

Ketamine for Pain Management

1049, North Harris County, TX

"Medic 528, respond to sports complex for a traumatic injury..."

You are responding to an athletic field. A teenaged boy weighing approximately 50 kilograms has slipped and fallen onto his extended left arm, sustaining an obvious closed fracture of his distal radius and ulna, with obvious deformity to the forearm. His left wrist has been immobilized by pain, and the entire area is swollen with moderate bruising. Bystanders have improvised a sling. The patient's hand does present with normal circulation, fine motor function and sensation. There are no other injuries. Upon arrival, he complains of pain rated 10/10 to his left wrist described as a constant, sharp stabbing; and denies loss of consciousness or head strike. The patient is very protective of the injury and is reluctant to move it. The patient has no significant medical history, but is allergic to penicillin and potentially morphine.

Considerations

Although this injury can be managed with basic techniques, it may result in permanent debility if it is improperly set or manipulated, and it will hurt a lot. Pain management in this patient is safe and appropriate and will result in a better experience for the patient, a greater value added by EMS and a more favorable public opinion. In many EMS systems, this patient would only receive a BLS response, but bystander first aid has already functionally reached the limit of what BLS is able to do. Realignment is not indicated due to normal circulation and sensation to the hand; and although cold packs can be applied, cryotherapy does not resolve severe pain, and although good splinting is always indicated, EMS can offer far more.

Initial Response

An IV is established in the patient's right antecubital space with a 20-gauge catheter and a maintenance drip of normal saline is established. 50 micrograms of fentanyl is administered over thirty seconds, but the patient's pain remains a 9/10 at rest; an additional 50mcg of fentanyl does not adequately relieve pain (down to 8/10). The patient's arm was splinted with a vacuum splint, but this did not relieve pain. At this point, the challenge is this: this patient has received a cumulative dose of 2 mcg/kg of fentanyl with minimal relief, which *is* within the therapeutic threshold for fentanyl. Despite its minor positive effect on reported pain, this patient is still in considerable pain, and the fentanyl that has been given will begin to wear off in approximately twenty minutes. This means that we will need to redose him to maintain even the level of analgesia that we currently have. In many systems, this introduces an additional challenge in that many EMS protocols are limited to 100mcg of fentanyl or less on standing orders and medical control may be reluctant to order more (for example, most of California). This leaves us facing the prospect of a patient in severe pain for the duration of the transport or needing to escalate to higher doses of opiates, with increased potential for respiratory depression, nausea and even hemodynamic collapse. Neither of these options is particularly attractive. A third option may be to administer a small amount of versed in order to provoke a deliberate amnestic effect, but mixing benzodiazepines and opiates is a risky proposition and can lead to significant unintended negative consequences. NSAIDs such as Toradol are a consideration, but this introduces clotting concerns and

does little for pain caused by tissue damage and nerve disruption. Renal and hepatic function also must be assessed prior to administering Toradol, and although these are not likely concerns with teenaged patients, they are concerns nonetheless.

With the pediatric trauma center approximately thirty minutes away by ground, there is a better option.

The Hammer of Opiates

The entire human body does not have opioid receptors. Most of the mu receptors that opiates bind to in the body are found in one of two locations- presynaptically in the periaqueductal grey region of the brain and in the superficial **dorsal horn** of the spinal cord (specifically in the substantia gelatinosa of Rolando, the apex of the posterior grey column of the spinal cord). They are also located in the olfactory bulb, the cerebral cortex, and in some of the nuclei of the amygdala in the brain; and in the intestinal tract. In order to successfully mitigate pain, we need to get the concentration of opioid in the bloodstream high enough to effectively block the mu receptors in the spinal cord. However, the spinal cord also serves as the body's nerve center, and this means that we need to titrate the dose of opiates we are giving to provide to dull afferent (sensory input) signals without removing muscle tone or blocking efferent (outward-bound) signals. In patients who are lighter or opiate-naïve; the threshold between therapeutic agonism of the afferent receptors and an overdose is narrow and increased doses may see diminishing returns in the decrease of pain. Think of opioid receptors as nails. When you are building something with nails, you need them in specific places to hold things together, and to use nails, you have various types of hammers- but nails are not appropriate for all projects. Sometimes we need a screwdriver.

Ketamine

Ketamine is a non-opioid **NMDA receptor agonist** that also has some effect on **mu** and **monoamine transporters**. It was discovered in 1962 and is on the World Health Organization's *List of Essential Medicines*. It is commonly used in veterinary medicine and for humans as an anesthetic, a sedative, and for analgesia. Ketamine's primary function is as a **non-competitive antagonist** of the NMDA receptor, with secondary weak agonist of the mu- and k-opioid receptors and very weak agonism of the delta opioid receptor. In its primary function, ketamine binds both in the open NMDA receptor site and at an allosteric site, which effectively blocks competing molecules from binding at that site. When this occurs, the central neurons of the dorsal core are unable to become sensitized, the production of **nitric oxide** is inhibited, and sigma and mu opioid receptors are somewhat agonized. Additionally, voltage-dependent calcium and sodium channels that normally facilitate the movement of pain neurotransmitters are blocked and the reuptake of serotonin and norepinephrine are inhibited. Alone, ketamine can cause disassociation, hallucinations and sedation in higher doses. When ketamine is administered in low doses in conjunction with fentanyl or another opiate, the majority of the mu receptors to the dorsal horn are blocked and the primary effect of the low-dose ketamine is to block the NMDA receptors without significant further mu/sigma inhibition, which means that ketamine is blocking the conduction of pain up the spinal cord and how the body is perceiving that pain. The inhibition of norepinephrine and serotonin reuptake causes blood pressure and heart rate to rise; and due to the lack of inhibition of the efferent (outward) nervous system, the patient's respiratory drive remains intact and unaffected. However, this also means that ketamine tends to *increase* cardiac workload, this makes it a poor choice for addressing ischemic chest pain.

Ketamine can be safely administered intravenously, intramuscularly, intranasally, or even orally via sublingual or buccal lozenges¹. In EMS, ketamine is generally administered via IV or IM routes, which allows for a more precise measurement of how much has been given and a more reliable timeframe of effect. In this case, we do not want to disassociate or sedate the patient, thus we will use a lower dose of ketamine. A common consensus dose for ketamine administration is 0.1 – 0.5 mg/kg. This dose allows for the inhibition of NMDA receptors without undue disassociation or sedation and places our patient at a minimal risk for hypersalivation, sedation or hallucination. In this patient, it is appropriate to start at the lower end of the therapeutic threshold- 0.2mg/kg of ketamine, administered intravenously. The duration of action of ketamine is approximately 5-15 minutes, with rapid recovery to baseline and a peak concentration at 1 minute after peripheral IV push². In these concentrations, it is unlikely to cause disassociation or hallucinations, and the patient's airway reflexes and respirations are maintained and stable. Mild increases in heart rate and blood pressure are frequently seen, but these are not dangerous and resolve as ketamine wears off and the body becomes acclimated to the non-reabsorbed norepinephrine³.

Armed with this knowledge, you can confidently identify the problem- the patient has not yet achieved a high enough percentage of mu-receptor agonism with fentanyl and his well-developed afferent nervous system is going to transmit pain effectively to his brain unless a colossal, potentially-dangerous and protocol-breaking dose of opioids is administered; thus, it is time to bring another tool- ketamine. Many EMS services that carry ketamine carry it in large vials- 500mg in 5mL, with an effective concentration of 100mg to 1mL. This means that we need to be aware of what syringe we are using and dilute the ketamine to effect. Three safe methods of administering ketamine in this high concentration are to use a 1mL syringe, use a 10mL syringe with 1mL of ketamine and nine of saline, or even mix one milligram in a 100mL bag of normal saline and have a 1mL/mg concentration. In this case, we are going to be administering 10mg of ketamine; so any method would work, but with such a small volume of ketamine per dose, the easiest answer is to use a 100mL bag as a reservoir and administer 10mL doses SIVP. For smaller patients, this is the safest option, as it provides adequate volume to safely infuse ketamine at a controlled rate.

Conclusion

One minute after administering 10mg of ketamine, the patient looks up at you and tells you that his pain is gone. He sits back and talks with you and his mother for the remainder of the trip. As your ambulance approaches the hospital, he reports that his pain has returned, going from a 0/10 to a 6/10 after approximately 12 minutes; and you administer another dose of 10mg of fentanyl in 10mL of saline solution. Once again, his pain resolves entirely, without any respiratory or hemodynamic compromise and without nausea, and the remainder of the transport is uneventful. The patient is pain-free at transfer of care. The patient is found to have a complex fracture of his distal radius necessitating surgery. Due to good prehospital pain management, he will have better memories of this unfortunate event, and he and his parents thank you for your efforts- they've really meant something to them. By coincidence, as your patient is registered, a neighboring agency brings in a patient with a similar injury who has not received ketamine; she is in considerable pain and presents a stark contrast to your patient. The receiving physician notices the difference and thanks you and your crew for providing appropriate pain management- it makes his job much easier. Ketamine has allowed you to provide better care to this patient.

Takeaways:

- Ketamine is a safe, effective and cost-efficient pharmacological solution to manage patient pain effectively.
- Use of small amounts of ketamine in conjunction with initial doses of opiates can provide dramatically-superior pain relief in comparison to opiate-only treatments. This also means that the use of opiates overall can be decreased with superior results.
- The concentration of ketamine requires caution in drawing and administration, but this concern can be alleviated by education and packaging considerations.
- Communities and states that currently do not field ketamine should consider adding it to their formularies in order to provide alternatives to high-dose or high-strength opiates such as dilaudid.
- Ketamine can offer options for treatment beyond pain management without additional cost and can facilitate better care at a lower cost with less overall use of medication.⁴

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References:

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Cypress Creek EMS is the sole 911 provider for a 177-square mile district of the Greater Houston metropolitan area and serves approximately 700,000 residents and persons working within North Harris County. Our average call volume exceeds 40,000 emergency calls annually. Cypress Creek EMS operates an exclusively-MICU fleet of fourteen ambulances and employs EMTs, Paramedics and EMD-trained dispatchers. Find out more at www.ccems.com!