The Benefits of Ketamine in the Prehospital Environment by Appropriately Trained Professionals

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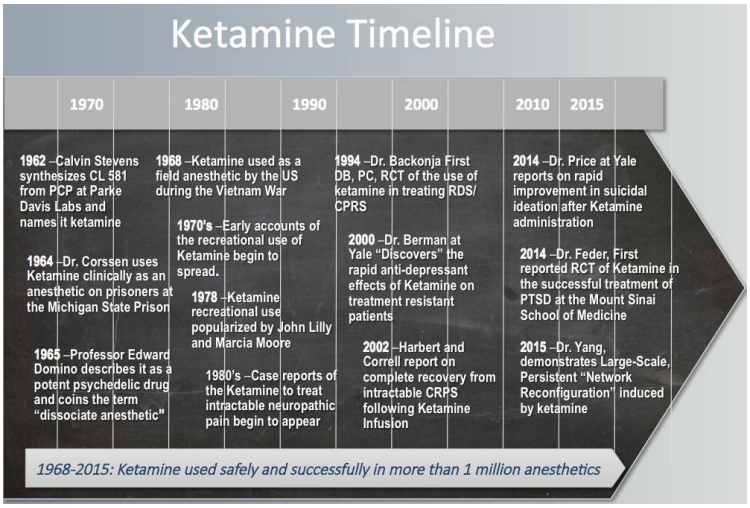
Introduction

First introduced in the 1960's as an alternative to PCP for anesthesia during the treatment of battlefield injuries, Ketamine's reputation as a safe and effective drug has gone through many evolutions. Demonstrating potent analgesic, sedative, and amnestic properties all the while preserving respiratory drive, airway reflexes, and hemodynamics, Ketamine has been used all over the world in regions underserved by a modern healthcare system to facilitate the administration of painful and distressing care. It has only been in the last 10 to 20 years that Ketamine has started to gain popularity as a viable treatment option for emergency room physicians in the US. However, concerns over adverse reactions stemming



from research conducted in the 1960's and 1970's have slowed its adoption into mainstream prehospital treatment protocols.

Since the 1970's, Ketamine as been the subject of numerous studies and retrospective reviews evaluating it's use in both the pediatric and adult populations. Consistently, this research has demonstrated the safety and effectiveness of Ketamine for the management of a wide variety of condition in both populations. Here we'll discuss the various properties of Ketamine and it's application to the treatment of patients outside of the Emergency Department.

Ketamine Overview

Ketamine works primarily as a non-competitive NMDA receptor antagonist within the central nervous system. The NMDA receptor is one of the chief neurotransmitter receptors in the brain responsible for basic brain activity and for creating memories. In dissociative doses, between 1-2mg/kg IV and 3-4mg/kg IM, blocking of the NMDA receptor creates a "trancelike state of sensory isolation," essentially disconnecting the patients brain from external stimuli, while "preserving spontaneous respirations and protective

airway reflexes." The patients brain simply can not detect external sensory stimuli such as pain or light, nor can it create memories. It is by this mechanism that the drug provides analgesia sedation.

Ketamine can also be given in sub-dissociative doses of .3-.5mg/kg IV or <3mg/kg IM for analgesia and mild relaxation, however, according to Green et al, IM administration of sub-dissociative doses of Ketamine have demonstrated higher incidents of emergency reactions. It is believed this is due to a lack of full disconnect of the brain from external stimuli while still producing a hypnotic state resulting in inappropriate interpretation of sensory input. IV administration of sub-dissociative doses of Ketamine has not demonstrated a similar increase in emergency reactions and is considered safe and preferable over IM administration in the adult patient.

In addition to providing reliable analgesia and sedation, Ketamine also exhibits sympathomimetic properties producing an slight increase in blood pressure by enhancing the transmission of dopamine and norepinephrine and blocking dopamine uptake. In the normotensive patient this effect has shown no increased risks, and in the hypotensive patient, or the parent at

risk for hypotension, this catecholamine effect helps guard against the iatrogenic effects of hypotension in the critically ill patient. However, despite supporting evidence, the American College of Emergency Physicians has recommended Ketamine be avoided in patients with “known or possible coronary artery disease, congestive heart failure, or hypertension” for fear of increased oxygen demand and further cardiac injury resulting from the hyperdynamic state.

One of the most controversial arguments surrounding Ketamine is the potential negative impact on patients with elevated ICP’s associated with trauma or stroke. Critics claim that the increase in sympathetic tone caused by Ketamine can cause an increase in ICP to potentially dangerous level. While some studies have shown a slight

Ketamine for intracranial hypertension

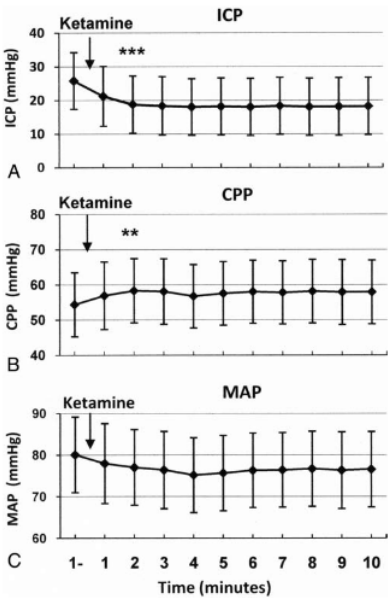


FIG. 1. Graphs showing ICP (A), CPP (B), and MABP (C; MAP) responses to ketamine administration in the entire study population (30 patients, 82 events). Intracranial pressure decreased by 30% within 2 minutes of ketamine administration. **p < 0.005, ***p < 0.001.

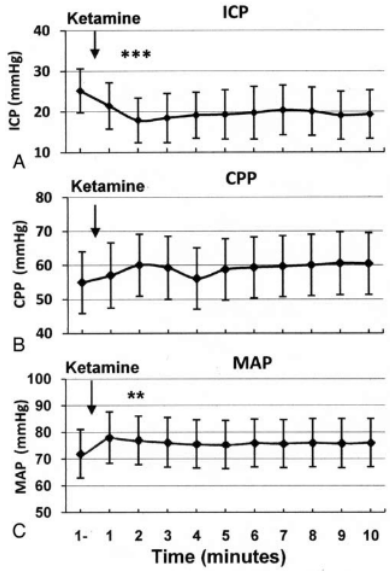


FIG. 2. Graphs demonstrating ICP (A), CPP (B), and MABP (C) responses to ketamine administration before a potentially distressing intervention in patients with intracranial hypertension (17 events, Group 1). Intracranial pressure decreased by ~ 20% within 2 minutes of ketamine administration and did not increase during the intervention. **p < 0.005, ***p < 0.001.

increase in ICP associated with Ketamine use, these studies also demonstrated a preservation of blood pressure and an increase in Cerebral Blood Flow. Furthermore, a number of studies have demonstrated either stable ICP's or an actual decrease in ICP in properly ventilated patients who received Ketamine. No studies have demonstrated an increase in risk associated with Ketamine's use in patients with elevated ICPs associated with trauma or stroke. These findings have reasonably refuted the idea that Ketamine use is detrimental to patients with non-obstructive elevated ICP's and has prompted the American College of Emergency Physicians (ACEP) to remove Head Trauma as a contraindication from their Clinical Practice Guidelines for Ketamine.

Unlike more traditional medications used for sedation and analgesia in the out of hospital environment such as Fentanyl, Versed, or Propofol that have a tendency to cause respiratory and hemodynamic collapse at higher doses, the effects of Ketamine does not increase along a traditional sedation or analgesia continuum. Once a patient is dissociated, further increased in dose only serve to prolong the duration of the medication but does not induce a greater level of sedation or pain relief. When a prolonged

period of sedation is desired, Ketamine may be administered as a continuous infusion. Furthermore, even in large dissociated doses of 2-3 mg/kg given slowly over 30-60 seconds, a patients respiratory drive and airway relax is preserved. This characteristic of Ketamine improves safety and ease of delivery by minimizing the risk of hypoventilation and aspiration while allowing providers to confidently deliver an effective dose without the need to worry about titration during a crisis situation.

Finally, in recent years Ketamine has been shown effective in the treatment of Refractory Status Epilepsy (RSE). Early in the progression of seizures, stimulation of inhibitory y-aminobutyric acid receptors on the surface of CNS cells is thought to disrupt seizure activity. Medications like benzodiazepines and propofol work by activating these specific receptors. However, as a seizure progresses these inhibitory receptors are translocated into the nerve cells and excitatory NMDA receptors are moved out to the surface of cell membranes. This redistribution of receptors seems to account for the decrease in responsiveness to standard seizure treatments the longer a seizure lasts. In the laters stages of RSE, Ketamine has been effective in terminating seizure activity, presumably due

to it's NMDA antagonist properties, and while there has yet to be any randomized control trials investigating Ketamine for the treatment of RSE, there is an abundance of pre-clinical evidence supporting it's effectiveness.

Pre-Hospital Application

Here's what we know about Ketamine:

- Ketamine reliably produces both analgesia and sedation.
- Ketamine can be effectively administered either IV or IM, or as a continuous infusion by trained providers.
- Ketamine can be delivered quickly and safely without the need to "titrate to effect."
- Ketamine can be used without the risk of respiratory collapse when administered appropriately.
- Ketamine can be given to patients with elevated ICP from trauma or stroke without concerns of further increase in ICP assuming the patient is adequately ventilated.
- Ketamine can be used as an effective treatment option for seizures refractory to standard first line medications.

Ketamine Dosing Response Curve		
Dose Classification	IV Dose	Special Notes
Analgesia Dose	0.1 - 0.3 mg/kg	Pain well controlled. No effect on perception or motion.
Recreational Dose	0.2 - 0.5 mg/kg	Pain controlled. Pt can talk, understand, and know what's going on. Pt is awake, but is STONED. Not what you want.
Partially dissociated	0.4 - < 1 mg/kg	Some are awareness, but not connected to body, world, or reality. Many can't talk or move, but are aware. Can be terrifying. This Is BAD. Can Freak out. Don't Go here. This is not where you want you're patient.
Full Dissociation	2-3mg/kg 1mg may not be enough in many patients and may be a partially dissociated dose	Complete isolated form external stimuli. Do not build memories Random movements common. Cardio and respiratory systems remain intact.

Amazing Podcast about Ketamine: SMACC - Ketamine: How to Use it Fearlessly For All its Indications by Reuben Strayer

Dr. Ruben Strayer's blog post on Ketamine: The Ketamine Brain Continuum

How can I apply this to my practices as a prehospital provider?

One of the riskiest skills we preform as prehospital providers is endotracheal intubation, especially in the hemodynamically compromised

patient or conscious patient with impending respiratory collapse. The ability to manage a patients airway without further compromising their safety using traditional medications can be tricky. Likewise, waiting for someone to decompensated to the point of necessitating a crash airway is just bad practice. Ketamine can be used as a pre-induction agent to help facilitate pre oxygenation and nitrogen washout with uncooperative patients, can provide some bronchodilators effect to the crashing asthmatic, and can improve the safety of performing RSI in the hypotensive, or potentially hypotension, patient. While Ketamine can not eliminate all the risks associated with airway management, it's unique properties certainly can help minimize certain risks.

As a critical care provider, you'll frequently be called upon to transport patients being mechanically ventilated from one facility to another who are sedated on a medication like Propofol or Versed. These are great medications for inside the hospital where the amount of stimulation can be minimized, but put that same patient into the back of an ambulance or aircraft subjecting them to all the stresses of transport and you'll see that they frequently require higher doses of medication to maintain an adequate

level of sedation. As you titrate up their medications you run the risk of compromising their hemodynamics. Ketamine can eliminate this problem by providing isolation from external stimuli and providing adequate analgesia and hemodynamic stability minimizing the risk of drug induced hypotension.

We've all had that patient who, for one reason or another, is presenting a danger to themselves or others and needs to be sedated. Maybe their withdrawing form drugs or alcohol. Perhaps their a combative diabetic in crisis. Or perhaps they in liver failure with hepatic encephalopathy. You gain enough physical control over them to be able to administer an IM dose of your favorite benzodiazepine, and then it happens. They stop breathing. While in most cases this can be easily managed with simple BVM ventilation and intubation, we've unnecessarily subjected our patients to the risks associated with advanced airway management. With few exceptions, Ketamine can be used to safely and effectively manage the combative patient without the risk of respiratory collapse.

Much of what we do in prehospital medicine is unpleasant for patients: extricating someone with multiple fractures from a vehicle, applying a pelvic binder, reducing a femur fracture, placing chest tubes, performing a surgical airway, placing an IO in a 3 years old. All of these scenarios can be extremely painful and distressing causing profound discomfort for an awake individual. Ketamine, with all of it's properties listed above, has been shown to improve patient comfort and satisfaction, minimize procedural complications, and help facilitate rapid execution of distressing procedures by trained health care providers.

Finally, the definition of a status seizure is one that lasts greater than 5 minutes without cessation or return to baseline mental status. It is well established that the longer a patient seizes, the greater the chance of them suffering permanent neurological damage. The goal for any provider is to terminate a seizure within the first 30 minutes from onset. Beyond 30 minute, it's believed permanent damage starts to occur, and seizures become more refractory to standard treatment options.

According to the National EMS Information System (NEMSIS), the national average time for EMS responders to arrive at the hospital from the time

National EMS Information System (NEMSIS Data)

Average EMS Response Times, Scene Times, and Transport Times (911 Response Only)

Exported from NEMSIS data cube 3/22/2012 (years 2010 & 2011) - www.nemsis.org

Definitions:

Avg EMS Response Time in Minutes: Time from Unit Notified by Dispatch to Unit Arrived on Scene
Avg EMS Scene Time in Minutes: Time from Unit Arrived on Scene to Unit Left Scene
Avg EMS Transport Time in Minutes: Time from Unit Left Scene to Patient Arrived at Destination

Urbanicity* Region:

(All)

	Pediatrics Overall (0-18 years)	*Adults Overall (19-100+ years)*
Avg EMS Response Time in Minutes	9.2	9.4
Avg EMS Scene Time in Minutes	12.6	14.9
Avg EMS Transport Time in Minutes	11.7	12.2
TOTAL COUNT OF EVENTS (N)	1,200,111	12,672,842

they are dispatched is 35 minutes. Based on these numbers, it's up to prehospital providers to terminate a seizure within that 30 minutes window before permanent damage occurs, and when traditional benzodiazepines fails to work, Ketamine may be a patients only other option.

Conclusion

According to the ACEP Clinical Practice Guideline for Ketamine,

> It is reasonable to assume that all such specialists who are knowledgeable about the unique features of ketamine and whose residency or fellowship training renders them skilled at procedural sedation and analgesia, resuscitation, advanced airway

> management and vascular access can be considered qualified for dissociative sedation…

Doesn't this description from the ACEP guidelines appropriately describe a paramedic? Our entire training is focused on managing emergency situations, providing appropriate analgesia and sedation, resuscitation, managing airways, and gaining vascular assess. It stands to reason then that as prehospital care professionals our managers and physician advisors should be confident in our ability to use Ketamine as a safe and effective treatment option under appropriate circumstances.

The pharmacological profile of Ketamine has been well studied in both the pediatric and adult populations. It's hemodynamic stability, complete and reliable analgesia, sedation, and amnesia, improved cerebral perfusion in patients with traumatic brain injury and increased intracranial pressures, and it's effectiveness in the management of refractory status seizures have been shown to greatly outweigh the minimal risks associate with proper administration of Ketamine by trained medical professionals. It is for these

reasons that I believe Ketamine to be an ideal medication for use in the prehospital environment.

Other Podcasts about Ketamine

ERCast - The Brain on Ketamine

EMCrit - Delayed Sequence Intubation

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