BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Intravenous Anesthetics for the Treatment of Chronic Pain

Policy #: 446
Category: Pharmacology

Latest Review Date: December 2020
Policy Grade: C

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Effective for dates of service on or after November 6, 2010:

Blue Advantage will treat **intravenous infusion of anesthetics** (e.g., ketamine or lidocaine) for the treatment of chronic pain, including, but not limited to chronic neuropathic pain, chronic daily headache, fibromyalgia, and psychiatric disorders as a **non-covered** benefit and as **investigational**.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

Intravenous (IV) infusion of lidocaine or ketamine has been used for the treatment of chronic neuropathic pain. Chronic neuropathic pain disorders include phantom limb pain, post-herpetic neuralgia, complex regional pain syndromes, diabetic neuropathy, and pain related to stroke or spinal cord injuries. IV infusion of ketamine has also been investigated for the treatment of depression and obsessive-compulsive disorder utilizing one or more courses of IV ketamine administered over a period of several hours or several days.

Intravenous Anesthetic Agents

Courses of IV anesthetic agents may be given in the inpatient or outpatient setting as part of a pain management program, with the infusion of a sub-anesthetic dose preceded by a bolus infusion to achieve desired blood levels sooner. Treatment protocols for the initial cycle may include infusion of subanesthetic doses of one to six hours for up to ten days.

Lidocaine

Lidocaine, which prevents neural depolarization through effects on voltage-dependent sodium channels, is also used systemically for the treatment of arrhythmias. Adverse effects for lidocaine are common and can be mild to moderate, including general fatigue, somnolence, dizziness, headache, periorbital and extremity numbness and tingling, nausea, vomiting, tremors, and changes in blood pressure and pulse. Severe adverse effects can be arrhythmias, seizures, loss of consciousness, confusion, or even death. Lidocaine should only be given IV to patients with normal conduction on electrocardiography and normal serum electrolyte concentrations to minimize the risk of cardiac arrhythmias.

Ketamine

Ketamine is an antagonist of the N-methyl-D-aspartate (NMDA) receptor and a dissociative anesthetic. It is the sole anesthetic agent approved for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Respiratory depression may occur with over dosage or too rapid a rate of administration of ketamine; it should be used by or under the direction of

physicians experienced in administering general anesthetics. Ketamine is a schedule III controlled substance. Psychological manifestations vary in severity from pleasant dream-like states to hallucinations and delirium, and can be accompanied by confusion, excitement, aggression, or irrational behavior. The occurrence of side effects with IV anesthetics may be reduced by the careful titration of sub-anesthetic doses. However, the potential benefits of pain control must be carefully weighed against the potential for serious, harmful adverse effects.

Indications
IV administration of anesthetic has been reported for a variety of conditions, including chronic pain of neuropathic origin, chronic headache, fibromyalgia, depression, and obsessive-compulsive disorders.

Chronic daily headache is defined as a headache disorder that occurs more than 15 days a month for at least three months. Chronic daily headache includes chronic migraine, new daily persistent headache, hemicranias continua, and chronic tension-type headache.

Neuropathic pain is often disproportionate to the extent of the primary triggering injury and may consist of thermal or mechanical allodynia, dysesthesia, and/or hyperalgesia. Allodynia is pain that occurs from a stimulus that normally does not elicit a painful response (e.g., light touch, warmth). Dysesthesia is a constant or ongoing unpleasant or electrical sensation of pain. Hyperalgesia is an exaggerated response to normally painful stimuli. In the latter, symptoms may continue for a period of time that is longer (e.g., ≥6 months) than clinically expected after an illness or injury. It is proposed that chronic neuropathic pain results from peripheral afferent sensitization, neurogenic inflammation, and sympathetic afferent coupling, along with sensitization and functional reorganization of the somatosensory, motor, and autonomic circuits in the central nervous system (CNS). Therefore, treatments focus on reducing activity and desensitizing pain pathways, thought to be mediated through N-methyl-D-aspartate (NMDA) receptors in the peripheral and CNS. Sympathetic ganglion blocks with lidocaine have been used for a number of years to treat sympathetically maintained chronic pain conditions, such as CRPS (previously known as reflex sympathetic dystrophy). Test infusion of an anesthetic has also been used in treatment planning to assess patient responsiveness to determine whether medications, such as oral mexiletine or oral ketamine, may be effective. A course of IV lidocaine or ketamine, usually at subanesthetic doses, has also been examined. This approach for treating chronic neuropathic pain differs from continuous subcutaneous or IV infusion of anesthetics for the management of chronic pain conditions, such as terminal cancer pain, which are not discussed in this policy.

Fibromyalgia is a chronic state of widespread pain and tenderness. Although fibromyalgia is generally considered to be a disorder of central pain processing or central sensitization, others have proposed that the nerve stimuli causing pain originates mainly in the muscle, causing both widespread pain and pain on movement. There are focal areas of hyperalgesia, or tender points, which tend to occur at muscle tendon junctions. Biochemical changes that have been associated with fibromyalgia include alterations in NMDA receptors, low levels of serotonin, suppression of dopamine-releasing neurons in the limbic system, dysfunction of the hypothalamic-pituitary-adrenal axis, and elevated substance P levels. Fibromyalgia is typically treated with neuropathic pain medications such as pregabalin, non-narcotic pain relievers, or low doses of antidepressants.

Use of IV ketamine has also been reported for treatment-resistant depression, defined as depression that does not respond adequately to appropriate courses of antidepressant medications. Particularly challenging are patients with treatment-resistant depression with suicidal ideation. Several studies are ongoing to test the efficacy of IV ketamine in patients with suicidal ideation who present to the emergency department.

KEY POINTS:

The most recent literature review was performed through October 10, 2020.

Summary of Evidence

For individuals who have chronic pain syndromes (e.g., neuropathic pain or fibromyalgia) who receive a course of IV anesthetics (e.g., lidocaine, ketamine), the evidence includes several RCTs. The relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, QOL, medication use, and treatment-related morbidity. Several RCTs have been performed using IV lidocaine or ketamine for PHN, CRPS, and diabetic neuropathy. Trials have failed to show a durable effect of lidocaine infusion on chronic pain. Two trials with a total of 100 patients provide limited evidence that courses of IV ketamine may provide temporary relief (2 to 4 weeks) to some chronic pain patients. Neither of the RCTs with ketamine infusion used active control, raising the possibility of placebo effects. Overall, the intense treatment protocols, the severity of adverse events, and the limited treatment durability raise questions about the net health benefit of this procedure. Additional clinical trials are needed to evaluate the long-term efficacy and safety of repeat courses of IV anesthetics for chronic pain. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have psychiatric disorders (e.g., TRD, obsessive-compulsive disorder) who receive a course of IV ketamine, the evidence consists of RCTs. The relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, QOL, medication use, and treatment-related morbidity. Two publications of double-blind trials were identified that compared repeated ketamine infusion with an infusion of saline for TRD. There is a possibility of publication bias due to the lack of publication of many other small trials. One study with 26 patients found no significant difference in a depression scale at the end of infusion. A larger RCT (n=68) found a significantly greater improvement in a depression scale during the 4 week infusion period, but the effect diminished over three weeks post-infusion. The trial did not use active control, raising the possibility of placebo effects and unblinding of patients and investigators. Common side effects of ketamine infusion include headache, anxiety, dissociation, nausea, and dizziness. The intense treatment protocols, the severity of adverse events, and the limited treatment durability raise questions about the net health benefit of this procedure. High-quality clinical trials, several of which are in progress, are needed to evaluate the long-term safety and efficacy of IV ketamine for psychiatric disorders. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

In 2018, the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine and the American Society of Anesthesiologists issued a joint consensus guideline on the use of intravenous ketamine for treatment of chronic pain. The

guideline found: Weak evidence supporting use of IV ketamine for short-term improvement in patients with spinal cord injury pain Moderate evidence supporting use of IV ketamine for improvement in patients with CRPS up to 12 weeks Weak or no evidence for immediate improvement with IV ketamine use for other pain conditions, including mixed neuropathic pain, fibromyalgia, cancer pain, ischemic pain, headache and spinal pain.

The American Psychiatric Association (2017) published an evidence review and consensus opinion of the use of ketamine in treatment-resistant depression. The Association noted that "while ketamine may be beneficial to some patients with mood disorders, it is important to consider the limitations of the available data and the potential risk associated with the drug when considering the treatment option."

U.S. Preventive Services Task Force Recommendations
Not applicable.

KEY WORDS:
Pain, Chronic, Intravenous Lidocaine, Chronic Pain, Fibromyalgia, Ketamine, Neuropathic pain disorders, complex regional pain syndrome (CRPS) , N-methyl-D-aspartate (NMDA), Psychiatric disorders, spinal cord injury, headache, IV anesthetic agents, dissociative anesthetics, post-herpetic neuralgia (PHN).

APPROVED BY GOVERNING BODIES:
IV lidocaine is approved by the U.S. Food and Drug Administration (FDA) for systemic use in the acute treatment of arrhythmias and locally as an anesthetic. IV lidocaine for the treatment of chronic pain is an off-label use.

Ketamine hydrochloride injection is FDA-indicated for diagnostic and surgical procedures that do not require skeletal muscle relaxation, for the induction of anesthesia before the administration of other general anesthetic agents, and to supplement low-potency agents, such as nitrous oxide. IV ketamine for the treatment of chronic pain is an off-label use.

BENEFIT APPLICATION:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:
CPT Codes:

96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour

96366	Each additional hour (list separately in addition to code for primary procedure)
96374	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug

HCPCS:

J2001	Injection, lidocaine hydrochloride for intravenous infusion, 10 mg

REFERENCES:

1. American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. Anesthesiology. Apr 2010; 112(4):810-833.
2. Amr YM. Multi-day low dose ketamine infusion as adjuvant to oral gabapentin in spinal cord injury related chronic pain: a prospective, randomized, double blind trial. Pain Physician 2010; 13(3):245-9.
3. Attal N, Gaude V, Brasseur L, et al. Intravenous lidocaine in central pain: A double-blind, placebo-controlled, psychophysical study. Neurology 2000; 54(3):564-574.
4. Baranowski AP, De Courcey J and Bonello E. A trial of intravenous lidocaine on the pain and allodynia of postherpetic neuralgia. J Pain Symptom Manage 1999; 17(6):429-433.
5. Blue Cross Blue Shield Association. Technology Evaluation Center (TEC) Assessment, Section: Prescription Drug. August 2011.
6. Carroll I, Gaeta R and Mackey S. Multivariate analysis of chronic pain patients undergoing lidocaine infusions: Increasing pain severity and advancing age predict likelihood of clinically meaningful analgesia. Clin J Pain 2007; 23(8):702-6.
7. Challapalli V, Tremont-Lukats IW, McNicol ED, et al. Systemic administration of local anesthetic agents to relieve neuropathic pain. Cochrane Database Syst Rev 2005; (4):CD003345.
8. 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. Jul 2018; 43(5): 521-546.
9. Correll GE, Maleki J, Gracely EJ, et al. Subanesthetic ketamine infusion therapy: A retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. Pain Med 2004; 5(3):263-75.
10. Eichenberger U, Neff F, Sveticic G, et al. Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds. Anesth Analg 2008; 106(4):1265-73.

11. Finnerup NB, Biering-Sorensen F, Johannesen IL, et al. Intravenous lidocaine relieves spinal cord injury pain: A randomized controlled trial. Anesthesiology 2005; 102(5):1023-30.
12. Hand PJ, Stark RJ. Intravenous lignocaine infusions for severe chronic daily headache. Med J Aust. Feb 21 2000; 172(4):157-159.
13. Hocking G and Cousins MJ. Ketamine in chronic pain management: An evidence-based review. Anesth Analg 2003; 97(6):1730-9.
14. Ionescu DF, Bentley KH, Eikermann M et al. Repeat-dose ketamine augmentation for treatment-resistant depression with chronic suicidal ideation: A randomized, double blind, placebo controlled trial. J Affect Disord, 2018 Oct 5;243:516-524.
15. Kiefer RT, Rohr P, Ploppa A, et al. Efficacy of ketamine in anesthetic dosage for the treatment of refractory complex regional pain syndrome: An open-label phase II study. Pain Med 2008; 9(8):1173-201.
16. Kim YC, Castaneda AM, Lee CS, et al. Efficacy and safety of lidocaine infusion treatment for neuropathic pain: a randomized, double-blind, and placebo-controlled study. Reg Anesth Pain Med. May 2018;43(4):415-424.
17. Kvarnstrom A, Karlsten R, Quiding H, et al. The effectiveness of intravenous ketamine and lidocaine on peripheral neuropathic pain. Acta Anaesthesiol Scand 2003; 47(7):868-77.
18. Kvarnstrom A, Karlsten R, Quiding H, et al. The analgesic effect of intravenous ketamine and lidocaine on pain after spinal cord injury. Acta Anaesthesiol Scand 2004; 48(4):498-506.
19. Liu H, Lu F, Zhou D et al. The Analgesic and Emotional Response to Intravenous Lidocaine Infusion in the Treatment of Postherpetic Neuralgia: A Randomized, Double-Blinded, Placebo-controlled Study. Clin J Pain, 2018 Apr 27;34(11).
20. Medrik-Goldberg T, Lifschitz D, Pud D, et al. Intravenous lidocaine, amantadine, and placebo in the treatment of sciatica: A double-blind, randomized, controlled study. Reg Anesth Pain Med 1999; 24(6):534-40.
21. Moulin DE, Morley-Forster PK, Pirani Z et al. Intravenous lidocaine in the management of chronic peripheral neuropathic pain: a randomized-controlled trial. Can J Anaesth, 2019 May 18;66(7).
22. Motov S, Mai M, Pushkar I, et al. A prospective randomized, double-dummy trial comparing IV push low dose ketamine to short infusion of low dose ketamine for treatment of pain in the ED. Am J Emerg Med. Aug 2017; 35(8):1095-1100.
23. Noppers I, Niesters M, Swartjes M et al. Absence of long-term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain: a randomized, prospective, double blind, active placebo-controlled trial. Eur J Pain 2011; 15(9):942-9.
24. Noppers IM, Niesters M, Aarts LP et al. Drug-induced liver injury following a repeated course of ketamine treatment for chronic pain in CRPS type 1 patients: a report of 3 cases. Pain 2011; 152(9):2173-8.
25. O'Connell NE, Wand BM, McAuley J et al. Interventions for treating pain and disability in adults with complex regional pain syndrome. Cochrane Database Syst Rev 2013; 4:CD009416.
26. Patil S, Anitescu M. Efficacy of outpatient ketamine infusions in refractory chronic pain syndromes: a 5-year retrospective analysis. Pain Med 2012; 13(2):263-9.

27. Pickering G, Pereira B, Morel V, et al. Ketamine and Magnesium for Refractory Neuropathic Pain: A Randomized, Double-blind, Crossover Trial. Anesthesiology. Jul 2020; 133(1): 154-164.
28. Przeklasa-Muszynska A, Kocot-Kepska M, Dobrogowski J, et al. Intravenous lidocaine infusions in a multidirectional model of treatment of neuropathic pain patients. Pharmacol Rep. Oct 2016; 68(5):1069-1075.
29. Rathmell JP and Ballantyne JC. Local anesthetics for the treatment of neuropathic pain: On the limits of meta-analysis. Anesth Analg 2005; 101(6):1736-7.
30. Reutens DC, Fatovich DM, Stewart-Wynne EG, et al. Is intravenous lidocaine clinically effective in acute migraine? Cephalalgia. Dec 1991; 11(6):245-247.
31. Sanacora G, Frye MA, McDonald W et al. A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. JAMA Psychiatry, 2017 Mar 2;74(4).
32. Sigtermans MJ, van Hilten JJ, Bauer MC, et al. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. Pain 2009; 145(3):304-11.
33. Singh JB, Fedgchin M, Daly EJ et al. A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression. Am J Psychiatry, 2016 Apr 9;173(8).
34. Sorensen J, Bengtsson A, Ahlner J, et al. Fibromyalgia—are there different mechanisms in the processing of pain? A double blind crossover comparison of analgesic drugs. J Rheumatol 1997; 24(8):1615-21.
35. Schwartzman RJ, Alexander GM, Grothusen JR et al. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. Pain 2009; 147(1-3):107-15.
36. Tremont-Lukats IW, Hutson PR and Backonja MM. A randomized, double-masked, placebo-controlled pilot trial of extended IV lidocaine infusion for relief of ongoing neuropathic pain. Clin J Pain 2006; 22(3):266-71.
37. Tremont-Lukats IW, Challapalli V, McNicol ED, et al. Systemic administration of local anesthetics to relieve neuropathic pain: A systematic review and meta-analysis. Anesth Analg 2005; 101(6):1738-49.
38. Vlainich R, Issy AM, Sakata RK. Effect of intravenous lidocaine associated with amitriptyline on pain relief and plasma serotonin, norepinephrine, and dopamine concentrations in fibromyalgia. Clin J Pain 2011; 27(4):285-8.
39. Wallace MS, Ridgeway BM and Leung AY. Concentration-effect relationship of intravenous lidocaine on the allodynia of complex regional pain syndrome types I and II. Anesthesiology 2000; 92(1):75-83.
40. Webster LR and Walker MJ. Safety and efficacy of prolonged outpatient ketamine infusions for neuropathic pain. Am J Ther 2006; 13(4):300-5.
41. Wertli MM, Kessels AG, Perez RS, et al. Rational pain management in complex regional pain syndrome 1 (CRPS 1)--a network meta-analysis. Pain Med. Sep 2014; 15(9):1575-1589.
42. Williams DR, Stark RJ. Intravenous lignocaine (lidocaine) infusion for the treatment of chronic daily headache with substantial medication overuse. Cephalalgia. Dec 2003; 23(10):963-971.

43. Wu CL, Tella P, Staats PS, et al. Analgesic effects of intravenous lidocaine and morphine on postamputation pain: A randomized double-blind, active placebo-controlled, crossover trial. Anesthesiology 2002; 96(4):841-8.

POLICY HISTORY:

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