

Clinical Use of Intravenous Lidocaine for Management of non-Oncologic Neuropathic Pain in Adults

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Uso clínico de lidocaína intravenosa para manejo de dolor neuropático no oncológico en adultos

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Abstract

Neuropathic pain is common in clinical practice; it is estimated that 2 to 3 % of the global population is affected; a considerable number of patients present pain refractory to existing treatments, making it a diagnostic and therapeutic challenge. The objective of this study is to describe the clinical use of intravenous lidocaine for the management of non-cancer neuropathic pain in adults. The information search was performed by consulting the HINARI, SciELO and PubMed databases. Articles with an obsolescence of no more than five years, both in English and Spanish, were selected. Original articles, clinical trials, bibliographic reviews and meta-analyses were used. The causes of neuropathic pain in which lidocaine has been used were postherpetic neuralgia, diabetic neuropathy, and trigeminal neuralgia. The use of intravenous lidocaine has been shown to decrease pain intensity; however, when compared with other first line drugs, there are no long-term differences. Most side effects occur in the nervous, gastrointestinal, and cardiovascular systems. Intravenous lidocaine as monotherapy for the management of non-cancer neuropathic pain, although effective in the short term with doses of 3-5 mg/Kg, does not have a persistent and long-lasting effect.

Keywords

Lidocaine, Infusions, Intravenous, Neuralgia, Analgesia.

Resumen

El dolor neuropático es común en la práctica clínica. Se estima que afecta entre el 2 y 3 % de la población a nivel global. Una cantidad considerable de pacientes presentan dolor refractario a tratamientos existentes, volviéndolo un reto diagnóstico y terapéutico. El objetivo de este estudio es describir el uso clínico de lidocaína intravenosa para manejo de dolor neuropático no oncológico en adultos. La búsqueda de información se realizó consultando las bases de datos HINARI, SciELO y PubMed. Se seleccionaron artículos en inglés y español de 2017 a 2021. Se utilizaron artículos originales, ensayos clínicos, revisiones bibliográficas y metaanálisis. Las causas de dolor neuropático en las que ha sido utilizada la lidocaína son la neuralgia posherpética, neuropatía diabética y neuralgia del trigémino. El uso de lidocaína intravenosa demostró que disminuye la intensidad del dolor; sin embargo, al compararlo con otros fármacos de primera línea no hay diferencias a largo plazo. La mayoría de efectos secundarios se presentan en el sistema nervioso, gastrointestinal y cardiovascular. La lidocaína intravenosa como monoterapia para manejo de dolor neuropático no oncológico, si bien fue eficaz a corto plazo con dosis de 3-5 mg/Kg, no tuvo un efecto persistente y duradero.

Palabras clave

Lidocaína, Infusiones Intravenosas, Neuralgia, Analgesia.

Introduction

The International Association for the Study and Treatment of Pain (IASP) defines neuropathic pain as pain caused by injury, dysfunction, or transient impairment of the nervous system. This pain is usually chronic, persisting continuously or intermittently.¹ It can result from etiologically diverse disorders

affecting the peripheral or central system, depending on the location of the nerve lesion or dysfunction². Estimations of world population affected are between 2 to 3 %.³

Its prevalence has been described in several countries, varying from 3.3 % in Austria to 6.9 % in France, 8 % in the United Kingdom, and Latin America, it is estimated to affect 2 % of the population.⁴

Neuropathic pain can be responsible for a substantial financial burden for those affected, as total costs per patient ranged from 9305 EUR in Italy to 14 446 EUR per year in Germany, with the majority spent on indirect costs associated with care.^{5,6}

Neuropathic pain associated with symptoms such as allodynia, hyperalgesia and paresthesia⁷ impairs the patient's psychological and physical state. It is a common symptom in clinical practice and considerably affects people's quality of life. Many patients present pain that is refractory to existing treatments;⁸ observations of patients with similar etiology reported that not all respond in the same way to the same treatments, so there is no single specific treatment for neuropathic pain, being it considered a more complex entity that is difficult to control, which presents a health problem.^{3,10}

Over time, the use of drugs in the management of neuropathic pain, such as antiepileptics, NMDA receptor antagonists, and antidepressants, has proved to be useful; nevertheless, studies on efficacy and safety are still in progress. However, while 50 % of patients achieve a reduction of 30 to 40 % of their pain measured on a visual analog scale, between 40 to 70 % of patients do not achieve complete pain control.^{11,12}

The IASP Neuropathic Pain Special Interest Group (NeuPSIG) Evaluation Committee proposes gamma-aminobutyric acid analogue anticonvulsants (gabapentin, pregabalin), tricyclic antidepressants (amitriptyline) and selective serotonin-norepinephrine reuptake inhibitors as first-line drugs. Intravenous lidocaine, capsaicin, and tramadol as second-line management, and opioids (morphine, oxycodone) were added as third-line treatment for neuropathic pain.⁷

A study by Wang *et al.* compared the use of morphine and pregabalin as monotherapy and combination therapy for neuropathic pain management. From a total of 320 eligible patients, 265 were excluded due to the adverse effects of these drugs, concluding that, of the 55 patients selected, those who received combined therapy had a better safety and efficacy profile in the management of neuropathic pain ($p < 0.01$), compared to patients who received morphine or pregabalin in monotherapy.

Epidemiological surveys show that a large proportion of patients with neuropathic pain do not receive adequate treatment.¹³ Evidence shows that less than 50 % of patients achieve appropriate pain control in the short term. It is increasingly important to reduce chronic complications and to comply with a sound safety profile.¹⁴

Lidocaine infusion has an adequate safety profile with several desirable properties in the clinical setting.¹⁵

Lidocaine is a local anesthetic of the amino amide type, which acts by decreasing the permeability of the neuronal membrane to sodium ions, inhibiting depolarization; therefore, it interrupts the propagation of the action potential and nerve conduction, resulting in a central anti-hyperalgesic effect.^{16,17} In recent years, intravenous lidocaine has been used as an alternative for the management of neuropathic pain at low doses of 1.5 mg/Kg to 3 mg/Kg, achieving a significant decrease in pain by visual analog scale in the short term.¹⁸

In a study by Kim *et al.*, intravenous lidocaine administered at a dose of 3 mg/Kg for one hour was found to reduce the numerical pain rating scale scores in patients with postherpetic neuralgia or complex regional pain syndrome type II compared to the control group ($p = 0,011$).¹⁹

This paper is a narrative literature review article. Information search was conducted by consulting HINARI, SciELO, and PubMed databases. Regarding data collection, published articles in Spanish and English from 2017 to 2021 were selected. Original articles, clinical trials, literature reviews, and meta-analyses using boolean connector AND: neuropathic pain AND intravenous lidocaine, lidocaine infusion, AND side effects were applied. The objective of this review is to describe the clinical use of intravenous lidocaine for the management of non-oncologic neuropathic pain in adults.

Discussion

Causes of non-oncologic neuropathic pain for which lidocaine is commonly used

Neuropathic pain is characterized by not directly affecting the pain receptors but rather, as a result of a lesion at the nervous system level: it can be of central or peripheral origin. Central origin causes are due to an alteration in the spinal cord or brain, such as multiple sclerosis, stroke, and spinal cord injury. They account for 1 to 12 % of neuropathic pain following the above-mentioned pathologies.^{20,21} As for peripheral origin, nerve plexuses, spinal cord roots, or directly to a peripheral nerve are affected²², the most frequent causes being polyneuropathy secondary to diabetes and HIV, post-herpetic neuralgia, post-surgical neuralgia, trigeminal neuralgia, and post-traumatic injury; the latter are the pathologies in which intravenous lidocaine has been used.²³

Postherpetic neuralgia is the most common complication of Herpes Zoster virus, affecting one in five patients. It is a pain that follows the dermatomic distribution; it presents as continuous or paroxysmal, evoked or spontaneous, lancinating with sensory alterations of the skin. Pain occurs in a sustained manner for at least 90 days; those over 60 years old are more likely (3.3 %) to develop the complication 12 months after infection.^{24,25}

Diabetic neuropathy is a loss of sensory function with onset in the distal parts of the extremities; most symptoms are numbness, weakness, and paresthesias. The early manifestations of this disease can often go unnoticed and may be detected at an irreversible point. At least 50 % of diabetic patients develop this complication.^{26,27} Daykin *et al.* found significant reductions in pain in postherpetic neuralgia and diabetic neuropathy using doses of lidocaine 1 mg/Kg and 5 mg/Kg for 60 minutes and one week apart. They also reported significant changes compared to placebo, but there were no differences between the different doses of lidocaine.²⁸ Yousefshashi *et al.* concluded that the use of intravenous lidocaine is effective in the management of postherpetic neuralgia and diabetic neuropathy in the short term, as opposed to 5 % lidocaine patches due to the limitation of not being able to cover the entire affected area.²⁹

Trigeminal neuralgia refers to a short electric shock-like pain of abrupt onset and termination, which manifests in one or more divisions of the trigeminal nerve.³⁰

In one study, Xu *et al.* performed a retrospective analysis of a cohort in which seven patients, refractory to surgical and pharmacological treatment for trigeminal neuralgia used the standard protocol of IV infusion of 1.25 g magnesium and 100 mg lidocaine in 100 mL of normal saline administered for one hour, once a week for a total of three weeks. They noted that all subjects experienced pain relief after combined intravenous infusion therapy using a numerical pain intensity scale at the end of four weeks.³¹

Moore *et al.* evaluated the role of lidocaine infusion in a double-blind randomized controlled study in 20 patients; they compared lidocaine (5 mg/Kg) in 250 mL of 5 % dextrose solution against placebo in one hour and found that both lidocaine and placebo reduced pain intensity at the end of each session. However, lidocaine achieved a higher reduction compared to placebo ($p < 0.001$).³²

Fibromyalgia is a condition characterized by chronic musculoskeletal pain, hyperalgesia in different regions, and

psychomotor symptoms such as anxiety, depression, and cognitive dysfunction, with a higher prevalence in women over 50 years old.³³ The pathophysiology or cause is not yet well established. Two theories under investigation mention alterations in the regulation of neurotransmitters or changes in the function of the immune system following a viral infection.³⁴

In a randomized, double-blinded study, Albertoni *et al.* evaluated the effect of intravenous lidocaine compared to saline in 42 patients for pain relief in fibromyalgia. They used doses of 240 mg in one week for a duration of four weeks without obtaining a significant impact on pain relief.³⁵

Dose-response and most appropriate treatment timeframe

Neuropathic pain results from aberrant up-regulated sodium channels responsible for neuronal hyperexcitability after nerve injury.³⁶ Lidocaine blocks these channels, and several studies show that intravenous lidocaine infusion provides significant relief.³⁷ The dose usually used is 1 mg/Kg as an initial bolus, followed by a continuous infusion of 0.5 to 3 mg/Kg for one hour, with the most commonly used and best-described dose being a continuous infusion of 2 mg/Kg for one hour.³⁸

In a retrospective study ($n = 85$) using intravenous lidocaine infusions at a dose of 5 mg/kg for 30 minutes once a week, Przeklasa *et al.* showed relief of pain symptoms using a numerical rating scale describing that the older the patients and the greater the number of infusions the better the therapeutic effect ($p < 0.05$, $p < 0.01$ respectively). (Table 1)³⁹

Regarding the duration of treatment, Tan *et al.* studied the therapeutic effects of daily intravenous infusion of lidocaine as monotherapy versus the usual therapy for postherpetic neuralgia in a population of $n = 60$, demonstrating that the one-hour infusion of 4 mg/kg for five consecutive days reduced the intensity of pain and the frequency of eruptive pain compared to the control group ($p < 0.001$). In addition, it reduced tramadol consumption in those patients who used this infusion ($p < 0.05$).⁴⁰

Clattenburg *et al.* compared the efficacy of intravenous lidocaine versus intravenous morphine in 32 patients in an unblinded, randomized, controlled study. They used bolus loading of 1.5 mg/Kg for 10 minutes, followed by 1.5 mg/Kg for 50 minutes for a total of approximately 3 mg/Kg/hr of lidocaine. They concluded that it provides clinically significant analgesia on the numerical

pain rating scale, with results similar to morphine, and also, it reduces opioid utilization. (Table 1)⁴¹

Liu *et al.*, in a randomized double-blind study in 197 patients, compared the use of lidocaine at 5 mg/Kg for 1.5 hours versus placebo (normal saline) to assess analgesic efficacy and emotional response. They found that, although there was a reduction in the visual analog scale score for pain, it was not statistically significant versus control group ($p < 0.05$). In contrast, there was an statistical significant decrease in analgesic consumption in the group that received lidocaine infusions ($p < 0.05$).⁴²

In contrast to the previous study in which only short-term infusions were used, Dwight *et al.* conducted a double-blind, randomized trial in patients with chronic neuropathic pain of peripheral nerve origin ($n = 34$), compared the use of intravenous lidocaine at a dose of 5 mg/Kg versus placebo (diphenhydramine), to determine significant relief of neuropathic pain and an improvement in quality of life in the long term (four weeks), concluding that there was no significant analgesic difference between the two groups in the long term ($p = 0.61$).⁴³

Side effects and their frequency

Considering the benefits of intravenous lidocaine for the management of neuropathic

pain, the safety profile regarding side effects and the dose used, should be kept in mind. According to the FDA, the dose of lidocaine without epinephrine should not exceed 5 mg/Kg; above these doses, plasma concentrations of 3 $\mu\text{g/mL}$, 5 $\mu\text{g/mL}$ (paresthesias, fasciculations, tinnitus), and 7 $\mu\text{g/mL}$ can be found, the latter being where convulsions, coma, and cardiorespiratory arrest appear.^{44,45} Most side effects occur in the nervous, gastrointestinal, and cardiovascular systems; these adverse effects resolve when the infusion dose is lowered or stopped completely.⁴⁶

In a study conducted by Zavaleta *et al.*, in which they used intravenous lidocaine 2 % in acute postherpetic neuralgia in doses of 2 to 5 mg x Kg of weight, they observed that side effects occurred in 100 % of the patients, especially drowsiness and metallic taste ($p < 0.01$).⁴⁷

In another retrospective analysis of a sample of 233 patients, Iacob *et al.* documented that 46 % of the participants reported mild side effects, the most frequent being at the nervous system level. They also reported that the duration of these effects did not persist for more than three hours. The researchers consider it important to take electrocardiograms, and serum lidocaine levels, and monitor vital signs during infusions every 3 to 5 minutes.⁴⁸ Guillén *et al.* reported no side effects using lidocaine at a dose of 2 mg/Kg; they also suggested taking

Table 1. Comparison of main articles in the literature review

Study	Type of study	n	Dosage	Clinical effect	Side effects
Reeves, DJ and Foster (2017)	Retrospective analysis	21	0.2-2.8 mg/Kg/h	Pain relief $p < 0.001$	Cognitive impairment, delirium, dizziness, perioral numbness and drowsiness.
Moulin <i>et al.</i> (2019)	Crossover, double-blind, randomized trial	34	5 mg/Kg	Pain relief $p = 0.61$	Drowsiness, xerostomia, abdominal discomfort and dizziness.
Zavaleta and Álvarez (2017)	Prospective, longitudinal, comparative and experimental	30	2-5 mg/Kg	Pain relief $p < 0.01$	Drowsiness, dysgeusia, hypotension, dizziness.
Iacob <i>et al.</i> (2018)	Retrospective analysis	233	1000 mg/h	Pain relief $p < 0.001$	Perioral numbness, dizziness, tinnitus, nausea, numbness.
Przeklasa <i>et al.</i> (2016)	Retrospective analysis	85	5 mg/Kg	Pain relief $p < 0.05$	None reported.
Guillén-Ramírez <i>et al.</i> (2019)	Controlled, randomized, triple-blind clinical trial	29	2 mg/Kg	Pain relief $p < 0.01$	None reported.
Kim <i>et al.</i> (2018)	Prospective parallel, double-blind, controlled, controlled study	42	3 mg/Kg	Pain relief $p = 0.011$	Chest tightness
Clattenburg E <i>et al.</i> (2019)	Controlled, randomized non-blind study	32	3 mg/Kg/h	Pain relief	Paresthesia, nausea, pruritus.
Liu <i>et al.</i> (2018)	Randomized double-blind study	197	5 mg/Kg/h	Pain relief $p < 0.05$	Dizziness, xerostomy, headache, drowsiness.
Tan <i>et al.</i> (2019)	Randomized double-blind study	60	4 mg/Kg/h	Pain relief $p < 0.001$	Drowsiness, xerostomy, paresthesias.

electrocardiograms and vital signs every 15 minutes during infusions.⁴⁹

Reeves *et al.* conducted a retrospective study of 21 patients with neuropathic pain using lidocaine at low doses of 0.5 to 2 mg/Kg; they reported side effects in five patients, at the nervous system and gastrointestinal level, such as drowsiness, dizziness, perioral numbness, among others. The researchers concluded that it is important to establish a specific dose for each patient and measure blood lidocaine levels; although no cardiac side effects were reported, they suggested having a history of cardiovascular medical history such as atrial fibrillation or sinus tachycardia should be available before administering the drug intravenously. (Tabla 1)⁵⁰

If studies continue to show encouraging results, lidocaine infusion may be a viable option for patients who have long struggled to find relief from their symptoms.

Conclusion

According to the consulted literature, intravenous lidocaine has been used as monotherapy for the management of non-oncologic neuropathic pain. Although it is effective in short-term pain control with variable doses in the range of 3 to 5 mg/Kg, it does not have a persistent and lasting effect. Regarding its safety, no serious adverse effects were reported; however, it is associated with a higher frequency of mild side effects at the nervous system and gastrointestinal level compared to other drugs. Further research with standardized protocols on intravenous lidocaine infusion therapy in neuropathic pain is needed to fully understand the efficacy of this medication.

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