Reviews

Role of Intravenous Lidocaine Infusion in the Treatment of Peripheral Neuropathy

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Purpose of Review

This is a comprehensive review of the literature regarding intravenous lidocaine infusion to treat peripheral neuropathy. The clinical symptoms of peripheral neuropathy occur on a broad spectrum and stem from many etiologies resulting in complex treatment approaches. This review presents the background, evidence, and indications for the use of intravenous lidocaine infusions as a treatment option for this condition.

Recent Findings

The clinical range of peripheral neuropathy symptoms includes pain, numbness, muscle weakness, paresthesia, balance difficulty, and autonomic dysfunction. However, severe neuropathic pain remains one of the most debilitating symptoms that significantly affects the quality of life. Current treatment options include antidepressants, anticonvulsants, and, in some cases, opiates, but these are often ineffective, creating the need for other therapeutic approaches.

The pathophysiology of neuropathic pain involves sodium channels which create abnormal pain responses. Intravenous lidocaine primarily functions by inhibiting membrane sodium channels which desensitize peripheral nociceptors, thus creating an analgesic effect. The research in using intravenous lidocaine for neuropathic pain is not fully complete and requires further evaluation.

Summary

Peripheral neuropathy is a manifestation commonly resulting from diabetes, alcohol abuse, vitamin deficiencies, and chemotherapy, among other causes. One of the most significant complications is neuropathic pain which is often resistant to multi-modal therapeutic regimens. Intravenous lidocaine infusions are a newer treatment option for neuropathic pain, which have additional anti-inflammatory effects with a minimal side effect profile. Studies have concluded it effectively treats neuropathic pain for weeks after administration, but results are variable depending on specific procedures. Further research, including additional direct comparison studies, should be conducted to fully evaluate this drug’s usefulness.

INTRODUCTION

Peripheral neuropathy is a condition that stems from a wide range of etiologies. It is experienced by millions of Americans worldwide and is increasing in prevalence each year.¹ Neuropathy is rarely a stand-alone disease and is usually...
a part of a systemic process that results in injury to peripheral nerve components like axons or myelin sheaths. Metabolic diseases like diabetes or uremia, inflammatory diseases (sarcoidosis), autoimmune diseases (lupus, rheumatoid arthritis), infections (HIV, HCV), injuries (burns, direct trauma), drug-induced toxicity from chemotherapy or antiretrovirals, rare genetic diseases such as Charcot-Marie-Tooth (CMT), and many other etiologies can result in the defects that are found in peripheral neuropathy.

While the etiologies are numerous, the pathophysiology converges on several common mechanisms: metabolic dysregulation, covalent modification of proteins, organellar dysfunction, ROS/RNS production, altered intracellular and inflammatory signaling, axonal transport defects, and ion channel dysfunction. Research on this topic is still ongoing as mechanisms continue to be discovered and understood.

Peripheral neuropathy can occur in different patterns; it can affect one nerve or multiple nerves, be symmetric or asymmetric, and be sensory, motor, sensorimotor, or autonomic. Peripheral neuropathy presents with different symptoms depending on which types of nerves are damaged and the severity of this damage. The most common cause of peripheral neuropathy is diabetes, which presents as a distal symmetric polyneuropathy.

Peripheral neuropathy can be asymptomatic or mild but can also cause pain, numbness, paresthesia, difficulty balancing, muscle weakness, autonomic dysfunction, and many other symptoms. Complications of peripheral neuropathy include severe neuropathic pain, ulcer formation, gangrene, amputation, injuries, falls, and difficulties performing daily living activities. Neuropathic pain is the most debilitating symptom of peripheral neuropathy. Higher pain levels can lead to reduced physical activity, trouble sleeping, and mental health issues like depression and anxiety. These issues correlate with overall poorer quality of life in those with significant symptoms.

Peripheral neuropathy is associated with greater morbidity and mortality in those with diabetes. Early detection of peripheral neuropathy through screening and diagnostic testing is extremely important in decreasing morbidity and preventing a decline in quality of life. These tests include nerve conduction studies, neuropathy disability score, skin biopsy, quantitative sensory testing, and corneal confocal microscopy. With such a high prevalence of peripheral neuropathy and such varying etiologies, research on peripheral neuropathy treatment is critical, especially since it can improve the quality of life in people suffering from the potentially disabling symptoms of peripheral neuropathy.

PERIPHERAL NEUROPATHY EPIDEMIOLOGY

Although recent epidemiologic studies and data on peripheral neuropathy prevalence are lacking, older studies show that this is an increasingly widespread condition, especially in middle-aged and elderly populations. A study from 2006 claims that of the United States population, 14.8% of people aged 40 and older have some form of peripheral neuropathy. Diabetes accounts for around half of neuropathy cases.

When looking at the statistics in the diabetic population, studies suggest that up to one-half of diabetic people will develop peripheral neuropathy in their lifetime. According to the CDC, 34.2 million people in the US currently have diabetes (10.5% of the US population). On the report of Abbott, Malik, et al., about one-third of patients with diabetic peripheral neuropathy will develop neuropathic pain, which is considered to be the most debilitating symptom of peripheral neuropathy.

It has also been reported that chemotherapy-induced peripheral neuropathy (CIPN) occurs in about 30–40% of patients taking neurotoxic chemotherapeutics. Scientists believe that the prevalence of peripheral neuropathy is underestimated and will continue to increase with the increasing prevalence of cancer survival, diabetes, obesity, and metabolic syndrome. The remaining studies performed on peripheral neuropathy have varying results due to inconsistencies between different etiologies, types of peripheral neuropathy, and populations examined.

PERIPHERAL NEUROPATHY RISK FACTORS AND PATHOPHYSIOLOGY

Risk factors for developing peripheral neuropathy include but are not limited to diabetes, alcohol abuse, vitamin deficiencies, certain infections, exposure to toxins, treatment with neurotoxic chemotherapeutics or antiretrovirals, a family history of neuropathy, or vascular problems that could cause ischemic damage to nerves.

The pathophysiology behind peripheral neuropathy is often multifactorial. Still, most mechanisms fall into the main categories of metabolic dysregulation, covalent modification of proteins, organellar dysfunction and ROS/RNS production, altered intracellular and inflammatory signaling, axonal transport defects, and channelopathies. Some systemic illnesses can dysregulate metabolic pathways, and the end products of this altered metabolism are often damaging for nerves. For example, hyperglycemia due to diabetes can cause the buildup of damaging reactive intermediates such as sorbitol and other polyols, which disrupt the axonal membrane, reduce a nerve's ability to propagate an action potential, and/or impair regeneration following axonal injury. NADPH depletion due to increased glucose levels also leaves a nerve cell more susceptible to oxidant damage and eventual apoptosis.

Some disease states can promote the covalent modification of proteins. Hyperglycemia is an example of this as well; it can lead to the formation of advanced glycation end products (AGEs) through nonenzymatic glycoxidation. AGEs can alter collagen, affecting blood vessels and increasing a nerve's risk of experiencing hypoxia-induced damage. Modification of laminin, an essential protein for proper development and health of Schwann cells and neurons, by AGES can limit peripheral nerve recovery after injury. AGEs can also damage DNA by modifying bases and producing double-strand breaks. Similar DNA damage is also caused by platinum chemotherapeutics, which tend to induce apoptosis in sensory neurons, leading to CIPN.

Alterations of intracellular and inflammatory signaling pathways can leave nerves susceptible to damage. AGE (RAGE) receptor acts to scavenge and clear AGE and pro-

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Proteins modified by AGE from the body.\textsuperscript{3} Levels of RAGE are decreased in some people with type II diabetes, increasing the risk of peripheral neuropathy.\textsuperscript{3} RAGE also releases cytokines that remodel blood vessels, similar to the remodeling seen in atherosclerosis.\textsuperscript{3} These released cytokines may also increase ROS production, and this event combined with the tissue remodeling converts the short-term inflammatory signaling of AGE into long-term inflammation.\textsuperscript{3} The loss of insulin and C peptide in type I diabetes leads to a reduced ability to upregulate neurotrophic factors, which generally assist in nerve regeneration after a crush injury.\textsuperscript{3} Nerve growth factor (NGF) signaling plays a role in the development of neuropathic pain; the pattern of NGF’s expression is dependent on the type of diabetes and can reduce regenerative ability if levels fall, which is seen later in the course of disease in some diabetic patients.\textsuperscript{5}

Various chemotherapeutic agents, like paclitaxel and HIV infection and treatment with antiretrovirals, increase inflammation, which damages nerves, ganglia, and axons.\textsuperscript{3} The cryoglobulinemia seen in some cases of HCV precipitates a more generalized peripheral neuropathy rather than a localized disorder due to IgGs binding and initiating immune attack of myelin, and small and medium vascular occlusion leading to ischemic nerve damage.\textsuperscript{3} In HCV without cryoglobulinemia, interferon-α (IFN-α) release can lead to peripheral neuropathy by damaging myelin and vasa vasorum, leading to ischemic nerve injury.\textsuperscript{3}

The endoplasmic reticulum (ER) is susceptible to injury by several toxicities, and its dysfunction can lead to peripheral nerve damage by triggering cell death through different pathways.\textsuperscript{3} Dysfunction of mitochondria, especially overproduction of reactive oxygen species (ROS), can cause neuropathy through cell death and injury due to oxidative stress.\textsuperscript{3} This problem occurs with diabetes, HIV, treatment with chemotherapeutics like paclitaxel, bortezomib, and oxaliplatin, and with some antiretroviral medications.\textsuperscript{3}

The nervous system is especially predisposed to free radical damage because of its high energy demands and increased lipid content.\textsuperscript{3,17} Natural antioxidants like uncoupling proteins (UCPs) protect cells from free radical damage, and depletion of these proteins due to decreased expression of UCP-3 in hyperglycemic states leads to nerve damage.\textsuperscript{3}

DNA damage from ROS like superoxide activates poly (ADP-ribose) polymerase (PARP) in several tissues, including Schwann cells and peripheral nerves.\textsuperscript{3} PARP depletes NAD\textsuperscript{+} levels, resulting in neurotoxicity and necrosis.\textsuperscript{3} With an increase in ROS usually comes an increase in the production of reactive nitrogen species (RNS); PARP activation by ROS increases iNOS activity in the nervous system and decreases eNOS activity in endothelial cells. The combination of increased RNS in the nervous system and impairment of NO’s vasodilatory effect on blood vessels causes a double insult to neurons through oxidant damage and hypoxia.\textsuperscript{3}

Defects in axonal transport can lead to peripheral neuropathy. Slowed axonal transport of cytoskeletal proteins has been observed in diabetes, resulting in reduced levels of important proteins distally.\textsuperscript{3} Glycation of actin and neurofilaments also occurs with hyperglycemia, which is thought to disrupt axonal transport, making nerves less efficient in response to injury or environmental changes.\textsuperscript{3} Microtubule stabilization by taxanes like paclitaxel can also alter transport dynamics in nerves, which is another mechanism behind CIPN.\textsuperscript{14} Alterations in axonal transport can also be seen in CIPN caused by cisplatin and bortezomib, but the mechanism behind this remains unknown.\textsuperscript{14}

When ion channel expression or dynamics in nerves are altered, this can cause peripheral neuropathy. Ion channel toxicity is a common cause of CIPN, especially with platinum chemotherapeutics and proteasome inhibitors, and in Guillain-Barré Syndrome (GBS).\textsuperscript{3,14} GBS is a syndrome of peripheral neuropathy caused by an autoimmune attack on gangliosides due to molecular mimicry of \textit{C. jejuni} antigens, and this alters ion channel activity in the nodes of Ranvier.\textsuperscript{5}

Diabetes, smoking, atherosclerosis, high blood pressure, and peripheral vascular disease can lead to inadequate oxygen supply to peripheral nerves and, in some cases, neuropathy.\textsuperscript{18} Burn injuries can also lead to peripheral neuropathy by direct injury or edema of soft tissues, inflammatory damage, or immobilization.\textsuperscript{17} Many of the mechanisms discussed here are inherently linked, with some pathologic processes enhancing others, creating a snowball effect of peripheral nerve damage. There are several other etiologies and pathophysiologic mechanisms that are still being discovered and explored further.

**CLINICAL PRESENTATION**

Peripheral neuropathy has a wide range of presentations depending on the underlying etiology. It can be asymptomatic or subclinical, where the patient has not noticed any symptoms, but this can predispose them to injuries or ulcer development. Symptoms will vary with the type of nerve fiber that is damaged. Damage to motor nerves may present with weakness, atrophy, fasciculations, or areflexia. In contrast, damage to large-fiber sensory nerves can cause loss of vibratory sensation or proprioception and can present with numbness, imbalance, falls, ataxia, paresthesia, or areflexia.\textsuperscript{6} Small-fiber sensory nerve damage can cause loss of pain/temperature sensation or can present with numbness or neuropathic pain described as burning, stinging, or aching.\textsuperscript{4} Autonomic nerve fiber damage can lead to postural dizziness due to orthostatic hypotension, dry mucous membranes, skin, coldness or flushing, bladder dysfunction, impotence, early satiety, skin changes, and hair loss.\textsuperscript{2}

The most common presentation of peripheral neuropathy is a length-dependent, slowly progressing, distal symmetric polyneuropathy (DSP).\textsuperscript{6} Diabetes is the most common cause of DSP and commonly presents with numbness, paresthesia, loss of pain sensation, imbalance, or dysesthesia.\textsuperscript{2} These neurological deficits gradually spread, starting in the toes and moving proximally, eventually affecting the upper limbs in what is classically described as a ‘glove-and-stocking’ pattern.\textsuperscript{6} Axons can be several feet long, and the most distal ends are more susceptible to damage, which explains the symmetric length dependency seen in DSP.\textsuperscript{17}

Presentation with asymmetric or non-length-dependent neuropathies is rarer and will change the differential diagnosis; for example, a mononeuropathy could be due to direct trauma via laceration or compression of nerves.\textsuperscript{2} Presentation with an acute or subacute course may suggest an infectious process, toxic exposure, or an autoimmune eti-
ology such as GBS or vasculitis.\textsuperscript{4,6} If motor symptoms prevail over sensory deficits, demyelinating disorders should be considered, including lead toxicity, porphyria, diphtheria, paraneoplastic neuropathy, multifocal motor neuropathy, chronic inflammatory demyelinating polyneuropathy, or a hereditary neuropathy such as Charcot-Marie-Tooth disease.\textsuperscript{6}

Later complications of long-standing peripheral neuropathy include ulcers, gangrene, distal calf atrophy, hammertoes, pes cavus, and lower extremity amputation.\textsuperscript{6}

CURRENT TREATMENT OF PERIPHERAL NEUROPATHY

ANTIDEPRESSANTS

Serotonin and norepinephrine reuptake inhibitors (SNRIs) have been shown to improve peripheral neuropathy pain symptoms in diabetic peripheral neuropathy (DPN), chemotherapy-induced peripheral neuropathy (CIPN), and drug-induced peripheral neuropathy (DIPN).\textsuperscript{20–22} Tricyclic antidepressants (TCAs) have also been shown to treat DPN; however, there is less evidence than SNRIs.\textsuperscript{20,21} Of all antidepressants, duloxetine has the most data supporting its use in treating peripheral neuropathy. Multiple reviews show duloxetine is the most effective at treating symptoms of DPN and CIPN.\textsuperscript{20,21,25,26} The American Diabetes Association and American Society of Clinical Oncology recommend duloxetine as first-line treatment for DPN and CIPN.\textsuperscript{25,26} Venlafaxine has also been shown to help treat DPN, although less effective than duloxetine.\textsuperscript{20,21} A 2017 review by Waldfogel et al. demonstrated that 7 RCTs are testing the efficacy of duloxetine and 2 RCTs testing the efficacy of Venlafaxine.\textsuperscript{20} Due to the limited data of Venlafaxine’s effectiveness, it is not recommended to treat peripheral neuropathies.\textsuperscript{26} These RCTs show that both drugs are effective treatments for DPN with a moderate level of evidence.\textsuperscript{20} Few RCTs are testing the efficacy of TCAs, but the data indicates that TCAs, specifically amitriptyline, nortriptyline, and imipramine are effective at treating DPN and DIPN.\textsuperscript{20,22}

ANTICONVULSANTS

Pregabalin and gabapentin are shown to be effective for treating pain related to DPN, with pregabalin and duloxetine being the recommended first-line treatment by the American Diabetes Association.\textsuperscript{25,27} While both pregabalin and gabapentin are recommended for use to treat DPN, pregabalin has been studied the most, with a recent review showing 16 RCTs investigating its efficacy versus placebo.\textsuperscript{20} The results from the RCTs show that pregabalin is effective in treating DPN but with a lower level of evidence than treatment with duloxetine.\textsuperscript{20} Gabapentin and Oxcarbazepine have also been studied in multiple RCTs but were less effective than treating DPN with pregabalin.\textsuperscript{20} Anticonvulsants are also used to treat CIPN and DIPN, but there is less evidence supporting their effectiveness.\textsuperscript{21,22}

OPIATES

Typical opiates have not shown any statistically significant evidence of effectiveness at treating pain related to DPN, CIPN, and DIPN. However, atypical opiates, such as Tramadol, show limited efficacy.\textsuperscript{20,27} Sometimes, opiates are used in cases where peripheral neuropathy symptoms are refractory to antidepressants and anticonvulsants, but data does not show a decrease in peripheral neuropathy symptoms.\textsuperscript{28} Opiates are the gold standard for treating peripheral neuropathy and nerve impingement in burn patients.\textsuperscript{29} To treat peripheral neuropathy in burn patients, combining morphine and gabapentin show an increased reduction in symptoms than either alone.\textsuperscript{29} Other than this specific case, opiates are generally not recommended for treating peripheral neuropathies.

OTHER/NON-PHARMACOLOGICAL TREATMENT

Many non-pharmacological options are being explored as many cases remain refractory to pharmacological treatment, but few have been tested in large RCTs. When treating DPN, the most crucial step is maintaining low Hemoglobin A1C levels. In type I and people with type II diabetes, tight glucose control is effective at preventing DPN.\textsuperscript{23} Other effective non-pharmacological agents for treating DPN include alpha-lipoic acid (ALA), botulinum toxin A, and spinal cord stimulation. Oral 600 mg ALA demonstrated the highest symptom relief compared to placebo, but some RCTs had an increased risk of bias.\textsuperscript{27,30} Multiple reviews show that intradermal injection into the dorsum of the foot with botulinum toxin A is more effective than placebo at relieving DPN.\textsuperscript{20,21,27,30} Spinal cord stimulation leads to reduced pain symptoms. Still, it is an invasive procedure with many harmful side effects.\textsuperscript{30} There are fewer recent investigations into non-pharmacological treatment for CIPN, but some RCTs have found that acupuncture improves symptoms when combined with other treatment methods.\textsuperscript{28} The studies regarding acupuncture have few participants and will require more extensive studies to prove its efficacy. Another recommended treatment by the American Society of Clinical Oncology is a topical compound gel consisting of baclofen, amitriptyline HCl, and ketamine.\textsuperscript{31} Regarding DIPN, the most important treatment is to stop the offending agent.\textsuperscript{22} If the symptoms persist beyond that point, the next step would be to move on to duloxetine.\textsuperscript{22} A less common etiology of peripheral neuropathy is due to systemic and non-systemic vasculitis syndromes. Severe systemic vasculitis is treated with corticosteroids initially, and cyclophosphamide or rituximab can be added if symptoms persist, while non-systemic vasculitis is treated with corticosteroids only.\textsuperscript{31}

MECHANISM OF ACTION

The pathophysiology of neuropathic pain is related to a change in the expression of sodium channels, which leads to aberrant pain responses.\textsuperscript{32} The main analgesic effect of lidocaine is mediated or modulated by desensitizing peripheral nociceptors through blockage of membrane sodium channels leading to adequate local anesthesia.\textsuperscript{32} This phys-
Role of Intravenous Lidocaine Infusion in the Treatment of Peripheral Neuropathy

The use of intravenous (IV) lidocaine infusions for treating peripheral neuropathy is a generally safe and effective treatment method for neuropathic pain. Potential adverse effects of or reactions to lidocaine infusion therapy (LIT) include but are not limited to dizziness, headaches, blurred vision, tinnitus, nausea, paresthesia, confusion, tremor, hypotension, bradycardia, arrhythmia, muscle twitching, seizures, cardiac arrest, and respiratory depression.4 Severe adverse effects were rare in the clinical trials reviewed below.

A randomized, double-blind, placebo-controlled, parallel study was conducted to evaluate the safety and efficacy of LIT in patients with postherpetic neuralgia or complex regional pain syndrome type II. Forty-two subjects were evenly and randomly split into two groups: the LIT group and the control group. The LIT group received lidocaine infusions dosed at 3 mg/kg over one hour; the control group received infusions of normal saline. Infusions were administered once a week for four weeks. The primary outcome measured was the percent change from baseline to after the final infusion on an 11-point numerical rating scale (NRS) pain score and NRS pain scores at the one-week and four-week follow-ups. Following the final infusion, the NRS pain score percent decrease was significantly higher in the LIT group than in the control group (P=0.011). At the one-week and four-week follow-ups, no significant decrease in NRS pain scores were observed from baseline in both groups. Participants did not experience any severe complications from LIT and laboratory tests were normal. LIT was briefly stopped for one patient who in the past experienced chest discomfort; treatment was resumed after the discomfort resolved 15 minutes later.4

Another randomized, controlled, double-blind trial also evaluated lidocaine as a treatment for peripheral neuropathy. This single-site study investigated IV lidocaine infusion and utilized an active placebo infusion of diphenhy-

PHARMACOKINETICS/PHARMACODYNAMICS

Following an IV infusion of lidocaine, plasma concentration rapidly falls and steadily declines at a slower pace with a half-life of roughly 100 minutes.38 Lidocaine reaches a wide distribution volume range of 0.6-4.5L/kg.39 It is then metabolized to monoethyllglycinexilidide (MEGX) and glycinexilidide (GX) by the hepatic enzyme CYP3A4.40,41 Less than 5% of lidocaine is renally excreted due to its lipophilicity.42 For renal excretion to occur, lidocaine must first be converted into its metabolites MEGX and 4-hydroxy-xylidine.41,42 GX is further converted into xylidine and then finally to 4-hydroxy-xylidine, which is then excreted renally.41 MEGX is a pharmacologically active metabolite with a longer half-life but less potency than a sodium channel blocker.39 When patients are administered the CYP3A4 inhibitor erythromycin, clearance decreases by half, steady-state volume increases, and half-life doubles.41 Similar results are seen when patients are administered cimetidine before receiving IV lidocaine. Oral cimetidine causes lidocaine clearance to decrease by 34%.43 Previous studies determined that infusion rate should not exceed 4 mg/min.44 The ideal plasma concentration of lidocaine should not exceed 5.0 ug/mL as higher levels lead to a greater chance of toxicity.44 Dosages need to be decreased in patients with cardiac or liver failure, as these patients are more likely than healthy patients to reach toxic plasma concentrations. Heart failure patients will have a longer half-life and a smaller volume of distribution.38 Liver failure patients have an increased half-life, larger volume of distribution, and decreased plasma clearance.38 Lidocaine dosing in patients with renal failure can remain the same as dosing in healthy patients. In these patients, half-life, the volume of distribution, and plasma clearance remained similar to healthy patients.42 There is limited evidence regarding therapeutic index and other pharmacodynamics and kinetics specific to treating peripheral neuropathy, as treating cardiac arrhythmias is the purpose of most studies investigating IV lidocaine infusion. Overall, the pharmacokinetics and pharmacodynamics of IV lidocaine vary significantly from individual to individual.

CLINICAL STUDIES: SAFETY AND EFFICACY

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Table 1. Clinical Efficacy and Safety

<table>
<thead>
<tr>
<th>Author</th>
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<th>Conclusions</th>
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<tr>
<td>Kim Y.C. et al.</td>
<td>A randomized, double-blind, placebo-controlled, parallel study on LIT in patients with postherpetic neuralgia or complex regional pain syndrome type II. 42 participants evenly split into LIT and control groups. LIT group received LIT dosed at 3 mg/kg over one hour. The Control group received normal saline over one hour.</td>
<td>Percent decrease in the NRS pain score from baseline post-infusion was significantly higher (P=0.011) in the LIT group compared to the control group. At the 1 week and 4-week follow-ups, there was no significant decrease in NRS pain scores from baseline in both groups.</td>
<td>LIT is effective after infusion and in the short term, but it is not effective for long-term pain relief. It is safe and well-tolerated, with serious complications being rare.</td>
</tr>
<tr>
<td>Moulin D.E. et al.</td>
<td>Randomized, controlled, double-blind trial on LIT for peripheral neuropathy. 34 participants were split into lidocaine and placebo groups with 16 and 18 participants, respectively. The lidocaine group received a 5 mg/kg dosage and the placebo group received 50 mg IV diphenhydramine. Infusions were given over 45 minutes. Results evaluated 4 weeks post-infusion, participants switched into the opposite group, experiment repeated.</td>
<td>The API was obtained before infusions, 6 hours after, and daily for 4 weeks. No significant differences were noted in API from baseline compared to 6 hours after infusions or any point thereafter. After 4 weeks, the API difference between the lidocaine group (6.58 mean, 1.56 SD) and the control group (6.78, 1.56 SD) was not significant (P=0.61).</td>
<td>LIT is not effective in the short or long term. It is safe and well-tolerated, with serious complications being rare.</td>
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<tr>
<td>Van Den Heuvel S.A.S. et al.</td>
<td>Cohort study with 9 patients to determine effects of IV lidocaine for treating CIPN. The infusion dose was 1.5 mg/kg over 10 minutes, followed by 1.5 mg/kg/hour over 5 hours.</td>
<td>Pre-infusion NRS scores ranged from 5-9 (7.7 average). Post-infusion NRS scores ranged from 0-7 (average 3.1). LIT resulted in a clinically significant decrease in NRS scores (P=0.01). 3 patients reported cessation of the effects immediately after completion of the infusion. 5 patients experienced analgesic effects ranging from 3-56 days (average 23 days) after completion of the infusion.</td>
<td>LIT is significantly effective at reducing pain during infusions. Results are mixed regarding the continuation of effects after treatment with some people. It is safe and well-tolerated, with serious complications being rare.</td>
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<tr>
<td>Liu H. et al.</td>
<td>Randomized, double-blind, placebo-controlled study regarding the LIT treatment of PHN. 197 patients were split into a lidocaine group (96 patients) and a placebo group (101 patients). The lidocaine group received an infusion dose of 5 mg/kg and the placebo group received normal saline over 1.5 hours.</td>
<td>14 patients withdrew, leaving 183 patients. The average baseline VAS of the lidocaine and placebo groups were 5.18 and 4.99, respectively. Post-infusion VAS scores reached their minimum in both groups after 2 weeks. Lidocaine group VAS: 2.74. Placebo group VAS: 2.99. VAS scores slightly increased at the 4-week mark.</td>
<td>The difference in VAS scores is not clinically significant and reduction of pain with LIT is comparable to the placebo. It is safe and well-tolerated, with serious complications being rare.</td>
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<td>Przekłasa-Muszylska A. et al.</td>
<td>85 patients with various neuropathic pain syndromes received LIT. 81 patients received 3-25 infusions and 4 patients withdrew after the first infusion. The average age of patients was 62.6 years, with 43% male patients and 57% female patients.</td>
<td>No significant difference between the sexes regarding pain/symptom reduction was found. The pre-infusion average NRS score was 7.01; the post-infusion score was 2.8. There was a 40% average reduction in pain. The older the patient, the more effective LIT is. Patients with higher NRS pain scores pre-infusion reported the most relief. These differences were statistically significant.</td>
<td>LIT is effective at reducing pain and symptoms of neuropathic pain. It is safe and well-tolerated, with serious complications being rare.</td>
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| Hutson P. et al.            | 69 patients received a total of 1650 infusions dosed at 500 mg lidocaine in 100 mL saline over 30 minutes (16.7 mg/min). | The average pain decrease was 3.6 points (SD 1.7). Most patients needed a dose reduction or rate adjustment. 89% | The study bases efficacy on the fact that 1579/
The initial high dosage is given to determine patient response and tolerance. of infusion rates ranged from 4-14 mg/min, an average of 9.1 mg/min. A significant number of patients experienced the greatest pain relief 24 hours post-infusion. A dose between 4-12 mg/min was the most tolerable effective dose. Patients experienced adverse side effects at an average of 13.1 mg/min. 1650 infusions (95.7%) were done on repeat patients as they continued treatment. LIT is safe and well-tolerated, with serious complications being rare.

| Papapetrou P. et al. (2015)51 | Case report of LIT to treat CIPN in a 63-year-old female. 5 mg/kg IV lidocaine was administered over 1 hour. Symptoms were immediately alleviated following the infusion and the results lasted 2 weeks. The treatment was repeated and yielded similar results. 3 more infusions were given over the next 9 weeks, and each infusion lasted 2-3 weeks LIT is effective at reducing pain for up to 3 weeks post-infusion. LIT is safe and well-tolerated, with serious complications being rare. |
|---|---|---|
| Kajiume T. et al. (2012)52 | Case report of a 5-year-old girl with severe neuropathic cancer pain due to meningitis caused by malignant T-cell lymphoma. The patient was co-administered IV infusions of ketamine (0.12 mg/kg/hour), fentanyl (0.83 μg/kg/hour), and lidocaine (9.3-14 μg/kg/min). This combination proved very effective as it significantly reduced her pain for two weeks. The combination administered was safe and very effective in this patient. |
| Park C.H. et al. (2012)53 | A randomized, double-blind, prospective, crossover study with 18 patients was conducted to evaluate the efficacy of LIT on FBSS. Each patient received 3 different IV infusions on 3 different days, 2 weeks apart. Infusions were given over the course of 1 hour. Patients randomly received either a 0.9% normal saline placebo, 1 mg/kg of lidocaine, or 5 mg/kg of lidocaine IV infusion per infusion day. VAS scores at baseline compared to post-infusion showed all 3 treatments demonstrated a significant decrease in pain (P<0.006). The NPS scale showed there was not a statistically significant difference in pain between the 3 treatments except for sharp, cold, dull, and deep pain. All 3 treatments were effective in reducing neuropathic pain due to FBSS, including the placebo. LIT was as effective as the placebo. Patients did not experience any serious complications during or after treatment. |

Lidocaine infusion dose was 1.5 mg/kg over 10 minutes, followed by 1.5 mg/kg/hour over 5 hours. Pain intensity was determined using the 11-point NRS scale before, during, and after treatment. Pre-infusion NRS scores ranged from 5 to 9, with an average of 7.7. Post-infusion NRS scores ranged from 0 to 7, with an average of 3.1. IV lidocaine treatment resulted in a clinically significant decrease in NRS scores at the group level (P<0.01). Three patients reported cessation of the analgesic effects almost immediately after completion of the infusion. Five patients continued to experience analgesic effects ranging from 3 to 56 days after completion of the infusion, with an average of 25 days.47 A randomized, double-blind, placebo-controlled study evaluated the analgesic effects of IV lidocaine infusion to treat postherpetic neuralgia (PHN). A total of 197 eligible patients were enrolled in the study, and they were randomized and split into a lidocaine group with 96 patients and a placebo group with 101 patients. The lidocaine group received an IV infusion dosed at 5 mg/kg, and the placebo group received normal saline over 1.5 hours. The visual analog scale (VAS) was used to assess pain at baseline and after the infusion. Post-infusion, eight patients received a paravertebral block due to no improvement in pain from the IV
dramine. Thirty-four eligible participants were enrolled and randomly split into a lidocaine group with 16 participants and a placebo group with 18 participants. In the first phase, the lidocaine group received an infusion dose of 5 mg/kg and the placebo group received a dose of 50 mg, infusions were given over 45 minutes. Results were evaluated four weeks post-infusion, after which participants were switched into the opposite group, and the experiment was repeated for phase two. The average pain intensity (on a scale of 0-10) difference between lidocaine infusion and placebo infusion four weeks post-infusion was the primary outcome measure. The average pain intensity (API) was obtained before infusions, 6 hours after infusions, and daily for four weeks. No significant differences were noted in API from baseline compared to 6 hours after infusions or any point after that. At the end of the four weeks, the API difference between the lidocaine group (6.58 mean, 1.97 SD) and the control group (6.78, 1.56 SD) was not significant (P=0.61). Participants did not experience any serious complications during or after treatment.46

Nine patients were enrolled in a cohort observational study to determine the effects of IV lidocaine on treating chemotherapy-induced peripheral neuropathy (CIPN). The orthopedic reviews
lidocaine; they withdrew from the study. Six patients were lost to follow-up for other reasons, resulting in 183 patients with eligible data. The average baseline VAS score of the lidocaine group was 5.18 and the placebo group’s average was 4.99. Post-infusion, the VAS scores decreased daily in both groups and reached their minimum scores after two weeks, with the lidocaine group having a score of 2.74 and the placebo group having a score of 2.99. This difference was determined not to be clinically significant; scores slightly increased at the 4-week mark. The reduction of pain using IV lidocaine was determined to be comparable to the placebo. Patients did not experience any serious complications during or after treatment.48

A total of 85 patients with various neuropathic pain syndromes were enrolled in a study that evaluated the efficacy of IV lidocaine. Eighty-one patients received 3 to 25 IV lidocaine infusions from this group, and four patients withdrew from the study after the first infusion due to inefficacy. Before each infusion, the patient rated their pain on the NRS scale. Each patient received an IV lidocaine infusion dosed at 5 mg/kg over 30 minutes once a week for 25 weeks. The average age of patients was 62.6 years, with 43% male patients and 57% female patients. There was no statistically significant difference between the sexes in terms of pain and symptom reduction. The pre-infusion average NRS pain value of all patients was 7.01; the post-infusion value was 2.8. The average percentage of relief in pain symptoms was over 40%. Przeklasa-Muszyńska et al., 2016 determined that LIT is more effective in older patients. The least efficacy was seen in the 20-to-30-year age group, effectiveness increased significantly in the 31 to 70 age group, and it was the most effective in the 71-90-year age group. It was also determined that the more infusions a patient received, the more effective the IV lidocaine therapy was. They also observed that the more intense the initial pain was reported to be, the more effective the treatment was to alleviate pain on the subjective NRS scale. These differences were found to be statistically significant. The length of time a patient had been experiencing pain did not affect the efficacy of the treatment as the difference in pain intensity on the NRS pre-infusion and post-infusion was significant irrespective of pain duration. Patients did not experience any serious complications during or after treatment.49

A study was conducted to determine the efficacy, safety, and toxicity of IV lidocaine infusions in treating neuropathic pain. The University of Wisconsin (UW) health infusions centers protocol is to administer 500 mg of lidocaine in 100 mL of saline over 30 minutes, which comes to 16.7 mg/min. This is done in the initial infusion to determine how and if the patient responds to and tolerates the therapy. A total of 69 patients received 1650 infusions. Only 262 of these infusions had comprehensive documentation, which included both pre-infusion and post-infusion NRS scores. The average decrease in pain was found to be 3.6 points (SD 1.7). Of the 69 patients, 58 were started on the institutional dose of 500 mg lidocaine over 30 minutes. Fifteen of the 58 patients developed adverse effects and could not tolerate the dosage or required a reduction. The actual administered dose average was 564 mg (SD 78 mg) with an average rate of 9.1 mg/min (SD 3.31 mg/min). A total of 45 patients continued with subsequent infusions. Of the 45 patients, 23 tolerated the initial rate of 16.7 mg/min. As well, 8 of these 25 patients received this rate on all future infusions. 89% of the IV lidocaine infusion rates ranged from 4-14 mg/min with an average of 9.1 mg/min when excluding the initial infusion of all patients. Of the 45 patients, 38 needed rate reductions and 26 of the 45 patients required a reduced dose. On average, patients received infusions every 19.4 days. Of the 1650 infusions, 38 were prematurely discontinued related to the development of adverse effects at a rate of 13.4 mg/min. The data revealed that 55 (79.9%) of the 69 patients developed adverse effects with an average rate of 13.2 mg/min. The most common adverse effect was light-headedness, and any harmful effects were reversed. A significant number of patients reported that they experienced the greatest amount of pain relief 24 hours after the infusion. A total of 1579 of the 1650 infusions (95.7%) were done on repeat patients; this can be used to measure the efficacy of the treatment as they chose to continue. A dose between 4 and 12 mg/min was found to be the most tolerable effective dose. The average dose at which patients experienced adverse side effects was 13.1 mg/min. Patients did not experience any serious complications during or after treatment except for one patient that developed hypoglycemia. However, as hypoglycemia is not associated with IV lidocaine, this was deemed circumstantial.50

A case report documented the efficacy of IV lidocaine infusions to treat chemotherapy-induced peripheral neuropathy. Many chemotherapy drugs can cause peripheral neuropathy. The incidence rate is approximately 30-40%. A 61-year-old female presented to a pain clinic with hand and foot pain after receiving chemotherapy for breast cancer. After four months of treatment, she started to experience pain, tingling, and bilateral numbness, which were not alleviated with amitriptyline and gabapentin. 5 mg/kg IV lidocaine was administered over 1 hour in the clinic. The patient’s symptoms were immediately alleviated following the infusion. The treatment lasted two weeks and was repeated once symptoms returned and yielded similar results. The patient has three more lidocaine infusions over the next nine weeks, and each infusion lasted 2-3 weeks. Treatment is safe and well-tolerated; the patient did not experience any severe complications.51

A 5-year-old girl was diagnosed with severe neuropathic cancer pain due to meningitis caused by malignant T-cell lymphoma. In children with terminal cancer, opioids are the go-to therapy selection. However, patients with tumors that have metastasized to the spine and have invaded nerves may need higher doses of opioids. This patient was administered IV infusions of ketamine, fentanyl, and lidocaine. The patient underwent chemotherapy and achieved remission. However, after one year after the onset of symptoms, she was diagnosed with a lymphoma recurrence. She was treated with chemotherapy, but complete remission wasn’t achieved. An umbilical cord blood stem cell transplantation was performed. She developed oral ulcers, fatigue, headache, neck pain, vertigo, vomiting, right oculomotor paralysis, pressure in her head, and sharp pain secondary to trigeminal nerve involvement over 59 days after transplantation. Her symptoms were not controlled with fentanyl (0.85 μg/kg/hour) alone and IV lidocaine (9.5-14 μg/
kg/min) was co-administered on day 62. She developed new neck and shoulder pain and on day 89 ketamine (0.12 mg/kg/hour) was co-administered with fentanyl and lidocaine to improve the analgesia. This combination of medication proved to be very effective as it significantly reduced her pain for two weeks, after which she died. The combination administered was safe and very effective in this patient.52

A randomized, double-blind, prospective, crossover study was conducted to evaluate the effects of IV lidocaine therapy on cases of failed back surgery syndrome (FBSS). Eighteen patients with FBSS were enrolled. Each patient received three different IV infusions on three different days, which were two weeks apart. Infusions were given over the course of 1 hour. The patients randomly received either a 0.9% normal saline placebo, 1 mg/kg of lidocaine, or 5 mg/kg of lidocaine IV infusion per infusion day. The pain was assessed using the visual analog scale (VAS) and neuropathic pain scale (NPS). VAS scores were measured pre-infusion, every 10 minutes during infusion, and 8, 16, 24 hours post-infusion. VAS scores at baseline were compared to scores post-infusion. All three treatments demonstrated a significant decrease in pain ($P=0.006$). According to the NPS scale, there was no statistically significant difference in pain between lidocaine dosages or between lidocaine and the placebo except for sharp, cold, dull, and deep pain. The three treatments were all effective in reducing neuropathic pain due to FBSS. However, the effects of the placebo did not differ from either lidocaine dosage. Patients did not experience any serious complications during or after treatment.53

CONCLUSION

Peripheral neuropathy is a common complication of several systemic illnesses, drug therapies, and toxic exposures. Standard treatment either focuses on the underlying mechanisms of peripheral neuropathy, such as better glycemic control in diabetic patients, or symptomatic treatment. Especially when the symptoms of peripheral neuropathy include neuropathic pain, pain management is the primary aspect of the treatment regimen. Antidepressants including duloxetine, epilepsy drugs such as pregabalin, local anesthetics/topical medications, and opioids have long been hallmarks of neuropathic pain treatment.8

Recently, several studies have examined the safety and efficacy of intravenous lidocaine infusion therapy in treating peripheral neuropathy. Lidocaine, a local amide anesthetic, has analgesic properties by blocking sodium channels and decreasing nociceptor sensitization. It also has strong anti-inflammatory properties with fewer side effects than other anti-inflammatory medications.37

Lidocaine infusion is not without its side effects, with the most common being light-headedness, dizziness, headache, tinnitus, lethargy, and paresthesia. These side effects were usually self-limiting and subsided shortly after the treatment ended; severe side effects were rare in the studies reviewed here. Lidocaine infusion therapy is especially promising due to its ability to provide pain relief for up to weeks after the drug is infused.37

Several studies have shown that intravenous lidocaine infusion is a safe and effective treatment for peripheral neuropathy. Even though some studies concluded that low-dose lidocaine infusions did not significantly affect placebo, higher doses showed significant pain improvement. The studies reviewed here showed a wide variation in administration, treatment timeline, and pain assessment, which may explain the variable results. More research with standardized measures on intravenous lidocaine infusion treatment for peripheral neuropathy is needed to fully understand the efficacy of this treatment. If studies continue to show encouraging results, lidocaine infusion can be a viable option for patients who have long struggled to find relief from their peripheral neuropathy symptoms.

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Table 2. Comparative Studies

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Groups Studied and Intervention</th>
<th>Results and Findings</th>
<th>Conclusions</th>
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<tbody>
<tr>
<td>Cousins M.J. et al. (2013)54</td>
<td>A double-blind, randomized, crossover trial was conducted to compare the efficacy of subcutaneous infusions of lidocaine (700 mg), KAI-1678 (25 mg), and a placebo in treating neuropathic pain in PHN patients. KAI-1678 is an inhibitor of epsilon protein kinase C.</td>
<td>KAI-1678 did not reduce NRS pain scores. Subcutaneous lidocaine infusions significantly reduced pain intensity on the NRS pain scale.</td>
<td>KAI-1678 is safe and well-tolerated.</td>
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<tr>
<td>Tremont-Lukats I. et al. (2006)55</td>
<td>A double-blind, parallel study was conducted to evaluate the dose-response effect and safety of CIT at various dosages in patients with peripheral neuropathy. Patients received an infusion over the course of 6 hours. The infusions were dosed at 1 mg/kg/hour, 3 mg/kg/hour, 5 mg/kg/hour, or the infusion was a saline placebo.</td>
<td>A significant difference in the PID% was found between the placebo group and the group that received 5 mg/kg/hour (P=0.012). Pain reduction in this group continued even after completion of the infusion up to 4 hours post-infusion. The results of the lower dosage lidocaine groups were comparable to the placebo.</td>
<td>LIT is effective for short term pain relief and it is safe and well-tolerated. Patients did not experience any serious complications during or after treatment.</td>
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REFERENCES


