INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Ketamine Use for Acute Pain***
-January 2025-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a clinical review of ketamine for acute pain. The use of ketamine in Emergency Departments nationwide has increased, leading to a consensus guideline from three medical societies on the indication, dosing, relative contraindications, and personnel needed.[1] Following clinical review and analysis, the NPTC made **no modifications** to the IHS National Core Formulary.

Discussion:

Between 45-78% of patients presenting to the Emergency Department (ED) have complaints related to pain.[2] The same is true for patients seeking care at IHS facilities; data for American Indian/Alaska Native populations from 2010-2011 indicate an elevated ratio for accidents – unintentional injuries were 2.5 times more likely when compared to all other races in the U.S.[3] This ratio does not include pain due to other complaints such as heart attacks or severe infections.

Ketamine was first synthesized in 1962 and approved by the FDA in 1970 as an anesthetic agent. The FDA approved indications are as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation, for the induction of anesthesia prior to the administration of other general anesthetic agents, and as a supplement to other anesthetic agents.[4] Ketamine is a non-selective, non-competitive antagonist of the N-methyl-D-aspartate receptor, an ionotropic glutamate receptor. It also has effects as an indirect and direct alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor agonist, hyperpolarization-activated cyclic nucleotide-gated channel antagonist, mu-, kappa- and delta- opioid receptor agonist, serotonin receptor 5-HT_2 agonist, dopamine 2 receptor agonist, and anti-inflammatory agent.[5] Ketamine is used off-label for pain (acute, post-operative), refractory status epilepticus, depression, and post-traumatic stress disorder.

Ketamine for acute pain has increased in popularity and can be used in conjunction with other pharmacological and non-pharmacological therapies for pain management. Advantages of ketamine use include the obvious avoidance of opioid use (contributing to the opioid epidemic), variable routes of administration, and depending on pain severity, better pain control compared to opioid and non-opioid alternatives. The 2018 consensus guidelines reviewed data and evidence for intravenous (IV) ketamine in acute pain management and detailed its indications which include; (1) perioperative use in surgery with moderate or severe postoperative pain, (2) perioperative use in patients with opioid tolerance, (3) as analgesia in opioid-tolerant patients with sickle cell crisis, and (4) as analgesic adjunct in patients with obstructive sleep apnea.[1] The recommend ranges for bolus dosing and infusions are; up to 0.35mg/kg, and up to 1mg/kg/hr, respectively. Relative contraindications are poorly controlled cardiovascular disease, pregnancy, psychosis, severe hepatic disease (avoid), moderate hepatic cirrhosis (caution), elevated intracranial pressure, and elevated intraocular pressure. The guideline also provided recommendations for required personnel, however it doesn't address the necessary qualifications of those who supervise or directly administer sub-dissociative dose ketamine (SDDK). Appropriately trained healthcare providers include (1) nurses with ACLS certification and additional training in the administration of moderate sedation and knowledge of ketamine pharmacology and (2) healthcare prescribers (e.g., anesthesiologist, intensive care physician, pain physician, emergency medicine physician, etc.).

SDDK has been compared to standard of care therapy for acute pain in the ED in multiple studies. A 2024 meta-analysis and systemic review reviewed both IV and intranasal (IN) ketamine versus standard of care.[6] Outcomes reported were pain intensity, requirement of rescue analgesic, and adverse drug reactions. There was no difference in pain management between SDDK and control groups using mean difference (MD) at 15 minutes (MD: -0.72, 95% CI: -1.55 to 0.12; I^2=95.4%; n=7), 45 minutes (MD: -0.04, 95% CI: -0.26 to 0.18; I^2=79.7%; n=20), and 60 minutes (MD: 0.11, 95% CI: -0.10 to 0.22; I^2=62.2%; n=10). However, at 30 minutes, there was notable reduction in pain levels for ketamine compared to the control group (MD: -0.27, 95% CI: -0.48 to -0.05; I^2=73.9%; n=15). Subgroup analysis showed reduction in pain levels for those who received IV ketamine (MD: -0.39, 95% CI: -0.72 to -0.07); those who received IN ketamine did not have the same reduction (MD: -0.10, 95% CI: -0.38 to 0.18). Ketamine did show improved pain scores versus morphine (MD: -0.25, 95% CI: -0.45 to -0.06) but were inconclusive when compared to fentanyl (MD: 0.02, 95% CI: -0.38 to 0.41). There was no difference in the use of rescue analgesic between ketamine and control groups (RR 0.96, 95% CI: 0.65 to 1.41, I^2=81.8%; n=12). Additionally, there were no differences in gastrointestinal, psychological or cardiopulmonary adverse events. However, for neurological side effects (i.e., emergence phenomenon, drowsiness, dysphoria/dissociation, dizziness), there was an elevated risk (RR 2.07, 95% CI:1.52 to 2.82, I^2=60.6%; n=18).

Another 2024 meta-analysis of 15 randomized controlled trials focused on SDDK versus morphine for acute pain in the ED.[7] SDDK showed lower numeric rating scale at 30 minutes (MD: -0.77, 95% CI: -0.93 to -0.61, $p<0.00001$), however morphine performed better at 120 minutes (MD: 0.33, 95% CI: 0.15 to 0.51, $p=0.0003$). Ketamine had better complete resolution of pain at 15 minutes (RR 3.2, 95% CI: 1.75 to 5.78, $p=0.0001$), but no difference at all other time points. There was no difference in use of rescue analgesia between ketamine and morphine. Neither group had serious or life-threatening adverse events. Most adverse events were transient and did not require intervention. Notably, ketamine required more antiemetics and morphine required more oxygen therapy than ketamine. In a subgroup analysis evaluating both IV/IN SDDK, intravenously-administered SDDK provided better pain control at 30 minutes. The authors concluded that ketamine had better analgesic effects in the early stages after administration, whereas morphine maintained more durable effects, and that IV ketamine was more effective than IN ketamine.

While efficacy of SDDK remained a common primary outcome, most studies included a review of adverse drug reactions. A year after implemented ketamine protocols in EDs for acute pain and agitation/delirium (2017), a large health system performed a focused review on the safety of ketamine use.[8] Contraindications for use per protocol were unstable vital signs, suspected acute coronary syndrome, unstable dysrhythmia, acute head/ocular trauma, suspected intracranial pressure, and history of or active psychosis. Protocol-required monitoring included vital signs assessments at baseline, 15 minutes, and 30 minutes after each dose for at least 30 minutes after administration. Additional requirements included continuous pulse oximetry, telemetry, and immediate availability of ED attending physician. Over the course of a year, 210 ED visits utilized the SDDK protocol in 170 unique patients. The median SDDK IV dose given was 0.26mg/kg. Only two patients (1%) reported serious respiratory adverse events requiring interventions (non-rebreather or nasal canula), which may have been due to simultaneous use of ketamine, fentanyl, and morphine. Authors concluded that SDDK was associated with minor and self-limited neuropsychiatric adverse events that resolved without further interventions.

The Veterans Health Administration reviewed data and recently updated (March 2024) their National Protocol Guidance for ketamine administration in ED and urgent care.[9] This provides a comprehensive overview of considerations when implementing the use of SDDK in the ED.

Findings:

Ketamine is an alternative option for moderate to severe pain management at sub-dissociative dosing (≤0.35mg/kg IV bolus) in the ED/Urgent Care setting. While adverse drug events at sub-dissociative doses are minimal, monitoring for these events following administration remains the same regardless of dose. Immediate access to qualified personnel who are privileged for airway management is recommended. Local adoption may be considered at sites where clinical expertise supports its use.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

References:

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