Rhode Island Hospital
The Miriam Hospital
Newport Hospital
Emergency Department

Sub-dissociative or low dose ketamine: Clinical guidelines on the use of ketamine for analgesia

Purpose:
Ketamine (Ketalar®) is a dissociative anesthetic and a potent sedative at doses greater than 1 mg/kg IV. However, it also has analgesic properties due to its n-methyl-d-aspartate (NMDA) receptor antagonism and these analgesic effects are still present even in lower, sub-dissociative doses (0.15 – 0.5 mg/kg IV). In addition, ketamine and opiates act at different levels of the pain signal pathways which further allows for synergism and lower total opioid doses.

Sub-dissociative or "low dose" ketamine has been increasingly studied in the setting of acute pain for patients with difficult to treat pain. Ketamine possess multiple benefits in a multitude of conditions and is likely suitable for treatment pain in a variety of circumstances including but not limited to: pain refractory to opioids, opioid induced hyperalgesia, acute pain in chronic opioid users, sickle cell pain crisis, neuropathic pain syndromes like reflex sympathetic dystrophy or complex regional pain syndrome, and acute pain in the setting of previous opioid addiction. Additionally, when used in conjunction with opioids, ketamine has shown to reduce opioid consumption. The purpose of this guideline is to provide administration suggestions, safe monitoring parameters, and information on potential adverse effects in the setting of low dose ketamine use.

Scope of Service:
Ketamine will be able to be administered in the critical care rooms and urgent sides at sub-dissociative dosing. It is recommended for use in addition to IV opioids, but may be given alone when the use of opioids is contraindicated or undesired. When ketamine is used as adjunct to opioids, the rapid stacking of opioid doses should be avoided to minimize opioid-related adverse effects such as but not limited to respiratory depression. Low dose ketamine should be ordered by patient's emergency medicine provider. This guideline is relevant to pharmacy and emergency department staff, including providers, nurses, and pharmacists.

Recommended Patient Population:
- Age ≥ 18 years old
- Presentation with acute moderate to severe pain (e.g. pain score ≥6) AND:
    - Pain is not relieved by opioids or opioids are contraindicated, OR
    - History of chronic opioid therapy or opioid tolerance, OR
    - History of opioid addiction/abuse

Absolute Contraindications:
- Known or suspected allergy to ketamine

Relative Contraindications:

- Known history of psychosis
- Age >65 years
- Alcohol intoxication
- Known ischemic heart disease, heart failure or unstable dysrhythmias
- History of adverse effect with ketamine
- Known liver failure
- Known end stage renal disease
- Known or suspected intracranial lesion
- Pregnant or breastfeeding
- Persistent, uncontrolled, severe hypertension (SBP > 180, DBP >110)
- Altered mental status or GCS < 13
- Respiratory depression

Dosing:
Low dose ketamine may be administered by either IV push or as a slow IV infusion over 15 minutes. Ketamine can be expected to produce dose-dependent effects. Expect anesthesia induction at doses approaching or exceeding 1 mg/kg.

Recommended IV push dosing of low dose ketamine is 0.15 mg/kg IV.

- **Initial dose:** 0.15 mg/kg (maximum dose of 20 mg) IV push over 60 seconds
- **Repeat:** 0.15 mg/kg (maximum dose of 20 mg) IV push no sooner than every 30 minutes if pain is not adequately relieved
- **Maximum cumulative dose:** 0.45 mg/kg or a total dose of 60 mg

Recommended dosing for slow IV infusion of low dose ketamine is 0.15-0.3 mg/kg mixed in 100 mL of 0.9% sodium chloride administered over 15 minutes.

- **Initial dose:** 0.15-0.3 mg/kg (maximum dose of 30 mg) in 0.9% sodium chloride 100 mL infused over 15 minutes
- **Repeat:** 0.15-0.3 mg/kg (maximum dose of 30 mg) in 0.9% sodium chloride 100 mL infused over 15 minutes, no sooner than 30 minutes after the completion of the infusion of the initial dose if pain is not adequately relieved
- **Maximum cumulative dose:** 0.45 mg/kg or a total dose of 60 mg

Monitoring:
Patients should be placed on a bedside cardio-respiratory monitor prior to drug administration. Central telemetry is not required. Baseline vitals and repeat vitals should be taken 20 minutes after administration of ketamine.

Adverse effects:
Ketamine at sub-dissociative doses is safe and well tolerated. At higher doses (e.g. dissociative doses used during anesthesia), ketamine has been associated with the below common and significant adverse effects.

Common side-effects typically seen at higher doses include:

- Transient tachycardia
- Transient hypertension
- Confusion
- Drowsiness
- Muscle twitching
- Nystagmus
- Nausea or vomiting
  (Consider giving a prophylactic dose of an antiemetic such as ondansetron (Zofran)).
- Loss of appetite
- Increased salivation
- Injection site reactions

Significant adverse effects seen at higher doses include:

- Emergence phenomenon characterized by agitation, hallucinations, and delirium
  - Emergence phenomenon is not expected to occur with sub-dissociative ketamine dosing, but benzodiazepines may used to treat such a reaction.
  - Warning patients of the potential psychomimetic reactions may reduce the likelihood that it is perceived negatively
- Transient laryngospasm

Summary and Recommendations:

Ketamine IV at sub-dissociative doses in the Emergency Department is allowed in the urgent and critical care areas for the management of acute pain when dosed as follows: 0.15 mg/kg IV push (maximum initial dose of 20mg) or 0.15 to 0.3 mg/kg slow IV infusion over 15 minutes (maximum initial dose of 30 mg), may repeat every 30 minutes to a maximum cumulative dose of 0.45 mg/kg IV (maximum cumulative dose of 60mg).

References:

Ahern T, Herring A, Anderson E, et al. The first 500: initial experience with widespread use of low-dose ketamine for acute pain management in the ED. American Journal of Emergency Medicine, 2015; 33: 197-201.

Beaudoin, F. Ketamine's troubled past, promising future. Emergency Physicians Monthly, April 29 2015.

Beaudoin F, 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. Academic Emergency Medicine, 2014; 21(11): 1194-1202.

Galinski M, Dolveck F, Combes X, et al. Management of severe acute pain in emergency settings: ketamine reduces morphine consumption. American Journal of Emergency Medicine, 2007; 25: 385-90.

Goltser A, Soyeyman-Zomalan E, Kresch F. Short (low-dose) ketamine infusion for managing acute pain in the ED: case-report series. American Journal of Emergency Medicine, 2015; 33: 601e5-601e7.

Greene SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department Ketamine dissociative sedation: 2011 update. Annals of Emergency Medicine, 2011; 1-13.

Jennings PA, Cameron P, Bernard S, Walker T, Jolley D, Fitzgerald M, et al. Morphine and ketamine is superior to morphine alone in out of hospital trauma analgesia: a randomized controlled trial. Pain Management and Sedation, 2012; 56: 497-503.

Ketamine- more mechanisms of action than just NMDA blockade. Trends in Anesthesia and Critical Care, 2014; 4:76-81.

Miller JP, Schauer SG, Ganem VJ, Bebarta VS. Low-dose ketamine vs morphine for acute pain in the ED: a randomized controlled trial. American Journal of Emergency Medicine, 2015; 33: 402-408.

Motov A, Rockoff B, Cohen V, Pushkar I, Likourezos A, McKay C, et al. Intravenous subdissociative-dose ketamine versus morphine for analgesia in the emergency department: a randomized controlled trial. Ann Emerg Med, 2015; 66: 222-229.

Motov S, et al. A prospective randomized, double-dummy trial comparing IV push low dose ketamine to short infusion of low dose ketamine for treatment of pain in the ED. *Am J Emerg Med*. 2017 Aug;35(8):1095-1100.

Product Information: ketamine hydrochloride IV, IM injection,Bioniche Pharma USA LLC, Lake Forest, IL, 2008.

Richards J, Rockford R. Low-dose ketamine analgesia: patient and physician experience in the ED. American Journal of Emergency Medicine, 2013; 31: 390-94.

Wilcock A, Howard P. Therapeutic reviews: ketamine. Journal of Pain and Symptom Management, 2015; 50: 268-278.