Review Article

Role of ketamine for analgesia in adults and children

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Abstract

Ketamine an N-methyl-D-aspartate (NMDA) receptor blocking agent and a dissociative anesthetic with neurostimulatory side effects. In recent years, multiple research trials as well as systematic reviews and meta-analyses suggest the usefulness of ketamine as a strong analgesic used in subanesthetic intravenous doses, and also as a sedative. In addition, ketamine was noted to possess properties of anti-tolerance, anti-hyperalgesia and anti-allodynia most likely secondary to inhibition of the NMDA receptors. Tolerance, hyperalgesia and allodynia phenomena are the main components of opioid resistance, and pathological pain is often seen in the clinical conditions involving neuropathic pain, opioid-induced hyperalgesia, and central sensitization with allodynia or hyperalgesia. All these conditions are challenging to treat. In low doses, ketamine does not have major adverse dysphoric effects and also has the favorable effects of reduced incidence of opioid-induced nausea and vomiting. Therefore, ketamine can be a useful adjunct for pain control after surgery. Additional studies are required to determine the role of ketamine in the immediate postoperative period after surgical interventions known to produce severe pain and in the prevention and treatment of chronic pain.

Key words: Analgesia, ketamine, N-methyl-D-aspartate receptor, periperative, side effects

Introduction

There are approximately 25 million inpatient surgical procedures performed every year in the United States. A primary concern and challenge for patients and physicians is adequate periprocedural pain care. Despite advances in technology including continuous peripheral nerve catheters and ultrasound guided nerve blocks, > 80% of patients report inadequate pain control resulting in persistent postoperative pain, extended hospital stay, and impaired rehabilitation.[1] Overtreatment may result in adverse events associated with excessive analgesic usage including increased morbidity and mortality, a higher risk of cardiac, pulmonary, gastrointestinal, and immune complications, and a higher rate of thromboembolic events. Other side-effects include central nervous system (CNS) mediated sedation and pulmonary complications including aspiration and atelectasis.[2]

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Pharmacological Properties

Ketamine has been found to be an ideal anesthetic due to its dose-dependent nature of producing analgesia, amnesia, unconsciousness, and akinesia.[2] The dosage is well-established single bolus and consistent across patients.[3] It has been suggested in animals that in addition to low-grade analgesia and high dose anesthesia ketamine could work in synergy with opioids at a dose termed the third dose range of ketamine where ketamine would be devoid of analgesic effects.[4] Clinical studies are required to confirm the third dose effect of ketamine in humans.

Ketamine is a noncompetitive antagonist at NMDA receptor with analgesic and anti-hyperalgesic properties. Its chiral center on the C_2 atom of the ketamine cyclohexane

ring gives rise to two enantiomers of ketamine (S(+)− and R(−)−).[5,6] It binds to the phencyclidinic site on postsynaptic channels and reduces the frequency and opening time of ion channels.[7] This blockade by ketamine at the NMDA receptors is dose-dependent in that the rate of onset and the recovery from blockade are increased by applying NMDA agonists.[8] The blockade at NMDA occurs by two different mechanisms. Firstly, by blocking the open channel, it subsequently reduces the mean open time of the channel. Secondly, upon binding to the closed receptor, it decreases the frequency of channel opening by an allosteric mechanism. Ketamine at lower concentrations predominantly causes blockade of the closed channel, whereas at higher concentrations it results in the blockade of both open and closed channels. These differences in the mechanism of receptor blockade based on ketamine concentrations have clinical implications. At low concentrations, analgesic properties are evident, whereas at higher concentrations anesthetic properties become apparent.[8] It's noncompetitive nature allows glutamate to continue binding to these sites. In chronic pain states, upregulation of the NMDA receptor results in increased central sensitization and hyperalgesia. As a result, antagonists such as ketamine have been seen to stop afferent nociceptive transmission to the brain.[6,9] Ketamine also maintains blood pressure and preserves spontaneous breathing and laryngeal reflexes.[10] The S(+) isomer increases anesthetic potency two-fold over the racemic mixture while decreasing the psychotomimetic side effects.[11] The second enantiomer, S(−) ketamine, has been suggested to have anti-hyperalgesic properties.[12]

Various *in vitro* studies have demonstrated that ketamine blocks the high-affinity state of the dopamine D2 receptor. This might explain the psychomimetic effects occurring during emergence, as well as explain the catalepsy seen during peak anesthetic effects.[13] Other *in vitro* studies have also demonstrated that ketamine has anti-inflammatory effects as it reduces tumor necrosis factor alpha, interleukin-6 (IL-6) and IL-8 levels, and also suppresses NF-KB expression which has a supposedly pivotal role in pro-inflammatory response. However, the exact mechanism by which it exerts the anti-inflammatory effect remains unclear.[14]

Routes and Doses for Ketamine

Ketamine can be given via different routes: oral (PO), subcutaneous (SC), continuous SC infusion, per rectum, intramuscular (IM), intravenous (IV) and transdermal. Intranasal solutions and powders have also been used. The most common route used postoperatively is the IV route.

Doses Vary Upon the Route of Administration

The usual PO starting dose is 10-25 mg q8h, and intervals of q4-12 dosing have been reported. The dose can be increased up to 0.5-1 mg/kg q8h. Maximum reported dose is 200 mg q 6 h. For transdermal administration use 5-15% in Pluronic Lecithin Organogel; it is often combined with ketoprofen 10% and lidocaine 5%. Table 1 contains some useful instructions for patients in need of ketamine therapy to ensure patient safety. The SC dose is 10-25 mg (0.2-0.5 mg/kg) administered intermittently as needed. For example, it is commonly used for wound dressing changes and wound debridements. Single analgesic doses of ketamine can range from 0.2 to 0.5 mg/kg IV and 0.5-1.0 mg/kg IM given over 1-2 min. Larger doses can cause respiratory depression.[7] Continuous IV infusions are usually started at 0.1-0.2 mg/kg/h. Small doses of an antisialogogue may be necessary to prevent excessive salivation.[15] At higher doses, dissociative states can be induced by disconnection of the thalamoneocortical and limbic systems.[16]

Ketamine for the Treatment of Chronic and Acute Pain

Ketamine has been used for the treatment of chronic and acute pain. An evidence-based study on the use of ketamine in chronic pain was done by Correll *et al.*[17] who conducted a retrospective review of 33 patients with the chronic regional pain syndrome (CRPS) on treatment with subanesthetic ketamine infusion therapy. The study demonstrated some evidence that low dose ketamine infusion may provide safe and effective treatment to selected patients with intolerable CRPS. The concerns in this study were hepatic dysfunction and CNS side effects.

A large retrospective study done on the efficacy and tolerability of ketamine for perioperative control of acute pain in adults was conducted by Bell *et al.*[18] Assessment of 37 trials revealed that 27 of 37 trials reduced pain intensity or rescue pain medication requirement or both perioperatively. Quantitative analysis showed that ketamine in the first 24 h after surgery reduced morphine requirements and decreased the incidence of postoperative nausea and vomiting. The authors did state that since the review was heterogeneous, interpretation of the data should be done with caution especially while suggesting a regimen for the use of ketamine.

For example, as shown in Table 2, the following ketamine flow sheet is used by the pain service at a tertiary care academic

institution. It is a conservative ketamine flow sheet with suggested ketamine infusion rates based on patient weight for starting a ketamine continuous infusion. The recommended ketamine dosage for initiation of therapy ranges from 60 to 120 μg/kg/h (0.06-0.12 mg/kg/h). It can be titrated to effect and increased appropriately with observation.

Norketamine is produced after IV injection. While little research has been performed on the analgesic characteristics of norketamine, a recent human study conducted to evaluate the effects of norketamine on acute ketamine analgesia suggests no correlation of norketamine to acute pain relief.[9]

Ketamine is a highly lipophilic compound, and it distributes rapidly from that the systemic circulation. It has been noted in humans up to that 47% of ketamine is bound to plasma proteins, and the free fraction is responsible for determining the rate of diffusion to the site of action.[19] Ketamine is metabolized by in the liver by the enzymes CYP3A4, CYP2B6, CYP2C9 via N-demethylation and oxidation to norketamine (its primary active metabolite) and dehyrdoxynorketamine (a minor inactive metabolite) respectively. Norketamine is one-third to one-fifth as potent as ketamine, but it may provide prolonged anesthesia.[20] It is subsequently metabolized by CYP2A6 and CYP2B6 to 4-,5-, and 6-hydroxynorketamine. After the glucuronidation of norketamines and hydroxyl norketamines in the liver, both are eliminated through the kidneys and bile.

Recent research has highlighted ketamine mediated analgesic properties and neuroprotection by its antagonism at the

Table 1: Patient education handout

Ketamine
Brand name(s): Ketalar®
There may be other brand names for this medicine
When this medicine should not be used
You should not receive this medicine if you have had an allergic reaction to ketamine
How to use this medicine
Injectable
A nurse or other trained health professional will give you this medicine
This medicine is given as a shot into one of your muscles. It can also be given through a needle placed in one of your veins
Drugs and foods to avoid
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products
Make sure your doctor knows if you are using any kind of narcotic pain medicine such as codeine, hydrocodone, oxycodone, OxyContin®, Percocet®, Tylenol® 3, or Vicodin®. Tell your doctor if you use a barbiturate such as phenobarbital
Make sure your doctor knows if you drink alcohol on a daily or regular basis
Warnings while using this medicine
Make sure your doctor knows if you are pregnant or breast feeding. Tell your doctor if you have blood circulation problems or untreated high blood pressure
This medicine may make you dizzy, drowsy, or confused for several hours. If you have had outpatient surgery, you will need someone to drive you home
This medicine may make you have unusual thoughts or behaviors after the surgery. You might feel confused or excited, or you might see or hear things that are not really there. You might feel as if you are dreaming while you are awake. Call your doctor if these thoughts or behaviors are severe or last longer than 24 h
Wait at least 24 h after you receive this medicine before you drive, use machines, or do anything else that could be dangerous if you are not alert
Possible side effects while using this medicine
Call your doctor right away if you notice any of these side effects
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Fast, slow, or uneven heartbeat
Lightheadedness or fainting
Redness, pain, or blistering where the shot was given
If you notice these less serious side effects, talk with your doctor
Cough
Eye twitching, or double vision
Muscle stiffness
Nausea, vomiting, or loss of appetite
Skin redness or mild rash
If you notice other side effects that you think are caused by this medicine, tell your doctor

Reference: UCLA Micromedex-Ketamine, with permission

Table 2: Suggested ketamine infusion rates based on patient's weight

Recommended Dosage: 60-120 mcg/kg/hr or 0.06-0.12 mg/kg/hr
Concentration: 2 mg/mL

	Infusion dose (mg/kg/hr)						
Weight (kg)	**0.06**	**0.07**	**0.08**	**0.09**	**0.1**	**0.11**	**0.12**
	Infusion rate (ml/hr)						
50	1.5	1.75	2	2.25	2.5	2.75	3
55	1.65	1.925	2.2	2.475	2.75	3.025	3.3
60	1.8	2.1	2.4	2.7	3	3.3	3.6
65	1.95	2.275	2.6	2.925	3.25	3.575	3.9
70	2.1	2.45	2.8	3.15	3.5	3.85	4.2
75	2.25	2.625	3	3.375	3.75	4.125	4.5
80	2.4	2.8	3.2	3.6	4	4.4	4.8
85	2.55	2.975	3.4	3.825	4.25	4.675	5.1
90	2.7	3.15	3.6	4.05	4.5	4.95	5.4
95	2.85	3.325	3.8	4.275	4.75	5.225	5.7
100	3	3.5	4	4.5	5	5.5	6

Mechanism = NMDA antagonist, Used as an analgesic in patients with severe opioid resistant pain, neuropathic pain, phantom limb pain, or chronic pain. Also used as an adjunct in opioid detoxification. Adverse events = Hypertension, tachycardia, increased cardiac output, paradoxical myocardial depression, increased pulmonary artery pressure, hallucinations, tonic-clonic movements. Ketamine infusion flow sheet.
Source: Modified with permission, from UCLA, Department of Anesthesiology

NMDA receptor. The amnesia and sedation produced by ketamine are associated with few cardiopulmonary adverse reactions, making it useful in procedural sedation, in particular with spontaneous ventilation commonly seen in the emergency room setting.[21] The large therapeutic window and low cost of ketamine make it an attractive choice in environments where monitoring and resources are sparse.[22]

Ketamine has morphine-sparing effects in subanesthetic doses, thereby increasing respiratory and hemodynamic stability. In addition, low doses of ketamine did not elicit the typical responses of increased heart rate and high blood pressure usually associated with ketamine administration.[23] The combined treatment can thus reduce the side effects of opioids, and protocols have evolved for low dose ketamine administration [Tables 3 and 4]. The psychomatic effects of ketamine leading to dissociative anesthesia, emergence agitation and nausea and vomiting have led to negative comments on its clinical role.

Newer Uses of Ketamine

The use of ketamine, a phencyclidine derivative as a potential analgesic was first identified in the early 1960s.[2] It was one of the 200 derivatives investigated for clinical use. However, concerns about ketamine-induced psychotomimetic effects decreased its popularity. Initial efficacy was focused primarily on the anesthetic properties of ketamine and as an induction agent; its analgesic properties were largely ignored until it came to market in 1970, following Food and Drug Administration approval.[2] Evolving research has suggested a positive role for ketamine for postoperative analgesia, applied either alone or in combination with other analgesics to adequately alleviate pain while maintaining hemodynamic stability. Ketamine is a highly lipid soluble dose-dependent anesthetic and analgesic that can be administered orally, rectally, intranasally, IV, IM, or intrathecally.[3] It has been successfully applied for nociceptive and neuropathic pain.[3] Although ketamine is known to increase intracranial pressure, it has been tolerated during neurosurgical procedures and patients have not sustained neurological damage following cardiopulmonary surgery.[4] Nociceptive stimuli are known to trigger the release of catecholamines. This causes disturbances in respiratory and immune function. Such complications can increase hospitalization time, raise costs, and create the potential for chronic pain state.[23] Ketamine offers better sedation and analgesia with fewer respiratory effects when compared to midazolam or fentanyl. In addition, it provides anxiolysis while maintaining cardiovascular stability.[7] Thus, recent studies suggest its benefits in treating chronic pain,[4] depression,[24] as an analgesic during burn care[2] and other complex and challenging subpopulations. Ketamine blocks nitric oxide, m-opioid and NMDA receptors.[2] These properties support its role for chronic pain management.

Ketamine as an Analgesic

Typical analgesics improve pain scores and decrease analgesic complications while allowing a quicker rehabilitation and mobilization period. Despite early reports of ketamine's undesired dissociative side effects, more recent research has overwhelmingly documented that the drug provides many advantages for use during surgical procedures. Addition of ketamine as an adjuvant to opioids in treating postoperative pain results in effective postoperative analgesia[25] as well as attenuation of acute analgesic tolerance to opioids, and prevents rebound pain that occurs following opioid usage. Therefore, a ketamine/opioid combination can result in decreased opioid consumption and extended analgesia.[26] In order to assess the efficacy of IV ketamine in minimizing postoperative analgesia, a randomized double-blind clinical trial was conducted in 40 patients undergoing elective laparoscopic cholecystectomy.[25] Patients > 18 years of age, American Society of Anesthesiologists (ASA) I and II have were included in the study. Those with body mass index of <18 or >35 kg/m^2, history of chronic substance/alcohol abuse, contradiction to opioids, ketamine and nonsteroidal anti-inflammatory drugs were excluded. Two groups were identified, a propofol group (administered propofol and alfentanil with saline) and a ketamine group

Table 3: Low dose ketamine infusion protocol

Low dose ketamine infusion

For use by acute, chronic and palliative care patients. This policy is not indicated for use in end of life pain and symptom control

Purpose

To provide effective, consistent, safe pain management for patients who have unrelieved pain even with the use of high dose of opioid or who have tolerance to opioid therapy. This policy provides for an interdisciplinary approach to pain management

Policy

General

Initiation of ketamine infusion must be started in ICU or PACU. After 4 h of assessment and vital signs monitoring, the patient may return to their home unit if stable

The pain management or palliative care services are to serve as a consultant for all patients (except those in picu) receiving ketamine infusions and will follow patients for 12 h after the infusion has been discontinued

The infusion of ketamine in the icu/pacu or general floors is to be used only as adjunctive analgesia for patients with intractable pain that is not controlled with conventional analgesic regimen as determined by pain management or palliative care service

A registered nurse must complete the ketamine education and competency prior to administering the ketamine infusion

All ketamine doses will be determined exclusively by the pain service or palliative care service

Ketamine must be infused using the continuous basal rate mode and must be used with a locked patient-control compartment (PCA pump is appropriate)

The patient is to be placed on a cardiac monitor with continuous pulse oximetry and with vital signs monitoring until the ketamine infusion is discontinued

Ketamine infusion will be prepared with NS in a syringe as 100 mg/50 ml with a concentration of 2 mg/ml or 500 mg/50 ml with a concentration of 10 mg/ml

Ketamine boluses may only be administered in the icu or pacu by the pain management or palliative care service

No additional iv, im, po narcotics, sedatives or cns depressants are to be given except as ordered by pain management or palliative care service

No blood draws are to be obtained from the port or IV line where the continuous ketamine is infusing

Procedures

Physician's responsibilities

The pain management or palliative care service, with the exception of patients in picu, shall solely determine which patients are eligible, and prescribe low dose (0.06-0.12 Mg/kg/h) of ketamine infusions. When necessary, the pain management or palliative care service may recommend a higher dose

The PCA pump programming orders are to include: Medication, concentration of the medication, mode, basal rate in mg/h

The pain management or palliative care service is to order the vital sign frequency and parameters, and notify nursing staff of any additional requirements as needed

Order initial ketamine using the low ketamine infusion order set (Form # xxxxx). change in ketamine infusion must be written on the pre-printed Low dose ketamine infusion order sheet

Nursing staff responsibilities

Institute falls precautions and instruct the patient and the family regarding the need to ask for assistance when ambulating to reduce the risk of falling

At the change of the shift or during any "hand off", the RN will verify the medication, dose, and settings with a second RN

Assess IV site for patency per unit standard and PRN

Do not "Y" connect any other IV medications into the Ketamine infusion with the exception of IV comparable opioid, i.e., morphine

A minimal fluid infusion rate may be used to keep the vein open

Assessment and monitoring parameters

In ICU's/PACU

Upon initiation of ketamine infusion, the patient must be monitored in pacu or icu with vital signs every 15 min × 4, then every 30 min ×2, then at a minimum of q 2 h

On the floor

Vital signs are to be assessed at least every 4 h or as ordered by the pain management or palliative care service throughout administration. If a dose is increased by the ordering service, vital sign ×1 is to be obtained in 30 min

Assess for signs of adverse psychological manifestations, pain management or palliative care service should be notified if patient experiences iii-vi

Pleasant, dream-like states

Vivid imagery

Hallucinations

Delirium

Nystagmus-early sign that the dose is too high (mild nystagmus is an expected outcome)

Confusion and nightmares-late sign that dose is too high

Continued

Table 3: (Continued)

The following are to be assessed
Medication, concentration, dose, mode, and basal rate
Vital signs with oxygen saturation per unit standard and PRN
Pain scores with vital signs per unit standard and PRN
Sedation score with vital signs per unit standard and PRN
Agitated, restless
Cooperative, oriented
Asleep, easily arousable
Asleep, arouses to voice
No response to verbal stimuli
No response to pain
Documentation
Pain assessment and reassessment will be documented based on using the appropriate age related pain scales
The following assessment is required to be documented in the medical record when a patient is on a ketamine infusion
Pain score at least every 4 h and PRN
Sedation level at least every 4 h and PRN
RR at least every 4 h and PRN
Oxygen saturation at least every 4 h and PRN
Total dose in mg infused every 4 h
Plan of care review every shift
Provide patient education handout [refer to Table 1]
Notify the pain management or palliative Care Service if
The following signs of adverse reaction occur
RR 30% <baseline
HR 20% >baseline
Systolic BP 20% >baseline
Diastolic BP 20% >baseline
Enhanced muscle stiffness

ICU = Intensive care unit, PICU = Pediatric Intensive care unit, PACU = Postanesthesia care unit, PCA = Patient-controlled analgesic, NS= Normal saline, IV = Intravenous, IM = Intramuscular, PO = Plus oral, CNS = Central nervous system, RR = Respiratory rate, HR = Heart rate, BP = Blood pressure.
Source: Modified with permission, from UCLA, Department of Anesthesiology

(administered propofol and alfentanil with ketamine). The number of additional doses of alfentanil and the total amount given intraoperatively were recorded. Assessment of pain and cumulative analgesic consumption were recorded at postanesthesia care unit (PACU) admission, PACU discharge, and postoperatively for 24 h. The study showed that patients in the ketamine group had better analgesia both intra- and post-operatively. Additionally, analgesic consumption in the ketamine group was reduced when compared to the propofol group. After this, its use as a drug for postoperative pain using patient-controlled analgesic became recognized.[27]

Epidural Ketamine

There has been increased interest in recent times of the use of ketamine via the epidural route for postoperative analgesia as part of a multimodal regimen. A study on 100 patients by Sethi *et al*. studied the role of ketamine via the epidural route for postoperative analgesia when combined with bupivacaine and morphine undergoing major upper abdominal surgery.[28] However, there are concerns for neurotoxicity in animals[29] and the report of spinal myelopathy after intrathecal injection of large doses of ketamine.[30] Preservative-free ketamine in a concentration of 0.2 mg/ml was used in their study to avoid possible neurotoxicity due to epidural ketamine.

Subramaniam *et al*. studied the use of ketamine via the epidural route in 46 ASA physical status I and II patients who underwent major upper abdominal surgery.[31] They found that in patients undergoing major abdominal surgery there was improved analgesia without the increase of side effects during administration of dilute epidural ketamine at a dose of 1 mg/kg with morphine 50 μg/kg. More clinical studies are warranted to evaluate the use of routine epidural ketamine administration.

Drawbacks of Ketamine

Nonmedical use of ketamine began to spread once its anesthetic and psychostimulatory properties were recognized. The use of ketamine as a "club drug" rose in popularity during the 1990s and has seen another wave of consumption in

Table 4: Orders for ketamine infusion

Physician Name: _____ ☐ Acute Pain Service ☐ Palliative Care Service
Orders to be written only by acute pain or Palliative Care Service
Recommended dosage: Ketamine infusion 60-120 mcg/kg/h (=0.06-0.12 mg/kg/h)
Medication (drug and concentration)
Patient weight: _____ kg
Baseline RR ____; HR ____; BP ____mmHg
☐ Ketamine 100 mg in 50 ml NS syringe (2 mg/ml)
☐ Ketamine 500 mg in 50 ml NS syringe (10 mg/ml)
Pump program parameters (delivered via locked patient-control compartment, i.e., PCA pump)
Mode: Continuous basal mode only
Units: mg
☐ Ketamine syringe concentration: ☐ 2 mg/ml ☐ 10 mg/ml
Dose: mcg/kg/h=_____mg/kg/h=_____mg/h
Must be completed by MD
Recommended: 60-120 mcg/kg/h = 0.06-0.12 mg/kg/h
Treatment of side effects
☐ Ondansetron 4 mg IV every 6 h PRN severe nausea
☐ Lorazepam 1 mg IV every 4 h PRN unpleasant dreams, mild hallucinations, or agitation
Assessment and monitoring parameters
Document vital signs, including BP, HR, RR, sedation level, and signs of adverse psychological manifestations
☐ In ICU's/PACU: Upon initiation of ketamine drip, the patient must be monitored in the PACU or ICU with vital signs q15 min ×4, then every 30 min ×2, then a minimum of every 2 h
☐ Floor (non-ICU) patients: Vital signs assessed upon transfer and at least every 4 h or as ordered by the Pain Management or Palliative Care Service throughout the administration of Ketamine infusion. After a dose increase, vital signs should be assessed in 30 min ×1, then q4 h and PRN thereafter
Assess for signs of adverse psychological manifestations, and notify the Pain Management or Palliative Care Service if patient experiences iii — vi
Pleasant, dream-like states
Vivid imagery
Hallucinations
Delirium
Nystagmus-early sign that the dose is too high (mild nystagmus is an expected outcome)
Confusion and nightmares-late sign that dose is too high
The following are to be assessed
Drug, concentration, dose, mode, basal rate
Vital signs with oxygen saturation
Pain scores with vital signs and PRN
Sedation score with vital signs and PRN
Notify Pain Management/Palliative Service for the following
☐ RR 30%< baseline, stop infusion then call Pain Service or Palliative Care physician
☐ HR 20%> baseline
☐ Systolic or diastolic BP 20%> baseline
☐ Sedation scale: If patient is unresponsive to verbal stimuli or pain
☐ Inadequate analgesia, after checking integrity of IV site, tubing, and pump
☐ Any severe adverse psychological manifestations listed above
☐ Muscle stiffness
☐ Other:_____
No additional narcotics, sedatives or CNS depressants are to be given except as ordered by the Acute Pain Service or Palliative Care Service
MD Signature: _____ Pager _____ Date: _____ Time: _____
RN Signature: _____ Date: _____ Time: _____

BP = Blood pressure, RR = Respiratory rate, HR = Heart rate, NS = Normal saline, PCA = Patient-controlled analgesic, IV = Intravenous, ICU = Intensive Care Unit, PACU = Postanesthesia Care Unit.
Source: Modified with permission, from UCLA, Department of Anesthesiology

contemporary times. Ketamine is also known under the street names of "special K," "vitamin K," and "LA coke," and is used recreationally by traditionally younger generations to produce altered states of consciousness, delirium, and slowed perception of time.[32] The drug is inexpensive and easily accessible and can be either ingested nasally in powder

form, smoked when added to cigarettes or administered IV or SC.[7] However, ketamine is also highly addicting, and multiple studies have demonstrated profound short-and long-term effects on the human body. Even occasional use of ketamine impairs working, episodic, and semantic memory.[33] Magnetic resonance imaging detectable changes in the brain were studied in 21 ketamine addicts to note the various regions in the human brain that are susceptible to chronic ketamine injury. The ages of the included subjects ranged between 19 and 48 years and those with a previous history of brain tumor or neurological disease were excluded from the study. The subjects had been using ketamine in doses of 0.2-3 g/day over duration of 0.5-12 years. Atrophy was evident in frontal, parietal, occipital cortices, prefrontal lobes, brain stem and corpus striatum of addicts with the severity of lesions depending on the duration of addiction.[34] This is especially concerning as users and abusers of ketamine tend to be adolescents or young adults. In this regard, ketamine can cross the placenta into fetal circulation, leading to atrophy of the fetal brain.[10] Another drawback of ketamine is its damaging effects on the bladder and renal system, leading to bleeding and incontinence.[32]

While ketamine alone or in combination with other drugs has proved successful in many realms, its usefulness is limited. Ketamine has been found to worsen the behaviors of individuals with obsessive-compulsive disorder, creating delayed-onset suicidal ideation.[35] Individuals with Kisbourne syndrome, also known as opsoclonus-myoclonus ataxia, appear to develop increased myoclonus and opsoclonia when administered ketamine and atropine.[36] Due to the potential for hallucinations, patients with psychiatric ailments or those abusing alcohol or amphetamines should not receive ketamine, as it may worsen preexisting conditions.[3]

Conclusion

In summary, ketamine is a strong analgesic employable in subanesthetic without major neuropsychiatric adverse effects. Ketamine decreases pain intensity in the postoperative period, and it has been shown clinically to decrease opioid consumption, decrease the side effects of opioids and increase the time for rescue analgesics-all these are attractive properties that suggest a role for ketamine as a useful adjuvant in the treatment of postoperative pain. In addition to further exploring the role of ketamine as an adjuvant for perioperative pain control, continued research is needed to determine if perioperative ketamine is useful for the treatment of pain after surgery known to result in severe pain and in the prevention and treatment of chronic pain.

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