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ACUTE PAIN MEDICINE (R URMAN, SECTION EDITOR)

Perioperative Use of Ketamine

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Abstract

Purpose of Review Postoperative pain continues to be one of the most common challenges following surgeries. Multimodal analgesia has been of particular focus as non-opioid alternatives have been encouraged due to concerns of the opioid epidemic. Ketamine has been an especially useful adjunct in multimodal pain regimens within the past few decades. This article highlights the current use and advances surrounding the perioperative use of ketamine.

Recent Findings Ketamine has antidepressive effects at subanesthetic doses. Intraoperative ketamine may be beneficial in reducing postoperative depression. Additionally, newer studies are exploring whether ketamine can be useful in reducing postoperative sleep disturbances.

Summary Ketamine continues to be a great tool in perioperative pain control, especially during an opioid epidemic. As its use continues to expand and gain more popularity in the perioperative period, more research could shed light on the additional nonanalgesic benefits of ketamine use.

Keywords Ketamine · Norketamine · Esketamine · Perioperative · Postsurgical · Acute pain

Introduction

Ketamine is an N-methyl-D- aspartate (NMDA) receptor antagonist that also acts on mu opioid receptors, muscarinic receptors, monoaminargic receptors, and several others. It was first developed in the 1960s for veterinary purposes. By the 1970s, ketamine was FDA-approved and has since been used as an anesthetic. Ketamine has a potent rapid-acting anesthetic effect, and its profound analgesic properties are due to its NMDA receptor antagonism. Ketamine absorption and distribution are very rapid, with it having a distribution half-life of 1.95 min. It has a bioavailability of around 93%. Ketamine metabolism is mainly through the hepatic system. Its major metabolite is norketamine, which is an active metabolite. Ninety-one percent of ketamine is eliminated renally in the form of its metabolites. Other routes of elimination are via bile and feces. The half-life of ketamine is about 186 min.

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Although ketamine has been a well-established drug for treating chronic and acute pain for decades, there has been a recent surge in its use in the acute setting. Ketamine has gained popularity in the acute pain and perioperative period due to its ability to reduce opioid consumption and pain scores [1•, 2]. Evidence supports that subanesthetic doses have been effective as a stand-alone analgesic and an opioid adjunct in providing perioperative analgesia [3••].

Intraoperative Ketamine

As ketamine use has grown in popularity, there has been a considerable amount of variability in its use. Ketamine is often administered intraoperatively. The literature reports varying bolus and infusion doses administered. In 2020, the American Society of Regional Anesthesia and Pain Medicine (ASRA), the American Academy of Pain Medicine (AAPM), and the American Society of Anesthesiologists (ASA) compiled consensus guidelines for the use of ketamine infusions in the acute pain setting. We will discuss indications, contraindications, and dosing of intraoperative ketamine.

Indications

Ketamine is an effective analgesic that aids in reducing postoperative pain and opioid consumption. Within the past few

years, ketamine has been shown to be of most particular benefit in procedures that are expected to be severely painful. This includes abdominal, thoracic, and major orthopedic procedures [3••, 4]. Whereas procedures expected to cause mild pain levels have not been shown to benefit from perioperative ketamine.

Patient-specific factors should also be accounted for when considering administering perioperative ketamine. Patients who are opioid dependent or those who have acute exacerbation in a chronic pain condition may benefit from the acute use of ketamine for perioperative pain reduction and possible reduction of acute opioid use [3••, 5]. A 2022 meta-analysis of randomized controlled trials revealed that there was limited evidence for reduced perioperative pain intensity in adults who were already consuming opioids preoperatively, but there was a cumulative reduction in opioid consumption [6]. Although there may not be a significant reduction in pain scores overall when combining ketamine with opioids, there is often opioid sparing.

Additional patient populations that may benefit from the use of ketamine perioperatively are those who are at increased risk for respiratory depression related to opioid administration, such as those with high body mass index (BMI) or patients with obstructive sleep apnea (OSA). Currently, there is a lack of high evidence regarding the use of ketamine in the OSA population. However, adjuncts that limit the amount of opioids administered to this population may be beneficial in reducing the risk of postoperative respiratory depression related to opioids. New research about whether ketamine use reduces postoperative opioid consumption and reduces length of stay after bariatric surgery is being conducted [7]. A retrospective study that included about 400 patients who underwent bariatric surgery was conducted. Findings showed that the patients who did not receive ketamine had greater lengths of stay. Results of this study suggested that there may be utility in including ketamine in Enhanced Recovery After Surgery (ERAS) protocols. Additionally, studies are being conducted to explore the use of opioid-free multimodal analgesia in bariatric surgery, as a 2022 protocol has been published [8]. Although there is currently a lack of evidence regarding the use of ketamine in high BMI and OSA population, the use of ketamine in these groups reduces the need for agents that cause respiratory depression, so perioperative ketamine administration seems promising in this population.

Dosing

Analgesic ketamine is supposed to be administered in subanesthetic doses to achieve its desired purpose. However, the dosing and a clear cutoff of what is considered subanesthetic has not been clearly defined in the literature.

Table 1 Ketamine Dosing suggestions

Purpose	Dosing
Anesthetic induction	1-2 mg/kg
Bolus dose (loading or supplemental)	0.1-.5mg/kg
Analgesia (for nonintubated patients)	1-5 mcg/kg/min
Sedation/analgesia (for intubated patients)	5-30 mcg/kg/min
Treatment resistant depression	0.5mg/kg over 40 min

Intraoperatively, ketamine has been commonly administered as a bolus, an infusion, or a bolus followed by an infusion. When reviewing several randomized control trials, common bolus doses in clinical practice have ranged from 0.2 to 1 mg/kg bolus with or without infusion. In the 2020 consensus guidelines by ASRA, AAPM, and ASA, the recommendation was that ketamine bolus doses do not exceed 0.35 mg/kg or 0.5 mg/kg for non-narcotic-naïve [3••]. In most studies, infusion dosing has been 0.1 to 0.5 mg/kg per hour. In the 2020 consensus guidelines, the recommendation was that ketamine infusions do not exceed 1 mg/kg per hour. Dosing suggestions are summarized in Table 1.

Contraindications

The relative contraindications for the use of perioperative ketamine are similar to the contraindications of ketamine use in the chronic pain setting. These include severe cardiovascular disease, elevated intracranial or intraocular pressure, severe hepatic dysfunction, acute psychosis, and pregnancy [3••] Table 2.

Postoperative Ketamine

There have been many studies evaluating the efficacy of perioperative ketamine as an adjunct to opioids. In most of these studies, ketamine was administered intraoperatively. Newer studies aim to explore the efficacy of ketamine

Table 2 Contraindications

Relative Contraindications of Ketamine Use
Elevated intracranial pressure
Elevated intraocular pressure
Severe Hepatic dysfunction
Psychosis
Pregnancy
Severe cardiovascular disease (coronary disease, poorly controlled hypertension)
Active Substance abuse

given in the Post Anesthesia Care Unit (PACU). In a 2023 prospective observational study, the use of ketamine as a rescue analgesic in the PACU was studied. One hundred patients who had opioid-resistant pain were given low-dose (max dose of 0.25/mg/kg) ketamine in the PACU and pain scores were evaluated 30 min after administration. They found that the administration of low-dose ketamine in the PACU for opioid-resistant patients led to a significant reduction in pain scores [9]. Another randomized single-center study in 2023 explored the administration of a single dose of 0.6 mg/kg bolus in the PACU after mastectomy [10]. They found that this single dose in the PACU resulted in a reduction of pain control up to 1 week after the study. Both studies showed that ketamine administration in PACU may result in better postoperative pain control. Studies with larger sample sizes and with varying patient populations should be conducted in the future to explore the efficacy of postoperative ketamine bolus. Additionally, it may be worthwhile to explore the effective dosing of postoperative ketamine.

New and Interesting Findings

Reduction of Postoperative Depression

Ketamine has antidepressant effects at subanesthetic doses. Surgery is often a psychological stressor for patients as it can incite anxiety and depression, which can lead to poorer postoperative outcomes, including poor postoperative pain and prolonged hospitalization. The effect of ketamine on postoperative depression has been controversial as some studies have shown a significant effect of ketamine in reducing postoperative depression, while others have shown that ketamine has no effect on the prevention or improvement of depressive symptoms [11•, 12•, 13••]. In a 2023 meta-analysis that included 15 studies and 1700 patients, it was found that perioperative ketamine does reduce postoperative depression but had an increased risk of adverse effects such as nausea, vomiting, headache, or hallucinations. In a randomized double-blind trial, ketamine was given to 210 patients undergoing cesarean section with spinal anesthesia. This study showed that ketamine did not reduce depression at one, two, or 4 weeks postoperatively [12•]. Whereas in a 2021 study, ketamine was given to neurosurgery patients undergoing intracranial tumor resection. This trial showed that ketamine could reveal moderate to severe depression in neurosurgical patients [14]. The data surrounding ketamine on the reduction of postoperative depression has been inconclusive. More research is needed to establish whether there is a significant effect and whether the effects produce lasting results. In addition, it would be interesting to explore whether surgery type, anesthesia type (general versus spinal versus sedation), confounds the effects of intraoperative ketamine administration on the reduction of postoperative depression.

Improving Perioperative Sleep Disturbances

Surgical patients often complain of postoperative sleep disturbance. Sleep disturbances have been shown to worsen pain perception. There is a sparsity of literature regarding the effect of ketamine on postoperative sleep disturbance. In a 2022 clinical trial, ketamine infusions were administered intraoperatively to 183 patients. Findings showed that ketamine was prophylactic in reducing postoperative sleep disturbances in patients undergoing gynecologic surgery [15].

Conclusions

Ketamine is an old drug that continues to be a great tool in perioperative pain control, especially during an opioid epidemic. As its use gains more popularity and expands, we are continuing to learn about possible additional benefits that the drug may provide. More research is needed to discover the ideal indications and dosing of ketamine in the setting of multimodal and perioperative pain control. Additionally, more research could shed light on other beneficial and adverse side effects.

Compliance with Ethical Standards

Conflict of Interest All authors declare that they have no conflicts of interests or competing interests to disclose.

Human and Animal Rights and Informed Consent This article does not contain studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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