THE CENTRAL ROLE OF KETAMINE IN PAIN MANAGEMENT

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Introduction
Surgery and trauma produce local inflammation and a change in the patient’s sensitivity to noxious stimuli. As the area of tissue injury becomes more sensitive, the threshold for subsequent stimuli decrease; this is termed primary or peripheral hyperalgesia and is a result of inflammatory mediators sensitizing local nociceptors. Hypersensitivity does not remain localized to the original site of injury but spreads to other parts of the body; this is termed secondary hyperalgesia. For example, following an ovariohysterectomy there is a decrease in the mechanical threshold at the incision site but also at remote sites such as the forelimb. When neurons in the dorsal horn are repeatedly stimulated by incoming afferent signals their rate of discharge dramatically increases over time resulting in central hypersensitization, which has more recently been termed central plasticity. Because of these changes, the response to subsequent incoming information is altered. Activation and modulation of N-methyl-D-aspartate (NMDA) receptors by the excitatory neurotransmitter glutamate is thought to be the primary mechanism in the development of central plasticity and secondary hyperalgesia and the dorsal horn of the spinal cord is where this happens. The goals of perioperative and trauma pain management are to prevent both primary and secondary hyperalgesia.

Ketamine has traditionally been considered a dissociative anesthetic but its role as a potential analgesic, or anti-hyperalgesic agent, has evolved over the years in human and veterinary medicine.\textsuperscript{1, 2} Ketamine is a non-competitive NMDA receptor antagonist. Ketamine may also have activity at opioid, monoaminergic and muscarinic receptors and at voltage sensitive Ca\textsuperscript{2+} channels and although these mechanisms are not fully understood they may also contribute to its actions. These effects occur at sub-anesthetic doses and in a clinical pain management setting ketamine is most often given as a continuous infusion and at the rates used, adverse side-effects are rare and the classic signs of dissociative anesthesia (muscle rigidity and salivation) are not seen.

Veterinary Studies
Several clinical studies in dogs undergoing surgery have shown beneficial effects of ketamine. In a study of female dogs undergoing ovariohysterectomy dogs received a sub-anesthetic dose of ketamine (2.5 mg/kg intramuscularly) pre-operatively or post-operatively (at extubation), or saline.\textsuperscript{3} Other analgesic agents were not given, and premedication was with acepromazine and anesthesia induced with thiopental. Mechanical nociceptive thresholds were measured, and pain scores recorded before premedication and post-operatively for up to 18 hours after extubation. Dogs in the control (saline) group required more rescue analgesics, showed more wound sensitivity and had higher pain scores throughout the post-operative period than those in the two ketamine groups. Administration of ketamine before surgery was more effective that administration after surgery. Ketamine should therefore not be used alone to alleviate acute pain but can be used as part of a multimodal perioperative pain management plan for major surgery or in trauma patients. Treatment should start prior to surgery and continued for up to 24 hours after surgery. Ketamine treatment should begin as soon as possible after initial triage. Wagner and colleagues studied the effects of adding low dose ketamine
infusion (a control group received saline infusion) to an already established analgesic protocol that included pre-operative morphine and intra- and post-operative fentanyl infusion in dogs undergoing forelimb amputation. The ketamine protocol used was: 0.5 mg/kg IV (bolus) given before surgery followed by 10 µg kg⁻¹ min⁻¹ during surgery and 2 µg kg⁻¹ min⁻¹ for 18 hours after surgery. At 12 and 18 hours after surgery the ketamine treated dogs had lower pain scores and on the third post-operative day this group were also significantly more active. A study of major soft tissue surgery (mastectomy) looked at two dosing regimens of ketamine given intravenously after surgery (low dose: 150 µg kg⁻¹ followed by 2 µg kg⁻¹ min⁻¹, high dose: 700 µg kg⁻¹ followed by 10 µg kg⁻¹ min⁻¹ with both infusions given for 6 hours) and compared these to a saline control group. All dogs received pre-operative morphine. There was no difference in the post-operative pain scores or in postoperative morphine requirements between the 3 groups however; the "high dose" ketamine protocol improved feeding behavior.

Another popular regimen is the combination of morphine, lidocaine and ketamine as a continuous infusion. This is anesthetic sparing (decreases inhalant anesthesia requirements) in dogs. Lidocaine infusion should not be used in cats due to adverse cardiovascular effects. Ketamine has been shown to reduce C-reactive proteins in dogs with pyometra and may have immunomodulating effects in the face of endotoxemia.

These clinical studies combined with extensive data in other species supports the use of ketamine in the perioperative period, in trauma patients and in patients with sepsis.

Less is known about low dose ketamine protocols in cats. In a research setting ketamine had minimal effect on thermal thresholds, however this may not be the correct model for assessing ketamine’s analgesic properties. Clinical experience suggests that ketamine can provide some analgesia in cats undergoing surgery, but as in dogs, ketamine is not considered sufficient as a sole analgesic agent for surgery.

**Recommended doses:**

**Dogs** - bolus (loading dose); 0.5-1.0 mg/kg IV followed by constant rate infusion (CRI) at 2-10 µg kg⁻¹ minute⁻¹ (0.12- 0.6 mg kg⁻¹ hour⁻¹); the higher infusion rates are used during surgery and then tapered following surgery.

**Cats** – bolus (loading dose); 0.5 mg/kg IV followed by constant rate infusion at 5-20 µg kg⁻¹ minute⁻¹ (0.3-1.2 mg kg⁻¹ hour⁻¹) during surgery and reduced to 2-5 µg kg⁻¹ minute⁻¹ (0.12-0.3 mg kg⁻¹ hour⁻¹) in recovery.

For both dogs and cats, if the patient is a trauma patient and not undergoing surgery, the bolus dose is usually given followed by a “mid-range” CRI based on the patient’s response.

If an infusion pump is used, the stock solution of ketamine (100 mg/ml) will require dilution; usually at least by 10-fold and normal saline or balanced electrolyte solution can be used as the diluent. If it is being added to a bag of intravenous fluids, instructions can be found at the Veterinary Anesthesia Support Group website: www.vasg.org/constant_rate_infusions.htm and http://www.vasg.org/drug_delivery_calculators.htm
A simple method for calculating how much ketamine to add to a fluid bag is shown below:

$$\text{Dose}^* = \text{diluent (mls)} \times \frac{\text{dose mg/kg/hr}}{\text{mls/kg.hour fluid rate}}$$

* This is the mg of drug to add to the bag

**Contraindications** – ketamine at anesthetic doses (≥ 5 mg/kg) is contraindicated in animals with head trauma and eye injuries or glaucoma as ketamine at these doses can increase intracranial and intraocular pressure; however, the low doses used for infusions are unlikely to cause problems and may be beneficial.

**The future of ketamine in human and veterinary medicine**

Ketamine is being used in a wide range of medical settings including the treatment of suicidal ideation and depression in humans.\(^{10,11}\) It is being used for reducing pain related to trauma, and for procedural sedation in children, with the advantage that it can be given intranasally.\(^{12,13}\) Its role as a treatment for peripheral and central pain following major limb injuries suffered in combat is well documented and initiatives are underway to optimize how it is used for neuropathic pain management.\(^{14,15}\) Much of this research comes at a time when the use of opioids for acute and chronic pain is being critically evaluated because of the opioid epidemic (and shortage) in the United States and is likely to help veterinarians establish new protocols for animals. To ensure rational use of ketamine in acute and chronic pain management in humans several medical groups have written consensus guidelines.\(^{16,17}\) Other areas where ketamine shows promise include ischemic and reperfusion injury and neuroprotection following acute injury to the central nervous system.\(^{18,19}\) In 2017 the International Anesthesia Research Society published an infographic titled “Villain to Victor: Ketamine in Acute Neurologic Injury”, stating that although still investigational, ketamine shows tremendous promise as a neuroprotectant.

**References**


