KETAMINE FOR ANALGESIA

SUMMARY

Ketamine is a dissociative/hypnotic agent historically used for anesthesia; however, in the 1980s, its analgesic properties were discovered and described leading to its increased use in pain management. A significant amount of data on the use of ketamine for management of pain in the perioperative setting currently exists. In this setting, ketamine has been shown to be a safe and effective treatment option, although optimal dosing strategies have yet to be established. In addition, controversy remains on which surgery type would benefit most from the use of ketamine as a component of multi-modal pain therapy.

RECOMMENDATIONS

- **Level 1**
  None
- **Level 2**
  - **Ketamine, at sub-dissociative doses (<0.5 mg/kg/hour IV), may be considered in patients with moderate to severe pain as part of a multimodal pain control strategy to decrease opioid requirements.**
- **Level 3**
  - **Low-dose Ketamine dosing strategies:**
    - **Ketamine IV 0.3-0.5 mg/kg bolus dose**
    - **Ketamine IV 0.1-0.3 mg/kg/hour x 24-72 hours for severe pain or surgeries associated with significant pain (major abdominal surgery, thoracotomies, orthopedic)**

INTRODUCTION

Ketamine is a dissociative/hypnotic agent initially developed as a derivative of phencyclidine (PCP) for general anesthesia. After widespread use during the Vietnam War, ketamine was approved by the FDA in 1970 as an amnestic agent. Ketamine mainly acts through antagonism of N-methyl-D-aspartate (NMDA) receptors causing functional and electrophysiological dissociation. The use of ketamine as an analgesic agent did not really begin until the 1980s when the NMDA receptor was discovered to have a major role in the processing of pain, particularly in the central nervous system. Through NMDA receptor antagonism, ketamine attenuates centrally-mediated pain processes to reduce the development of opioid tolerance and opioid-induced hyperalgesia (1). In addition to action on NMDA receptors, ketamine also acts as a weak opioid receptor agonist, alpha-1 and beta-2 receptor agonist and muscarinic acetylcholine receptor inhibitor (2,3). The analgesic properties of ketamine are observed at sub-anesthetic doses (<1 mg/kg IV bolus dose and <0.5 mg/kg/hr IV continuous infusion).

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

Ketamine has a rapid onset of action of 1-1.5 minutes and duration of action of 30-60 minutes (2,3). Ketamine is highly lipid soluble and therefore crosses the blood brain barrier to exert its central nervous system (CNS) effects. Ketamine undergoes extensive first pass metabolism and has poor absorption orally; therefore, intravenous dosing is most likely the optimal mode of administration.

When utilized for analgesia, ketamine is administered at doses lower than when used as an anesthetic agent. Compared to anesthetic doses, sub-dissociative dosing (<1 mg/kg IV bolus dose and <0.5 mg/kg/hr IV continuous infusion) of ketamine is advantageous due to the lower risk of side effects. Adverse effects include neurologic (psychotomimetic effects), cardiovascular (hypertension and tachyarrhythmias), and respiratory (hypersalivation and laryngospasm). Although rare, cystitis has also been reported. The most notable of these are the psychotomimetic effects which include delirium, delusions, bad dreams, and hallucinations. These side effects can be mitigated with concomitant use of benzodiazepines, with midazolam being the most common. Psychotomimetic effects are dose-dependent; therefore, the risk of development is higher with increased doses. Psychotomimetic effects occur in 7-8% of patients given sub-dissociative doses compared to 3.6-5% in placebo patients (1). Cardiac adverse effects including hypertension and tachyarrhythmias result from ketamine's action on alpha and beta-receptors. These effects are often transient, do not require treatment, and are most often associated with anesthetic doses (1). Ketamine can also cause increases in secretions leading to hypersalivation, although this has not been reported at sub-anesthetic doses. Hypersalivation can be treated with an antisecretory agent such as glycopyrrolate or scopolamine.

Ketamine is a potent analgesic at sub-dissociative doses ranging from 0.1-0.5 mg/kg when used for bolus dosing (8,9). Administration of continuous infusion ketamine for analgesia ranges from 0.06-0.6 mg/kg/hr (1-10). Of note, doses <0.1 mg/kg/hr are less likely to be effective. Several studies have assessed the use of low-dose ketamine infusion for post-operative pain control and demonstrated a 20-30% reduction in morphine use (4-10). Although utilization of ketamine as a component of multimodal pain control has demonstrated reduction in opioid usage, studies have not consistently shown a reduction in pain scores when compared to standard pain management consisting of mainly opioids. The lack of positive results with pain scores as an outcome could be misleading due to the fact that patients in the control groups were receiving pain medications to treat elevated pain scores; therefore, reduction of opioid use is most likely the more important outcome. Additionally, the long-term effects of administration of continuous infusion ketamine greater than 72 hours have not been assessed (1).

An advantage of ketamine over opioid agents for analgesia is that it does not cause respiratory depression making it an attractive agent for patients who are not mechanically ventilated. In addition, ketamine maintains hemodynamic stability through action on alpha and beta receptors suggesting an advantage in patients with concern for hemodynamic instability. These attributes make ketamine an attractive option for patients who have undergone procedures associated with significant chronic pain (i.e., abdominal, thoracotomies, etc…) or injuries associated with significant pain (i.e., rib fractures, orthopedic injuries). However, few studies have assessed the utilization of ketamine for specific surgical procedures or injury types.

With minimal risk of causing significant adverse effects, low-dose ketamine does not require extensive monitoring. Therefore, with appropriate education of nursing staff, bolus dosing and continuous infusion of low-dose ketamine can be administered on all levels of care. This is supported in the literature with institutions describing the safe and effective use of low-dose ketamine in patients admitted to general medical/surgical floors (11,12).

LITERATURE REVIEW

Postoperative Pain Management

Guillou et al. compared the use of ketamine to placebo in a randomized, double-blinded study of surgical intensive care unit patients who had undergone major abdominal surgery. The primary outcome of the study was morphine consumption. All patients received a morphine patient-controlled analgesia (PCA) pump for 48 hours. Ninety-three patients were included in the study. The mean age was 60 years in both groups and the most common surgeries performed were hepatectomy followed by esophageal surgery. Mean Simplified Acute Physiology Scores (SAPS) were 30 for both groups indicating a relatively low

mortality rate. Patients in the ketamine group received an initial bolus of 0.5 mg/kg followed by an infusion of 0.12 mg/kg/hr for the first 24 hours followed by 0.06 mg/kg/hr for another 24 hours. The study found that although visual analog pain scale scores were not significantly different, there was a significant difference in morphine consumption between the ketamine group (53 mg) compared to the morphine-only group (80 mg). There was no significant difference in adverse effects between the two groups (4).

Adriaenssens et al. conducted a double-blind, randomized study of thirty laparotomy patients administered a ketamine infusion of 0.15 mg/kg/hr for 48 hours along with a morphine PCA pump for post-operative pain compared to placebo. There was no difference in visual analogue pain scores. The study found a significant reduction in morphine consumption at 48 hours; 28 mg in the ketamine group compared to 54 mg in the morphine group ($p=0.0003$). There was no significant difference in adverse effects except for less nausea in the ketamine group ($p=0.03$) (5).

Remerand et al. compared the use of continuous low-dose ketamine to placebo for 154 patients who underwent total hip arthroplasty with the primary outcome of 24-hour morphine use. The ketamine group received an intraoperative ketamine bolus of 0.5 mg/kg followed by a continuous infusion of 0.12 mg/kg/hr for 24 hours. In addition to ketamine and morphine, all patients received a single dose of paracetamol and scheduled ketoprofen postoperatively. The study found a 28% reduction in morphine consumption within the first 24 hours of ketamine infusion. There was no significant difference in pain score between the two groups and a non-significant reduction in the incidence of nausea in the ketamine group (6).

Yamauchi et al. assessed two different ketamine infusion strategies versus placebo in 200 post-cervical or post-lumbar surgery patients. The primary outcome of the study was postoperative fentanyl consumption. Patients in the ketamine group received either a bolus of 1 mg/kg followed by a continuous infusion of 0.042 mg/kg/hr or a bolus of 1 mg/kg followed by a continuous infusion of 0.083 mg/kg/hr for 24 hours. All patients received a fentanyl PCA programmed to administer a basal infusion along with an on-demand dose every 6 minutes. For both post-cervical and post-lumbar surgery patients, there was a significant decrease in pain score in patients who received infusions of 0.083 mg/kg/hr compared to the 0.042 mg/kg/hr or placebo groups. Additionally, post-cervical surgery patients received lower overall fentanyl and NSAID consumption. Post-lumbar surgery patients received less fentanyl compared to placebo up until 6 hours of the infusion. The only significant adverse effects noted were nausea and vomiting which were lower in the higher ketamine infusion group (7).

Laskowski et al. conducted a meta-analysis of 47 double-blind randomized studies of intravenous ketamine used for perioperative or postoperative pain control. Patients who underwent abdominal or thoracic procedures showed the greatest reduction in opioid use. Patients who underwent orthopedic, intra-abdominal and pelvic surgeries also showed decreased opioid use. Although no serious adverse effects were noted, patients who received ketamine experienced increased neuropsychiatric effects (7.4% versus 3%) and decreased post-operative nausea and vomiting (25.6% versus 30.4%). The majority of studies utilized doses less than 0.5 mg/kg. The meta-analysis did not report the mean duration of ketamine administration (8).

Jouguelet-Lacoste et al. conducted a systematic review of 39 clinical trials and five meta-analyses assessing perioperative low-dose intravenous continuous infusion or intravenous bolus of ketamine. All the meta-analyses found a reduction in pain scores and opioid consumption postoperatively. In studies assessing postoperative infusions of ketamine, the majority of studies utilized infusions between 0.042-0.18 mg/kg/hr. There was limited reduction in opioid consumption in trials which utilized ketamine infusions <0.10 mg/kg/hr. Only one study of postoperative ketamine infusion utilized pain score reduction as the primary outcome and concluded administration of ketamine reduced postoperative pain. The studies utilized ketamine postoperatively for 24-48 hours with or without IV boluses prior to initiation of the infusions. The analysis concluded that low dose administration of ketamine was safe and effective for management of postoperative pain (9).

Analgesia in Trauma Patients

Polomano et al. conducted a retrospective review of 19 patients with combat wounds with major limb trauma treated with low-dose continuous infusion ketamine for 3 days. Patients had failed conventional

pain treatments including multimodal analgesia and regional anesthesia techniques. The majority of patients sustained traumatic or surgical amputations of one limb. Ketamine infusions were initiated at 0.12 mg/kg/hr with dose adjustments in only three patients. Overall, there was no significant reduction in opioid requirements. However, patients experienced a significant decrease in reported pain while on ketamine compared to opioid therapy alone (13).

Losing et al. described a case series of three multi-trauma patients treated with low dose continuous infusion ketamine for pain control. Patient ages ranged from 26-65 years old and all patients suffered from rib fractures. Ketamine dosing ranged from 0.06-6 mg/kg/hr. Opioid requirements decreased in all patients after initiation of ketamine. A dissociative adverse effect occurred in one patient requiring reduction of the ketamine infusion and subsequent discontinuation (14).

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