Ketamine Infusions: Role and Use in Ambulatory Surgery Centers

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Abstract

As many patients are refractory to traditional methods of treatment for chronic neuropathic pain and psychiatric illness, physicians and researchers looked to other avenues for alternative treatment possibilities. Ketamine, which has actually been around for over 50 years, is a dissociative anesthetic, used historically mostly for induction of anesthesia and functions via N-methyl-d-aspartate receptor complex inhibition. While the undesired dissociative effects have caused it to have limited, but necessary, utility as an induction agent, ketamine delivered at subanesthetic doses has shown to improve pain and depressive symptoms in patients suffering from chronic pain or depression refractory to standard treatment. Ketamine infusions are quickly becoming more popular among patients and providers as treatment alternatives for pain or depression that is not responding to the traditional method of treatment. Patients across the United States continue to be at risk of opioid abuse as the search for powerful non-opioid analgesia is still ongoing. Ketamine infusions delivered at subanesthetic doses may also be a possibility as treatment for patients suffering from opioid addiction. Currently, ketamine infusions are offered around the United States as an off-label treatment for chronic pain, post-traumatic stress disorder (PTSD), depression, and a variety of other psychiatric and neuropathic pain conditions. In this chapter, we discuss the role of ambulatory surgery centers in ketamine infusions and benefits for patients and providers.

Introduction

Ketamine, a phencyclidine derivative, received FDA approval for clinical use in 1970. It has been a uniquely useful anesthetic over the last 50 years, but lately interest has grown exponentially for its uses outside the realm of the operating room. Ketamine is becoming a more popular treatment option for neuropathic pain refractory to traditional treatments and is also fast becoming an alternative route and treatment option for psychi-
tric illnesses refractory to traditional methods [1–4]. As the opioid crisis came to a peak, the search for non-opioid analgesic medication led to renewed interest and use of ketamine. Ambulatory surgery centers (ASC) are commonly the setting of choice for the administration of ketamine infusions. Although costs for the patient might be slightly higher than if administered in-office, the safety benefits for the patient and provider heavily outweigh what is offered in an office or clinic setting. In an ASC, patients receive some of the highest levels of care, monitoring, access to personnel, and equipment available in modern medicine. ASCs provide a setting that allows patients to avoid excessive hospital fees and time wasted in a hospital system. ASCs as a setting for ketamine infusions not only lessens the financial burden on the patient, but it also wastes less healthcare dollars as patients are not inpatient in most cases.

**Pharmacology**

Ketamine is a commonly used intravenous anesthetic producing its effect through inhibition of the N-methyl-D-aspartate receptor complex [5]. Ketamine has two clinically relevant forms that have been shown to induce NMDA-mediated sensory blockade. (S)-Ketamine is about four times more potent than (R)-Ketamine [6, 7]. The (S)-Ketamine isomer has also been shown to be associated with a reduction of adverse effects without reducing or altering its analgesic and anesthetic properties. Ketamine is oxidatively metabolized in the liver into norketamine, which is considered to be the major metabolite in humans, although recent studies have begun to refute that. Eventually it is hydrolyzed and conjugated to a water-soluble inactive glucuronide metabolite excreted by the kidneys [8]. Norketamine can be measured in plasma about 2–3 minutes of intravenous ketamine bolus with a maximum plasma concentration reaching after 30–60 minutes [5]. Ketamine is rapidly distributed throughout the body with a distribution half-life of 11 to 16 minutes. The elimination half-life of ketamine is 2–3 hours, and it is cleared at 12–17 mL/kg/min [9]. A single induction dose of ketamine is generally 1–2 mg/kg intravenous (IV) or 4–8 mg/kg intramuscular (IM). Patients lose consciousness in 30–60 seconds after IV administration and 2–4 minutes after being given IM injection. Patients can regain consciousness after 10–20 minutes, but they might take 60–90 minutes to fully recover from the dissociative effects. Repeated dose and repeated infusions of ketamine will result in the accumulation of the drug as it has a context-sensitive half-life comparable to that of propofol. Ketamine has a large volume of distribution at 3 L/Kg. Infusions can run anywhere from 45 minutes to several hours as a standard infusion protocol has not been established yet [10, 11]. Ketamine can also be administered as a nasal spray called esketamine; however, it is still quite new and currently very expensive and not cost-effective for the management of treatment-resistant depression unless the price is lowered by 40% or more [12].

**Use in Surgery Centers**

Our primary concern as healthcare providers is patient safety and consideration of all contributing factors to minimize harm. Treatments must be individualized to patients and that includes choosing the optimal setting for treatment administration. The use of ketamine is expanding beyond the idea of just being an anesthetic, and physicians must take heed of multiple factors such as contraindications to ketamine and location of administration of infusion when considering treatment protocols involving the use of ketamine.

Ambulatory surgery centers provide a safe environment where ketamine infusions can be administered because of the level of care they are required to provide. The ASA has created practice guidelines for non-anesthesiologists for the delivery of medications for moderate and deep sedation. The recommendations include ensuring NPO status, use of supplemental oxygen during deep sedation, monitoring of patient consciousness level, hemodynamics, ventilation, and oxygenation prior, during, and after the infusion.
Discharge occurs once certain criteria have been met [13]. Ketamine is associated with adverse psychomimetic effects such as dysphoria, hallucinations, nightmares, and vivid dreams. It is also associated with negative GI symptoms [14, 15]. Proper monitoring of the patient during infusion can possibly help limit the severity of these adverse effects and prevent other more serious adverse effects.

Consensus guidelines and recommendations on the use of intravenous ketamine infusions for acute and chronic pain management have been created by the American Society of Regional Anesthesia and Pain Medicine (ASRA), the American Academy of Pain Medicine (AAPM), and the American Society of Anesthesiologists (ASA) [11, 16]. The evidence was evaluated according to the US Preventive Services Task Force grading of evidence defining the levels of evidence based on magnitude and certainty of benefit [17]. The ASRA/AAPM/ASA recommend that the setting of administration must contain resuscitative equipment and immediate access to rescue medications and personnel trained in treating emergencies. The supervising clinician should be experienced with ketamine, such as an anesthesiologist, who is ACLS certified and trained in administering moderate sedation. The administering clinician is a registered nurse or physician assistant who has completed formal training in safe administration of moderate sedation [11]. While these recommendations hold true for ketamine infusions offered in clinic settings, an ambulatory surgery center (ASC) provides access to far superior resources. Infusions administered in office-based settings are not always under the supervision of an anesthesiologist or individuals trained in moderate to deep sedations. These situations are not always the safest of environments for patients under moderate to deep sedation and are not always set up properly in case of unintended adverse sequelae.

Ambulatory surgery centers must have written transfer agreements with a local hospital, or all physicians who perform surgery at that surgery center must have admitting privileges at a designated hospital. In an ASC, in case of emergencies, patients can be transported to the operating room and managed till emergency transportation arrives to transport to a hospital. If patients experience an aspiration or airway event, patients can be taken to the operating room and have a protected airway till emergency services can transport them to a hospital. If patients were to suffer from an unexpected cardiac event, surgery centers generally have more space for medical staff and personnel to work around and maneuver leading to easier access of the patient. The level of care provided by an ambulatory surgery center (ASC) is greater than what is typically available in a standard clinic setting as conversion to the operating room and maintenance on volatile gases are options while emergency transportation is on their way to the facility. While surgery centers have many safeguards and backups in place, complications resulting in hospital admissions are rare.

Surgery centers are a “goldilocks” option for patients and providers as the location for the administration of ketamine infusion. Many providers performing ketamine infusions prefer to only perform the treatment at an ASC as it guarantees a higher level of monitoring and confidence in the availability of properly trained and equipped personnel. Patient safety is maximized by the increased level of care and monitoring provided by an ASC while costing less out-of-pocket payment from the patient versus if it were performed at a hospital inpatient setting [18].

### Typical Workflow of an Infusion

An example of a typical patient workflow of a ketamine infusion in an ASC is as follows. The patient should arrive 30 minutes prior to their scheduled appointment time to check in at the front desk. This time will allow for any necessary paperwork to be filled out by the patient and allows time for the pre-op nurses to admit the patient including obtaining a history and vital signs. The patient must have fasted for a minimum of 6 hours. Patients should have been instructed to take any medication they currently take daily for comorbidities such as blood pres-
sure control and asthma. A thorough review of any medications taken that day and reconfirmation of nothing to eat or drink are performed again. Any remaining paperwork and consent forms must be discussed and signed. Next, the patient is taken to the area where they will be seated for the duration of the procedure. Many facilities have comfortable reclining chairs set up in the post-anesthesia care unit or near the preoperative area. It is recommended that patients be placed in an area with soft, dim lighting away from any loud or sudden noises. As the medication can have adverse psychoactive effects, it is best to create an environment in which the patient can relax. Many providers have calming music playing in the background of the facility, or they provide noise-cancelling headphones for the patients. Some providers allow their patients to bring their own music; however, it is recommended patients choose soothing music as this experience can trigger emotions. Artwork can also evoke a soothing feeling or calmness for some patients, and as such facilities should be aware when adding artwork to rooms.

When the patient is seated comfortably, they will then be attached to monitors and an initial reading of their vital signs including blood pressure, heart rate, respiratory rate, and oxygenation recorded. The supervising anesthesiologist will then perform a focused preoperative evaluation including a history and physical. Once they have cleared the patient and have ruled out any contraindications to the procedure that day, they can next obtain intravenous access. The nurse or qualified individual will obtain peripheral intravenous access with an 18-gauge or 20-gauge needle, and an IV line will be attached to the patient and to an infusion pump from which the ketamine is administered. Pump settings are chosen based on the IV pump and confirmed by the supervising physician before leaving the patient. As the patient is now beginning to settle down for their treatment, they are then given a sleep mask and offered ear plugs or headphones or just listen to the sound of the room if it has soothing music.

The infusion is run through a liter of normal saline. The nurse will continue to monitor the patient, and the supervising anesthesiologist will also monitor the patient and will check in on them from time to time as the patient is receiving their infusion. Once the infusion is completed, the nurse will then disconnect and remove the IV from the patient. The IV site is sometimes left if the patient is to return for another infusion in the next few days. If it is the case, the patient is instructed to avoid tampering with it at all costs and to shower and bathe with it protected and covered with plastic. If the IV site is to be removed, the nurse can remove it and clean the site with alcohol and place a band aid or tape with gauze over the puncture site.

Discharge from the ASC after infusion can follow a modified Post Anesthesia Discharge Scoring System as follows in Fig. 15.1. Other post-anesthesia care unit discharge scoring systems can be used; this is mostly dependent on provider experience and/or protocol set by the ASC. The patient should expect to feel relaxed and calm after the infusion and can resume eating and drinking normally. Patients must have a ride home as they are not allowed to drive themselves home or operate heavy machinery for 12 to 24 hours post-infusion. They should also receive instructions to not operate any kitchen equipment or power tools. They should avoid any strenuous activities and any recreational activities such as swimming, hiking, hunting, fishing, etc. for the next 12–24 hours. They should be instructed to avoid alcohol consumption for the next few days and avoid any recreational substances they might take. Any medications that were stopped prior to the procedure can now be resumed. Some providers will prescribe a very weak benzodiazepine for sleep aid, and others might recommend the use of over-the-counter diphenhydramine if they have trouble sleeping. Patients might be slightly nauseous and/or fatigued after the infusion but should be able to communicate more clearly than when they were receiving the infusion. If patients notice any unusual side effects or changes, they should contact their physician or call 911 if it is an emergency.
New avenues in the study of pain management, neurology, psychiatry, and other specialties have shown potential uses for ketamine. Neuropathic pain is highly prevalent and is estimated between 6% and 10% of the population [1]. It has been shown that low-dose intravenous ketamine reduces opioid consumption by 40% while also reducing pain scores in patients receiving a continuous infusion or boluses of low-dose ketamine for postoperative analgesia [15]. It is known that excessive activation of glutamate receptors enhances excitatory transmission of nociceptive pain pathways in chronic pain. Comprehensive review of literature has shown that NMDA receptor antagonists can help treat neuropathic pain [19]. Producing significant analgesia when delivered at anesthetic doses, recently ketamine infusions administered at subanesthetic doses have produced long-term and effective pain relief in patients with complex regional pain syndrome type 1 (CRPS-1) refractory to standard pain treatments [4, 20]. (S)-Ketamine administered as a multiple-day infusion has been shown to reduce pain in chronic CRPS-1 patients [4]. New evidence also shows possible neuroprotective effects of (S)-Ketamine [21]. Ketamine provides a new therapeutic option for patients with depression refractory to standard treatment. Several publications have shown ketamine infusions demonstrating efficacy in the treatment of major depressive disorder and marked improvement of depressive symptoms [2, 22]. Ketamine in its current use should not be viewed as a “one-and-done” cure, but as an alternative treatment management option to traditional methods for treating psychiatric disease. A single infusion of ketamine has shown very rapid efficacy in treatment for major

| Vital Signs | 2= within 20% of preoperative values
| 1= 20% to 40% of preoperative values
| 0= 40% or more of preoperative values |
| Activity and Mental Status | 2= and oriented to time, person, place, AND has steady gait
| 1= oriented to time, person, place, OR has steady gait
| 0= unable to ambulate |
| Nausea/Vomiting | 2= Minimal to none, treated with oral medication
| 1= moderate nausea, treated with parenteral/Intravenous medication
| 0= persistent nausea/vomiting refractory to medication |
| Surgical Bleeding | 2= Minimal requiring no dressing change
| 1= Moderate
| 0= Severe requiring 3 or more dressing changes |
| Intake and Output | 2= voiding with input
| 1= difficulty voiding
| 0= retention of fluids |
| Total Pads Score=10 | Consider for discharge when score is ≥ 9 |

Future and New Directions in Pain Management and Beyond

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depressive disorder and bipolar disorder for a week [22]. Patients with chronic migraines or new daily persistent headache might also benefit from treatment with subanesthetic ketamine infusions [23]. Concern regarding NMDA receptor antagonism impairing neurodevelopment has been a question, and now with an increase in ketamine use, further studies are warranted on the specific mechanism of ketamine-induced structural changes in the central nervous system synapses and brain [24]. As the use of ketamine expands, facilities such as ambulatory surgery centers will be used more due to the medical direction of an anesthesiologist, thus allowing for a safe environment in which the medication can be administered.

As the cost of healthcare continues to rise, physicians and other allied professionals working in healthcare must do their share to adopt cost-saving measures in their practice. Physicians and providers should maximize cost-saving tactics without compromising on the safety of patients. In an ASC, costs are significantly reduced as patients are ambulatory and are discharged the same day versus inpatient settings resulting in unnecessary cost and burden on the patient and healthcare system. Even during the COVID-19 pandemic, ASCs were demonstrated to be safe locations for patients to undergo elective surgery if patients received proper preoperative screening [25].

Economics

While the cost of ketamine is relatively low (solution (ketamine HCl injection) 10 mg/mL (per mL), $1.21; 50 mg/mL (per mL), $0.43–$0.98; 100 mg/mL (per mL), $1.97–$2.78), the cost of any infusion treatment can vary from $300 to $800 with some even exceeding $1000. Multiple treatments are often recommended to achieve the best outcomes. While this may seem excessive when compared to the cost of the drug, it tends to be similar to the cost of other intravenous infusion treatments. This is primarily due to the need for monitoring and staff that must be present for an infusion, particularly a sedative. While ketamine infusion treatment claims can be submitted to insurance companies, they are usually not approved as chronic pain and psychiatric treatments and are off-label uses. Esketamine as an intranasal treatment is usually cheaper than an IV ketamine infusion due to elimination of IV supplies. While ketamine is usually readily available, the Food and Drug Administration does list it as currently in a shortage, particularly the 100 mg/mL 5 mL vial. This will continue to change as COVID-19 and other circumstances evolve.

Summary

Ketamine is revealing itself to be much more useful than previously thought. An infusion of ketamine delivered at subanesthetic levels is still considered administration of an anesthetic, and as such, extra care and precautions must be taken while monitoring patients. Ambulatory surgery centers as compared to a standard physician clinic or office are much more equipped for emergencies, since they generally have to adhere to different building and staffing requiring more space, allowing for easier maneuvering, and availability of medical staff experienced in airway management such as a physician anesthesia supervisor. Ambulatory surgery centers offer providers peace of mind knowing their patients are monitored by an anesthesiologist with the facility having all the tools to convert to an operating room environment if need be, albeit unlikely. Ambulatory surgery centers have all the tools a physician would want in a facility where they choose to administer their ketamine infusions. Further, more long-term studies are needed to determine the incidence of adverse events possibly leading to hospitalization in patients receiving ketamine infusions and then comparison of rates of unexpected admission from patients receiving infusions at a clinic versus ambulatory surgery centers.
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