of epinephrine in cardiac arrest, for instance.

Another objection to ketamine in the setting of acute agitation may be that, while it may result in sedation, it does not treat the underlying mental illness. Allusion to this deficiency is made in the American College of Emergency Physicians Clinical Policy cited above. Yet while it is true that ketamine does not treat psychosis, in the case of severe agitation requiring immediate sedation, when the purpose of the intervention is to control behavior rather than treat the underlying psychiatric disorder, the primary emergency needing treatment is agitation, not psychosis. The objection that alternative agents are superior because ketamine does not treat psychosis is misplaced in this context. Once safety has been achieved for the patient and staff caring for him, attention may then be turned to the treatment of the underlying mental illness.

Ketamine acts quickly, has a wide safety profile over a range of doses, can be used by a variety of routes, generally preserves respiratory drive, and facilitates the care of patients while emergent preintubation measures are implemented. In the combative, head-injured patient who
requires immediate sedation, ketamine is a superior alternative to other commonly used sedatives.

3. How would you manage a similar patient in the future?

I would use ketamine.

REFERENCES