Delivery of IV Ketamine in the Outpatient Clinic for Pain Management

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Faculty Disclosure

	Nothing to disclose
X	**Yes, as follows:**

Honoraria/Expenses	
Consulting/Advisory Board	
Speakers Bureau	Salix (OIC), Averitas (PDPN)
Funded Research (Individual)	
Funded Research (Institution)	
Royalties/Patent	
Stock Options	
Ownership/Employee	
Other	

Off-Label Product Use

Will you be presenting or referencing off-label or investigational use of a therapeutic product?

	No	
X	**Yes, as follows:**	The use of IV Ketamine is only FDA approved as a sole anesthetic agent for diagnostic and surgical procedures.

Learning Objectives

- Identify which patients should be considered for outpatient IV ketamine infusion.
- Describe safety and monitoring parameters of patients undergoing outpatient IV ketamine infusion.
- State elements needed to appropriately administer IV ketamine in the ambulatory setting.

Patient Selection & Indications

Why for chronic pain?

- Ketamine's mechanism of action is complex → multiple binding sites including NMDA receptors, opioid receptors, Na channels, L-type calcium channels (Kohrs & Durieux, 1998; Yang, et al., 2020)
- High affinity → dopamine D2 & serotonin 5-HT2 binding sites and significantly inhibits their uptake (Kapur & Seeman, 2002; Jaso, et al., 2017).
- **Chemotherapy-Induced Neuropathic Pain** (Pascual et al., 2010).
- **Nerve-Injury-Induced Neuropathic Pain** (Mei et al., 2010; Orhurhu, et al., 2019).
- **Diabetic Neuropathic Pain** (Mak et al., 2015).
- **Other neuropathic pain** (Tajerian et al., 2015; Orhurhu, et al., 2019).

Patient Selection & Setting Expectations

- Setting expectations
  - Similar as with any intervention
  - Assess patients' ability to cope with poor outcomes
  - Goal setting
  - Explain how treatment fits into the whole multimodal paradigm
  - For chronic pain
- Patient selection
  - Prior levels of compliance
  - Level of resilience, self actualization/locus of control
  - Primary mental health diagnosis
  - Prior experience with ketamine
  - History of substance abuse
  - Not pregnant/hepatic/renal compromise/unstable CV disease

Contraindications/Considerations

- May be contraindicated or (special precautions) for some sub-populations.
  - History of schizophrenia, psychotic symptoms, post-traumatic stress disorder (PTSD).
  - Has been shown to exacerbate and/or elicit psychotic symptoms in these patients. (Lahti et al., 2001; Xu et al., 2015).
  - Use of benzodiazepines to help prevent development of psychotic symptoms (Krystal et al., 1999; Sinner & Graf, 2008).
- Patients with cardiovascular or hepatic compromise.
  - Increased cardiac stimulation which may be harmful to patients with unstable cardiovascular disease (Dahan et al., 2009).
  - Hepatotoxic, especially with chronic use, and exhibits a rise in liver function tests (LFTs) in up to 80% of patients (Kiefer et al., 2008).
- Patients with unrealistic/unclear expectations.

Adverse Effects

- Hallucination, dysphoria, dizziness, visual disturbance, sedation (Stoker, et al., 2019)
  - Can be dose dependent.
  - Occurrence rate lower in patients diagnosed with depression. Hypothesis is that increased NMDA-receptor activity seen in depression is protective against psychotic effects of ketamine.
- Cognitive Effects
  - Dissociative and psychomimetic effects.
  - Sense of a general “euphoria” & disconnection from their surroundings.
  - Formal thought disorder and impairments in both working/semantic memory function.
    - In chronic ketamine abusers, these memory impairments have been shown to persist even after abstinence from ketamine suggesting permanent damage to the brain.
- Cystitis
  - Reported in over 25% of long-term ketamine abusers with occurrence related in a dose & frequency. Also of importance is that only 51% of respondents reported improvement in symptoms following cessation of ketamine (Winstock et al., 2012).

Adverse Effects

- Hepatotoxicity
  - Frequency of this drug induced hepatotoxicity caused the authors to end their proposed study earlier than anticipated (Noppers et al., 2011).
  - Sixteen of twenty (80%) of CRPS patients treated with ketamine infusions for refractory pain experienced transient elevations in lever enzyme (AST, ALT, GGT) levels that decreased back to baseline within 10–14 days following treatment (Kiefer et al., 2008).
- Cardiovascular Effects
  - Ketamine acts directly on cardiac myocytes as a negative inotropic agent. However, due to its central inhibition of norepinephrine reuptake in adrenergic nerves → increase in cardiac output via elevations in HR & BP (Suleiman et al., 2012).
  - Ketamine acts like a sympatho-mimetic on the cardiovascular system.
- Neurotoxicity
  - Concern of neurotoxicity arise from animal studies → dose & time-related increases in neuronal apoptotic cell death in the frontal cortex and other areas of the brain during development (Zou et al., 2009).

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Policy Title: Pain Management - Ketamine Intravenously for Complex Pain

I. **PURPOSE:**

The purpose of this procedure is to safely and effectively administer Ketamine for complex pain syndrome treatments in an outpatient setting.

Who May Perform: Registered Nurse (RN) with Advanced Cardiac Life Support (ACLS) certification.

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II. SUPPORTIVE INFORMATION:

A. PRECAUTIONS

1. Supervision:
    a. A physician with ACLS certification needs to be available on the premises.
    b. The Attending of the day (A1) pain clinic physician provides updated orders as needed based on patient's status and treatment plan each day.
2. Exercise caution in administration if there is increased intracranial pressure, increased intraocular pressure, ischemic heart disease, thyrotoxicosis, psychosis, hepatic impairment, acute alcoholism, substance abuse and pregnancy.
3. Possible side effects:
    a. Elevated blood pressure (BP) and increased heart rate.
    b. Sedation.
    c. Nausea and/or vomiting.
    d. Urinary retention.
    e. Emergence phenomena.
    f. Cardiovascular stimulation.
    g. Hyper-salivation.
    h. Nystagmus.
    i. Skin rash.
4. Respiratory depression is not usually observed.

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B. INDICATIONS

1. Ketamine is used to reduce or eliminate chronic pain in adult patients at least 18 years of age.
2. Diagnosis can include but not limited to:
    a. Complex regional pain syndrome.
    b. Neuropathic pain and chronic pain refractory to conventional treatments.

C. CONTRAINDICATIONS

1. Hypersensitivity to Ketamine.
2. Uncontrolled hypertension.
3. Stroke.
4. Head trauma.
5. Intracranial mass.

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III. EQUIPMENT/SUPPLIES

A. IV infusion supplies.
B. IV pump.
C. Medications:
    1. Ketamine:
        i. For Infusion: obtain medication from pharmacy. Usually compounded by pharmacy based on planned dosing for each day of infusion:
            1. 200 mg in 100 ml Normal Saline
            2. 500 mg in 250 ml Normal Saline
    2. Clonidine tablet 0.1 milligram (mg) as ordered.
    3. Midazolam 1 mg IV as ordered.
    4. Zofran 4 mg IV as ordered.

IV. PATIENT AND FAMILY TEACHING

A. Explain procedure to the patient.
B. Inform patient and/or family of when to notify clinic of any side effects or complications.
C. Inform patient not to drink alcohol or drive for 24 hours after ketamine infusion.

Need for Informed Consent: who, why, when

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V. PROCEDURE:

A. RN obtains baseline assessments:

1. Negative pregnancy test available on record within 1-month prior to infusion for all females of child-bearing age with intact uterus.
2. Baseline Electrocardiogram (EKG) within 6 months or less if patient with recent cardiac event or has poorly managed hypertension. Abnormal results reviewed by MD.
3. Complete Metabolic Panel (CMP) results within 6 months. Abnormal Results reviewed by MD. MD may consider repeat mid-series CMP for infusion longer than 5 days.
4. Vital signs, pain score and sedation scores using Richmond Agitation Sedation Scale (RASS, see appendix A).
5. Current medication and drug allergies verified to ensure no contraindications to Ketamine.
6. Verify order for Ketamine from patient's electronic medical record (EMR) and for any other diagnostic tests ordered.

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B. Pre-infusion:

1. Verify patient's identity using two forms of identification per SHC policy.
2. Verify physician's orders. If necessary, clarify orders with A1 physician and/or pharmacist.
3. Check patient's allergy.
4. Perform hand hygiene per SHC policy.
5. Don gloves and start peripheral IV using Normal Saline or Lactated Ringers (LR).
    a. See "Intravenous Infusion: Peripheral Line Infusion & Care" policy.
6. Document vital signs and pain score.
7. Give Clonidine 0.1 mg PO at initiation of infusion as ordered. Hold for systolic BP < 95 or with vagal reaction symptoms including lightheadedness, dizziness and nausea.
8. May give Midazolam 1 mg IV as ordered at the start of infusion or if side effects develop. May repeat x1 as needed.
9. May give Zofran 4 mg IV as needed for nausea. May repeat one time.
10. May give Benzodiazepines to attenuate cardiovascular effects and prevent emergence phenomena after discussion with MD and written orders entered in EMR.

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C. Infusion:

1. Prior to infusion, verify medication order with the label on medication bag.
2. Verify patient's identity, by checking patient's name and medical record on patient's identification band. If no ID band, verify full name and date of birth.
3. Follow the rights of medication administration.
4. Requires two RNs or RN/MD verification of the medication and order prior to start of infusion and all infusion rate changes.
5. Initiate the infusion after discussion with A1 physician.
6. Titrate infusion to optimize analgesia and minimize side effects maintaining a RASS score of +1 to -2.
7. Recommended titration schedule for first time Ketamine infusion:
    a. Day 1: Start 0.2 mg/kg/hour (hr.) for 30 minutes, increase to 0.25 mg/kg/hr. for 30 minutes, and increase to 0.3 mg/kg/hr.
    b. Day 2: Start 0.3 mg/kg/hr. for 30 minutes, increase to 0.4 mg/kg/hr.
    c. Day 3: Start 0.4 mg/kg/hr., increase to 0.5 mg/kg/hr.
    d. Day 4-10: Start 0.5 mg/kg/hr. for 30 minutes, increase to 0.7 mg/kg/hr.
8. First time infusions are typically given over 4 hours and are ordered as daily for a total of 5-10 days.
9. Booster infusions may be started at highest dose previously tolerated up to 0.7 mg/kg/hr.
10. Booster (subsequent) infusions are typically given over 4 hours and ordered for a total of 2-5 days.
11. Maximum dose for any pain clinic outpatient Ketamine infusion is 50 mg/hr.
12. For patient with higher body weight, adjust starting dose for first time infusion to no higher than 25 mg/hr.
13. Monitor patient's vital signs every 15 minutes during the infusion.
14. Monitor patient's cardiac status via 3-lead EKG monitor throughout infusion and post-infusion/recovery.

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D. Post Infusion:

1. Monitor patient for post-infusion side effects or complications for 30 minutes.
2. Document vital signs, sedation and pain scores for 30 minutes post Infusion.
3. Discharge patient to responsible adult.

DOCUMENTATION

A. Document all medications given including name, dosage, route, time medications were given and any rate changes to the infusion with second verification by RN or MD.
B. Record Intake and Output (I&O).
C. Note patency of IV site.
D. Record vital signs and RASS at appropriate intervals.
E. Document patient's pain score before and after infusion.
F. If administered, document patient's response to and tolerance of PRN medications.

Follow-up

- Call patient day after infusion, assess efficacy & any residual adverse effects.

- Decide on when next infusion:
  - Generally, effects with in-patient infusion for chronic pain (5-day continuous infusion), last longer (6-12 months)
  - Ambulatory infusions (4-6 months)
  - “mini-infusions” – in between hospitalizations
  - Consider routine monitoring of labs (CMP, EKG, pregnancy) if routine, long-term treatment
  - Updated medication list
  - Monitor risk (ketamine is a controlled substance, mental health implications, addictive)

Summary

Be mindful of Insurance issues (clinic versus hospital infusions for chronic pain)

- Identify which patients should be considered for outpatient IV ketamine infusion.
  - Without history hepatic/renal compromise
  - Appropriate diagnosis (central/neuropathic/nociplastic pain)
  - Caution with mental health diagnosis, prior history of trauma/PDST
  - Setting expectations/compliant patients/ability to understand directions
- Describe safety and monitoring parameters of patients undergoing outpatient IV ketamine infusion.
  - Cognitive effects (also balance)
  - Other psychomimetic symptoms (during infusion/possibly reactive)
  - Renal/hepatic function prior –EKG-consider rapid urine drug screen
  - Review list of current medications (particularly what was taken that day)
- State elements needed to appropriately administer IV ketamine in the ambulatory setting.
  - ACLS, oxygen, infusion pump, IV access, clinic policy for non-clinicians, clinician on site

Resources

TABLE 2 | Compiled clinical evidence supporting ketamine's analgesic effects.

Authors	Pain condition	Study type	Ketamine treatment	Sample size	Results	Comments
Intravenous ketamine infusion						
Schwartzman et al. (2009)	Chronic regional pain syndrome (CRPS)	Double-blind placebo controlled	Maximum of 0.35 mg/kg/h × 4 hr × 10 days	19	Intravenously ketamine administered via outpatient setting significantly reduced several pain parameters	Avg. Pain decrease 27% vs 2% placebo. Co-administered w/clonidine and midazolam
Orhurhu et al. (2019)	Mixed neuropathic and non-neuropathic	Meta-analysis	Varies, median 0.35 mg/kg/h for 5 h	211	Ketamine has significant analgesic benefit up to 2 weeks after cessation of administration. High-dose ketamine significantly more effective than low-dose	No significant difference in ketamine efficacy based on pain condition
Lossignol et al. (2005)	Intractable cancer pain	Case series	1.5 mg/kg/day ketamine	12	Ketamine infusion improved pain controlled and reduced total daily morphine use by an average of 50%	Infused concomitantly w/ morphine. Only moderate side effects (dizziness)
Oral ketamine						
Rigo et al. (2017)	Refractory neuropathic pain	Double-blind active controlled	3 mg methadone OR 30 mg ketamine OR 3 mg methadone +30 mg ketamine (3× daily)	14	Ketamine is superior to methadone and methadone/ketamine combination in treating neuropathic allodynia	All treatments reduced VAS score by at least 40%. No differences in burning/shooting pain reduction
Lauretti et al. (1999)	Cancer pain	Multi-arm treatment	0.5 mg/kg 2× daily	15	Low-dose ketamine significantly reduced daily morphine consumption and reduced somnolence in patients suffering from cancer pain	No somnolence reported with oral ketamine. Lower rates of adverse effects compared to morphine, nitroglycerin, and dipyrone groups
Kannan et al. (2002)	Neuropathic cancer pain	Case series	0.5 mg/kg 3× daily	9	Seven of nine patients report decrease in pain score ≥3 compared to when solely taking maximally tolerated opioid dose	Adverse effects: Nausea (×4), loss of appetite (×2), sleepiness (×8, improved to ×3). Three pts withdrew due to effects
Marchetti et al. (2014)	Intractable cancer pain	Case series	1.5–3 mg/kg daily (varied schedules)	51	Pain reduced or abolished in 2/3 of patients with ketamine treatment	Patients on opioid therapy had lower failure rate of ketamine treatment than non-opioid group
Intranasal ketamine						
(Carr et al. (2004)	Breakthrough cancer pain	Double-blind crossover	10–50 mg (1–5 sprays)	10	After treatment with intranasal ketamine, 65% of breakthrough cancer pain patients achieved an NPIS score that was at least 40% lower than pre-treatment levels compared to 20% of placebo patients	No reports of auditory or visual hallucinations. Adverse effects: Change of taste (×4), rhinorrhea (×1), BP elevation (×2)
Topical ketamine						
Finch et al. (2009)	Chronic regional pain syndrome	Double-blind placebo controlled	10% ketamine cream	20	KET cream reduced CRPS associated allodynia and hyperalgesia within 30 min of administration	Systemic ketamine concentrations below detectable limit
Gammaitoni et al. (2000)	CRPS, lumbar radiculopathy, post-herpetic neuralgia	Case series	1% ketamine cream	5	Reduction in pain scale ranging from 53–100% 15 min after application of cream	No side effects reported
Heir et al. (2008)	Orofacial neuropathic pain	Case-control series	4% KET, 4% carbamazepine, 1% ketoprofen, 4% gabapentin	39	41% of patients had a decrease in pain level of at least 30%. This proportion is similar to systemic and systemic + topical treatment modalities	Pain relief lower in magnitude than systemic treatments, but shorter time to onset.
Everton et al. (2007)	Post-herpetic neuralgia	Double-blind placebo controlled	2% ketamine +4% amitriptyline	118	46% of AmiKet patients reported a decrease in daily pain score of at least 30% compared to 19% in placebo group	Only 5% of patients had detectable systemic ketamine or amitriptyline levels

TABLE 3 | Compiled evidence of ketamine's analgesic effect in the pediatric population.

References	Pain condition	Study type	Ketamine treatment	Sample size	Results	Comments
Bredlau et al. (2013)	Chronic pain	Prospective case series	Oral (3x daily). 25–1.5 mg/kg/dose	12	Five of twelve children reported experienced marked improvement in pain scores lasting >4 weeks off ketamine treatment	Two children forced to withdraw treatment due to dose-limiting toxicities
Finkel et al. (2007)	Cancer pain	Retrospective case series	Infusion 0.1–1 mg/kg/h	11	Sub-anesthetic dosages of ketamine infusion resulted in subjectively improved pain control and a reduction in required opioid dosage ranging from 28 to 100%	Administered with lorazepam, no psychotropic effects reported. Patients more awake and alert than on opioids alone
Mulder et al. (2018)	Acute pain (pancreatitis)	Case report	Infusion 2 μg/kg/min	1	Rapid reduction in pain score from 8.3 to 4.4. Total daily oral morphine equivalent reduced from 1,375 to 375 mg/day	N/A
Weber et al. (2018)	Neuropathic pain	Case report	Infusion 7 μg/kg/min	1	Self-reported 70% reduction in pain. Pain relief lasted five months after initial ketamine infusion	Suicidal ideation also resolved. Patient retreated at 5-months mark with same results

Resources

Appendix A: **Richmond Agitation and Sedation Scale (RASS)**

Score	Term	Description
+4	Combative	Overly combative, violent immediate danger to staff.
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive.
+2	Agitated	Frequent non-purposeful movement, fights ventilator.
+1	Restless	Anxious but movements not vigorously aggressive.
0	Alert and calm	Awake, alert and oriented.
-1	Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to voice for >10 seconds (verbal stimulation).
-2	Light sedation	Briefly awakens with eye contact to voice /verbal stimulation (<10 seconds).
-3	Moderate sedation	Movement or eye opening to voice/verbal stimulation but no eye contact.
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation.
-5	Unarousable	No response to verbal or physical stimulation.

Procedure for RASS Assessment:

Score	Description	Assessment
0 to +4	• Patient is alert, restless or agitated.	Observe patient
-1 -2 -3	• Patient awakens with sustained eye opening and eye contact. • Patient awakens with eye opening and eye contact, but not sustained • Patient has any movement in response to voice but no contact.	If patient is not alert, state patient's name and say to open eyes and look at speaker.
-4 -5	• Patient has any movement to physical stimulation • Patient has no response to any stimulation	When no response to verbal stimuli, physically stimulate patient by shaking shoulder and/or rubbing sternum

Resources

Consensus Guidelines on the Use of Intravenous Ketamine Infusions for **Acute Pain Management** From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists (2018)

Schwenk, E. S., Viscusi, E. R., Buvanendran, A., et.al.(2018). Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Regional anesthesia and pain medicine, 43(5), 456–466.

Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists (2018)

Cohen SP, Bhatia A, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018 Jul;43(5):521-546.

GUIDELINES FOR SAFE ADMINISTRATION OF LOW-DOSE KETAMINE (Revised: October 7, 2020)
Ketamine Guidelines.pdf (pa.gov)

This pain management guideline was written by the staff of the Children's Pain Management Service for the Royal Children's Hospital, Melbourne.
[This guideline may NOT be suitable for use in other institutions]
Nurse competencies, Indications, Ketamine infusion set up, Concurrent drugs, etc.
https://www.rch.org.au/anaes/pain_management/Ketamine_Infusion/

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