

Purpose:

The purpose of this policy is to establish criteria for the use of ketamine sedation by experienced physicians in Emergency Departments within the State of Rhode Island. This criteria covers the use of ketamine relative to indications, dosing protocols, monitoring, contraindications and recovery/discharge from the Emergency Department.

Policy:

It is the policy of the State of Rhode Island Department of Health to establish guidelines for the safe usage of sedative amnestic analgesics. Ketamine has a distinctive mechanism of action whose use in emergency rooms is emerging with broader application and increased frequency. Ketamine is inexpensive, widely available, and has fewer hemodynamic and respiratory adverse events when compared with opioids making it an attractive option for use in the emergency room setting.²⁰ As such, the goal of this directive is to provide clear guidance for the use of ketamine for ED practitioners.

History:

Ketamine, a phencyclidine derivative, was first approved for human use in the 1970s. It is a short-acting anesthetic agent approved by the FDA in 1970. It is most commonly used in both human and veterinary medicine in minor surgical procedures as an anesthetic and analgesic. Ketamine's mechanism of action is mainly by noncompetitive antagonism of the N-methyl D-aspartic acid (NMDA) receptor. It also interacts with opioid receptors, monoamine, cholinergic, adrenergic and adrenoreceptor systems as well as having local anesthetic effects.¹ Ketamine's primary effect is on antagonizing the N-methyl-aspartate (NMDA) receptor causing a dissociative effect between the thalamocortical and limbic regions. Recipients of the drug often report feeling an out-of-body experience in which they are aware of events but have no painful sensation.

Typical historical methods of ketamine delivery included intravenous or intramuscular injection, although it may also be used orally, rectally, or intranasally. Historically, ketamine has been important for use in emergency situations on the battlefield as it maintains cardiac output and is less likely to suppress respiration. Ketamine has a stimulating effect on heart rate and blood pressure due to its action on cholinergic, muscarinic and adenosine receptors. One of the major advantages of ketamine use is its minimal effect on respiratory drive, pharyngeal/laryngeal reflexes and bronchodilation demonstrated by fully anesthetized patients who maintain their airway during the sedation.

For these reasons ketamine has enjoyed resurgence in popularity in the emergency clinical setting.

Introduction:

Pain is often a component of the ED visit and clinicians need to be able to manage pain in a safe manner. The current pharmacological approach to pain relies heavily on opioids and Nonsteroidal anti-inflammatory medications. Opioids have a narrow therapeutic window. Adverse effects include over sedation, respiratory depression, nausea, hypotension, tolerance and dependence.⁶ Additionally, higher pain tolerance may occur with escalating doses of opioids, which limits utility in the clinical setting. NSAIDs are an effective pain medication however often fails to control severe pain independently. The use of NSAIDs is limited as they carry the risk of nephrotoxicity, gastropathy and cardiac toxicity. Ketamine can produce improved quality and level of the analgesic effect for breakthrough pain that cannot be achieved with opioids alone.^{7, 8, 9, 10, 11} This effect is likely due to central inhibition of opioid-induced hyperalgesia a peripheral potentiation of the analgesic effects of opioids.¹²

In clinical practice, chronic pain, psychological distress, and behavioral disorders frequently overlap.^{13, 14} Ketamine is unique among the analgesics in that it has powerful antidepressant effects and has been shown to influence the affective component or emotional coloring of the pain experience, in addition to the peripheral perception of pain.^{15, 16, 17} The anti depressive properties of low dose ketamine, however, provides an intriguing therapeutic option in the difficult to treat population.¹⁸

Indications of Ketamine Use in the Emergency Room:

Ketamine has been used extensively in the ED for procedural sedation and rapid sequence intubation and is ideal for short, painful procedures, especially those requiring immobilization, on awake patients. Predominant use of ketamine in the ED has been as a dissociative agent (1.5 – 2 mg/kg) typically given IV to facilitate procedural sedation.³

As the scope of practice continues to evolve in the ED clinicians may be called on to manage more chronic pain, psychological distress and behavioral agitation opening up increasing possibilities for ketamine usage.

Administration and Dosing Protocols:

Low dose ketamine or subanesthetic or subdissociative dose ketamine is defined as less than 1 mg/kg and is often much lower at 0.1 – 0.3 mg/kg. When studied at the low doses, ketamine is proven to be a potent analgesic (0.1-0.3 mg/kg). Research conducted over the last 15 years has demonstrated that such low dose ketamine (LDK) is safe, effective and improves pain management when combined with opioid analgesics.^{20, 21} Ketamine can be dosed intravenously, intramuscularly, orally, rectally and intranasally.

Specifically low dose ketamine (15 mg) combined with hydromorphone (0.5mg) has been studied and proven to provide rapid and profound pain relief with few significant side effects and high patient satisfaction.¹⁹ When comparing morphine directly to low dose ketamine, ketamine achieved a maximum reduction in pain score immediately after infusion and was sustained for 5-10 minutes. The morphine group had a similar maximum reduction in pain scores, however the best pain control was reached 100 minutes after the morphine infusion.³ The rapid decrease in pain provided by low dose ketamine is an advantage compared with morphine for the treatment of acute pain.³ Many studies of subanesthetic administration of ketamine, termed low-dose ketamine (LDK) suggest that it provides effective analgesia with minimum adverse effects when administered along with or as an adjunct to opioids.^{22, 23, 8, 9, 24}

Dosing protocols:

Typical low dose ketamine protocols include 0.1-0.3 mg/kg but can range up to 1 mg/kg. Subdissociative or subanesthetic doses defined at IV dose of less than 1 mg/kg have been shown to decrease the amount of morphine required for pain control, with minimal oxygenation desaturation and respiration depression.^{9,19, 49} An advantage of ketamine is rapid onset of action with preservation of airway reflexes and the ability to administer IM or IV. Sedation is achieved reliably with single ketamine dosing.²⁵

Ketamine should be dosed according to ideal body weight and infused over 1 to 2 minutes. Weight-based dosing is recommended however due to a large therapeutic window it can be safely dosed based on an estimated weight when an actual weight is difficult to obtain.

Ketamine is unique in its predictable effect when administered by the intramuscular route, with peak levels occurring within 4-6 minutes.^{32, 33} When ketamine is given intravenously it causes dissociation within 1-2 minutes and when given intramuscularly dissociation occurs at approximately 10 – 15 minutes, an advantage when compared to fentanyl/midazolam.^{32, 33}

Ketamine is found to be compatible with midazolam, haloperidol, opioids, ketorolac and metoclopramide.⁴⁸

Ketamine effectively provides anesthesia for procedural sedation and protects patient safety. Its duration of action is 20 to 40 minutes intravenously, an advantage when compared to fentanyl/midazolam.^{32, 33} When administered orally the onset of action is less than 20 minutes and the half-life is approximately 3 hours. The rapid onset of action by ketamine in less than 5 minutes also compares favorably to haloperidol when peak sedation can take more than 20 minutes.³⁵ analgesia onset is approximately 1-3 min for intravenous and intramuscular administration, respectively, with an en elimination half-life of approximately 10-15 min.⁵⁰

Monitoring

Continuous hemodynamic monitoring including pulse oximetry is the standard of care for procedural sedation. When administering low dose ketamine, literature demonstrates the safety of this action and thus no formal monitoring is supported when administering low dose ketamine as a single agent. Literature demonstrates that low dose ketamine (< 1 mg/kg) constitutes minimal sedation and requires no special monitoring equipment or training. ^{19, 35}

The primary concern of the ED clinician is hemodynamic instability. Ketamine has demonstrated a high degree of safety. In more than 70,000 patients described in a recent literature review only a single adverse cardiorespiratory event was attributed to ketamine and the case report was lacking in detail and unclear at best. ²⁸ When specifically looking at changes in blood pressure and heart rate after administration of low dose ketamine no significant changes were appreciated within 1 hour of administering low dose ketamine as compared with triage values. (*** need reference) One retrospective study showed that within 4 hrs of administration the highest recorded SBP was an average increase of 17 (+/- 25) mmHg from the patient's baseline. ²⁵ In this same study the lowest recorded SBP in the same period showed an average drop of 14 mmHG over baseline. ²⁵ Oxygen saturation data, with a preadministration average of 98 % (+/- 2%), showed an average postadministration increase of 1.1 % (+/- 1.7%). ²⁵ No patients became hypoxic in this 27 patient study. ²⁵ Overall these mild hemodynamic effects are not a concern in most ED patients and there are no reports of ketamine induced myocardial ischemia. Furthermore, the literature is replete with studies showing safe use of ketamine in the elderly including those with coronary artery bypass grafting. ³⁴

One study looked specifically at the use of ketamine in the intoxicated population. This bears special mention given the frequency that alcohol intoxication is encountered in ED patients. In this study ketamine was safely used without significant major adverse effects on vital signs, even in a population with 21.9% alcohol intoxication. ²⁵

Numerous studies have looked at the combination of ketamine and opioids. One study did note a small percentage of patients had transient oxygen desaturation and this was more common if given concomitant opioids with low dose ketamine. ²⁶ However, all responded quickly to 2-4 L nasal cannula O₂, suggesting that if opioids are used in combination with ketamine that monitoring of oxygen saturation would be beneficial. Adding low dose ketamine to standard morphine sulphate dosing improves the pain/nausea scores and hemodynamic parameters compared to morphine sulphate alone. There is adequate analgesia from small doses of additional ketamine, with stable vital parameters, however with a tendency of increased frequency of nausea and vomiting. ²⁷ In another study looking at hydromorphone with ketamine, lower rates of emesis were appreciated in patients receiving ketamine than those being treated with hydromorphone. ²⁶ Low dose ketamine, defined at IV dose of less than 1 mg/kg, has been shown to decrease the amount of morphine required for pain control, with minimal oxygenation desaturation and respiration depression. ^{19, 49}

When administering ketamine clinicians should expect that eyes will usually be open and will often have a vertical nystagmus. Caution is advised when using ketamine in patient's with renal and hepatic insufficiency because of lack of information regarding the safety and dosing of ketamine. As with any medication that impacts the sensorium physicians must be prepared to recognize and manage airway obstruction, cardiorespiratory adverse events are rare and typically do not affect outcomes.

Adverse Effects/ Contraindications to Ketamine Use:

There have been no studies producing evidence indicating any significant adverse effects of the use of ketamine in the emergency clinical setting. Airway and breathing are rarely compromised when ketamine is used as a monotherapy.²⁸ Primary limitation of ketamine in clinical use is its dose-dependent psychomimetic effects that include dizziness, confusion, hallucinations, and emergence reactions.^{37, 41, 43}

Ketamine can cause both sedation and psychomotor agitation, hallucinations, altered sensorium, agitation, emergence reactions. Rate of mild dysphoric effects has been reported to be 16-26% however negative reactions are universally short lived and differ substantially from emergence phenomenon.^{19, 9, 28, 43} Actual emergence phenomena has not been reported with subdissociative dosing of ketamine below 0.3 mg/kg.^{38, 39} Low dose ketamine patients do frequently experience dizziness, changes in vision and a floating sensation.^{38, 39} These effects occur in the first several minutes after administration and are typically short lived. Some patients find the experience unpleasant, others are not bothered by it and many seem to enjoy it.^{38, 39} The likelihood of experiencing strange symptoms should be discussed with all patients before administration.^{38, 39} Although these minor unpleasant psychomimetic effects rarely require treatment, small doses of a benzodiazepine typically prove effective.^{38, 39} Providers who administer low dose ketamine should routinely coach patients just before administration, reassuring them that any dysphoric reaction will be short lived and create as calm an environment as possible.²⁶

The increase in salivation produced by ketamine can be troublesome and may produce laryngospasm in children. Premedication with an antisialogogue may be needed.^{41, 42}

The two absolute contraindications are age less than three months and known or suspected schizophrenia.⁴⁹ Multiple relative contraindications to ketamine use exist and are (1) uncontrolled seizure activity, (2) severe signs of elevated intracranial pressure, (3) renal and/or liver failure and (4) women who are pregnant or breast feeding. Concerns for increased cerebral perfusion pressure had previously designated traumatic brain injury as a contraindication, but recent studies have shown that ketamine's positive hemodynamic profile prevents cerebral ischemia that is often a complication of other sedatives.^{44, 45}

Recovery & Discharge

Inconclusive anecdotal evidence suggests that excessive noise or stimulation during recovery from ketamine can provoke or exacerbate recovery reactions.^{32, 33, 35} However one ED study found no correlation between recovery agitation and the degree of external stimulation in children.⁵¹ When feasible, consider recovery in a well-monitored location with muted lighting, noise, and physical contact. Recovery time from ketamine dosing is longer than with propofol and etomidate, but ketamine offers analgesia that outlasts sedation – a benefit to the patient who is expected to have postprocedure pain.³⁶

There is insufficient evidence for specific minimum discharge criteria after dissociative sedation. Given that delayed serious adverse events after ED ketamine administration have not been reported this would be difficult to study. Typical recommendations include a return to pretreatment level of verbalization, awareness, and purposeful neuromuscular activity.⁵² One study has shown that important adverse events did not occur 30 minutes beyond final drug administration in children sedated with either ketamine or midazolam.⁵³ The evidence is insufficient to support pre-discharge requirements after dissociative sedation however general observation to attain pretreatment level of verbalization, awareness, and purposeful neuromuscular activity seems reasonable and readily attainable given the short duration of action of ketamine.

It is important to advise and counsel patients that after receiving ketamine, patients can experience ataxia for hours, and close family observation is warranted to prevent falls.^{32, 33, 35} Oral intake should be delayed for a discrete period after discharge because of potential emesis.

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