

Sub-dissociative Dose Ketamine for Analgesia *Policy Resource and Education Paper (PREP)*

This policy resource and education paper (PREP) is an explication of the policy statement
“Sub-dissociative Dose Ketamine for Analgesia”

Why

Physiologic pain and injury remain among the most common reasons for patient presentation to the emergency department (ED) and the treatment of this pain is one of the primary goals of emergency medicine. The opioid analgesics are among the most common analgesics in current use. Unfortunately, the misuse and abuse of opioids has led to an opioid epidemic in the United States, with record levels of addiction, overdose, and death. For this reason, many EDs are limiting the use of opioids as primary analgesics for mild and moderate pain, while searching for alternatives to opioids for patients with more severe pain.

One such agent that has been identified for use in the ED is ketamine. Though it has historically been used in the ED primarily as an anesthetic agent for moderate to deep procedural sedation, low dose or sub-dissociative dose ketamine (SDK) may be utilized as an adjunct to opioids or as a single agent in the emergency setting. With a protocolized intravenous dose range of 0.1-0.3 mg/kg, ketamine acts not as an anesthetic, but rather as an analgesic. Due to its unique pharmacological properties, SDK does not produce many of the potentially adverse respiratory or hemodynamic effects of other analgesics and may be used as a safe and effective alternative or adjunct to opioids.

When given as a stand-alone analgesic or in combination with other pain medications including opioids, SDK lowers pain scores and has functionally equivalent efficacy to morphine for short-term analgesia in the ED. When given in combination with opioids, SDK reduces the overall dose of opioid analgesics and the need for re-dosing. As a result, a majority of patients receiving SDK and patients receiving a combination of SDK/opioid report a positive experience and would elect to receive it again under similar circumstances.

Who

SDK may be used in any patients in whom opioids and/or other non-opioid analgesics are absolutely or relatively contraindicated. SDK may also be used as a first line analgesic when its low risk factor profile and analgesic effects are desired over that of an opioid. Some examples of people in whom SDK may be desired include those with: chronic use of high doses of opioids, opioid addiction or risk of addiction, inadequate pain relief with more traditional agents, a contraindication to non-opioid analgesics (predominantly non-steroidal anti-inflammatory agents or acetaminophen) such as bleeding, renal insufficiency, liver failure, and those with hypotension due to conditions such as trauma or sepsis.

Examples of clinical circumstances in which SDK is beneficial are: acute traumatic and non-traumatic pain, complex regional pain syndrome, gastroparesis and functional abdominal pain, migraine headache, neuropathic and radicular pain, sickle cell crisis, and other non-specific or non-physiologic chronic pain syndromes.

Contraindications to SDK include infants less than three months of age due to the risk of laryngospasm (due to airway physiology, not ketamine itself) and those with stated adverse reactions or allergies to ketamine. While some believe the use is contraindicated in patients with mental illness due to potential exacerbation of underlying psychosis, there is little evidence of adverse reactions or exacerbation of psychosis when ketamine is used in a sub-dissociative manner.

How

Research on the safety of SDK dates back to the 1970s and reveals a strong safety profile for intravenous doses up to 0.5 mg/kg. In this dose range and the more common 0.1-0.3 mg/kg dose range typically used for sub-dissociate analgesia, the most common side effects are dysphoria, nausea, and dizziness. In addition to being short-lived and self-limited, these symptoms are typically mild in nature and do not require any acute intervention or rescue. Furthermore, a recent trial found that the frequency of these effects is significantly reduced if SDK is dosed as a short infusion rather than as an IV bolus. SDK does not cause respiratory depression, hypoxemia, or hypotension as do many other similar analgesic agents. It also does not increase intra-cranial or intra-ocular pressure. Similarly, while many fear patients having “emergence reactions” after the administration of SDK, these reactions have not been noted at the typical dosages used in SDK protocols.

Typical Dosing Schedule

Bolus dosing at 0.1-0.3 mg/kg over 10 to 15 min with option of continuous infusion at 0.15-0.2 mg/kg/hr. One may also dose IM, though the exact therapeutic dose range has not been definitively established and analgesic effects are less predictable IM than IV. Some observational data and studies have shown benefit with doses as high as 0.6 mg/kg, but the findings of other studies have shown dissociative effects starting at doses in the 0.43-0.65 mg/kg range, supporting the use of lower dose protocols.

Many officials, physicians, administrators, nurses, and pharmacy staff may be unfamiliar with the use of SDK, such that there may be existing policies or regulatory barriers that limit its use or require moderate sedation type monitoring precautions. Though a breach of written hospital protocols is not recommended, ancillary staff and services may be assured that emergence and severe adverse reactions such as clinically significant respiratory or CNS depression are not typically seen at sub-dissociative doses. Providing national backing of this concept, in its 2017 statement entitled Optimizing the Treatment of Acute Pain in the Emergency Department, ACEP states that “Administration of sub-dissociative ketamine should commence under the same procedures and policies as other analgesic agents administered by the nursing staff in the ED setting.”

Despite this and its low-risk profile, most studies have placed patients on cardiorespiratory monitoring in conjunction with SDK administration. Check your local or hospital protocols regarding monitoring requirements during the administration of analgesic agents for guidance on what expectations should be met on the local level.

What’s Next

Though SDK has been shown to be both safe and effective to relieve and control pain in the emergency setting, there are still questions. Most importantly, further research, ideally randomized clinical trials, is needed to better define the maximally effective and safe SDK dose and the best method of administration (bolus, infusion, titrated-dosing, combination with other analgesics or agents). Similarly, many hospitals, pharmacy departments, and state regulators still do not understand the nature and use of SDK. As a result, its use is often outright prohibited, or its use is mis-labeled as sedation requiring moderate sedation protocols and unnecessary barriers to its efficient and effective use.

Overview

SDK is effective and safe for use in the emergency setting, though many hospitals and state regulators are

slow to ease restrictions on its use in this setting. It may be safely administered by nursing under the same provisions and protocols as other typical emergency analgesics such as opioids and tends to receive positive feedback from both patients and providers.

Developed by members of the Emergency Medicine Practice Committee – October 2017

Reviewed by the Board of Directors – November 2017

Resources

1. American College of Emergency Physicians. “Optimizing the Treatment of Acute Pain in the Emergency Department.” Policy statement. Approved April 2017.
2. Ahern TL, Herring AA, Miller S, et al. Low-dose ketamine infusion for emergency department patients with severe pain. *Pain Med.* 2015;16(7):1402-1409.
3. Beaudoin FL, Lin C, Guan W, et al. Low-dose ketamine improves pain relief in patients receiving intravenous opioids for acute pain in the emergency department; results of a randomized, double blind, clinical trial. *Acad Emerg Med.* 2014;21(11):1193-1202.
4. Bowers K, McAllister K, Ray M, et al. Ketamine as an adjunct to opioids for acute pain in the emergency department: a randomized controlled trial. *Acad Emerg Med.* 2017 Jun;24(6):676-685.
5. Cohen L, Athaide V, Wickham ME, et al. The effect of ketamine on intracranial and cerebral perfusion pressure and health outcomes: a systematic review. *Ann Emerg Med.* 2015;65(1):49-51.
6. Miller JP, Schauer SG, Ganem VJ, et al. Low-dose ketamine vs. morphine for acute pain in the ED: a randomized controlled trial. *Am J Emerg Med.* 2015;33(3):402-408.
7. Motov S, Mai M, Pushkar I, et al. A prospective randomized, double-dummy trial comparing intravenous push dose of low dose ketamine to short infusion of low dose ketamine for treatment of moderate to severe pain in the emergency department. *Am J Emerg Med.* 2017;35(8):1095-1100.
8. Pourmand A, Mazer-Amirshahi M, Royall C, et al. Low dose ketamine use in the emergency department, a new direction in pain management. *Am J Emerg Med.* 2017 June;35(6):918-921.
9. Richards JR, Rockford RE. Low-dose ketamine analgesia: patient and physician experience in the ED. *Am J Emerg Med.* 2013;31(2):390-394.
10. Smith RK, Messman A, Wilburn J. Low-dose ketamine emerges as effective opioid alternative.” *ACEP Now.* August 2017. Available at: <http://www.acepnow.com/article/low-dose-ketamine-emerges-effective-opioid-alternative/> Accessed: September 15, 2017.