

## The Effect of Intravenous Lidocaine on Post Herpetic Neuralgia in Palliative Care Unit: A Randomized Double Blind Placebo Controlled Trial


Jain R.<sup>1</sup>, Patel N.<sup>2\*</sup>

<sup>1</sup> Roopesh Jain, Professor, Department of Anaesthesiology, L.N. Medical College, Bhopal, MP, India.

<sup>2\*</sup> Narmada Prasad Patel, Associate Professor, Department of General Medicine, L.N. Medical College, Bhopal, MP, India.

**Introduction:** Post herpetic neuralgia (PHN) is a painful complication of herpes zoster (shingles). Its therapeutic approach is challenging as the first line treatment often does not help and may cause intolerable side effects. The aim of our randomized double blind, placebo controlled, crossover study was to investigate in a prospective way the effect of intravenous lidocaine in patients with post herpetic neuralgia in palliative care unit. **Material and Method:** Twenty patients met our inclusion criteria and completed the study. Each patient underwent four weekly sessions, two of which were with lidocaine (5 mgs/kg) and two with placebo infusions administered over 60 minutes. **Results:** Intravenous lidocaine was superior regarding the reduction of the intensity of pain, the allodynia, and the hyperalgesia compared to placebo. Also contrary to placebo, lidocaine managed to maintain its therapeutic results for the first 24 hours after intravenous infusion. **Discussion:** Although, intravenous lidocaine is not a first line treatment, when first line medications fail to help, pain specialists may try it as an add-on treatment.

**Keywords:** Post Herpetic Neuralgia, Herpes zoster, Lidocaine, Allodynia, Hyperalgesia

Corresponding Author	How to Cite this Article	To Browse
Narmada Prasad Patel, Associate Professor, Department of General Medicine, L.N. Medical College, Bhopal, MP, India. Email: <a href="mailto:narmadapatel2006@rediffmail.com">narmadapatel2006@rediffmail.com</a>	Roopesh Jain, Narmada Prasad Patel, The Effect of Intravenous Lidocaine on Post Herpetic Neuralgia in Palliative Care Unit: A Randomized Double Blind Placebo Controlled Trial. Biomed Rev J Basic Appl Med Sci. 2016;3(1):156-161. Available From <a href="https://www.biomedicalreview.in/intravenous-lidocaine-post-herpetic-neuralgi-palliative-double-blind-placebo-research-article">https://www.biomedicalreview.in/intravenous-lidocaine-post-herpetic-neuralgi-palliative-double-blind-placebo-research-article</a>	

Manuscript Received  
2016-06-07

Review Round 1  
2016-06-09

Review Round 2  
2016-06-16

Review Round 3  
2016-06-23

Accepted  
2016-06-30

Conflict of Interest  
Nil

Funding  
Nil

Ethical Approval  
Yes

Plagiarism X-checker  
16%

Note



© 2016 by Roopesh Jain, Narmada Prasad Patel and Published by Siddharth Health Research and Social Welfare Society. This is an Open Access article licensed under a Creative Commons Attribution 4.0 International License <https://creativecommons.org/licenses/by/4.0/> unported [CC BY 4.0].



## Introduction

Post herpetic neuralgia (PHN) is the most frequent chronic complication of herpes zoster (shingles) [1]. Herpes zoster (HZ) represents a reactivation of the varicella zoster virus (VZV), a ubiquitous, highly neurotropic, exclusively human  $\alpha$ -herpes virus. Primary infection causes varicella (chickenpox), after which VZV becomes latent in sensory ganglia along the entire neuraxis. With the decline in VZV-specific cell-mediated immunity in elderly and immunocompromised individuals, VZV reactivates to cause HZ, characterized by a painful maculopapular or vesicular rash in all or part of the skin territory innervated by a single dorsal root ganglion [2]. The most common site of HZ is thoracic, comprising about half of all cases, followed by trigeminal (usually the ophthalmic branch), cervical, and lumbar distributions. HZ generally resolves within a few weeks, minority of patients experience pain (PHN) persisting for months, years, or even a lifetime. According to a recent systematic review, the incidence of HZ is 3–5 cases per 1000 person-years. PHN risk increases with age. The age-specific incidence rates of HZ were similar across countries, with a steep rise after 50 years of age. The incidence was 6–8 cases/1000 person-years at 60 years of age and 8–12 cases/1000 person-years at 80 years of age [3].

Treatment guidelines, published from the International Association for the Study of Pain (IASP), recommends Tricyclic antidepressant (TCAS) or gabapentinoids as first choice treatment of PHN and lidocaine patches (5%) or capsaicin patches (8%) or tramadol as second choice [4].

However, some patients may experience intractable pain despite adequate treatment with these medications or their combination. On the other hand, some patients may experience intolerable side effects that lead to discontinuation, although recommended treatments have achieved sufficient reduction of their pain. Lidocaine is a common amino amide-type local anesthetic and anti-arrhythmic drug [5]. It is mainly used to relieve cancer or postoperative pain [6, 7], however, it has also been used to relieve several kinds of neuropathic pain, including postherpetic neuralgia [8]. This therapeutic potential lies in the fact that systemic lidocaine and its oral congeners can block sodium channels in a dose dependent fashion

[11, 12] in both the peripheral and the central nervous system [13]. In the literature, only few retrospective studies of the effect of intravenous lidocaine on PHN exist. The aim of our randomized double blind, placebo controlled, crossover study was to investigate in a prospective way the effect of lidocaine in patients with PHN.

## Materials and Methods

**Participants:** Following the approval of the Institutional Ethical Committee of L.N. Medical College and JK Hospital, Bhopal, all consecutive patients suffering from PHN who visited the Outpatient Pain and Palliative Care OPD were invited to participate in the study. To be enrolled, the patients had to meet the following inclusion criteria: (1) confirmed diagnosis of PHN according to IASP definition [25], (2) age equal to or greater than 18 years, (3) visual analogue scale (VAS) score equal to or greater than 3 (out of a maximum 10), (4) Douleur Neuropathique 4 Questionnaire (DN4) score equal to or greater than 4 (out of a maximum 10), (5) having received the recommended medications for PHN (tricyclic antidepressants, gabapentin, opioids) for an adequate period without therapeutic results, (6) PHN duration of at least 12 weeks, (8) no history of allergy to lidocaine, (9) no history of substance abuse, (10) absence of severe psychiatric diseases, (11) not being pregnant, (12) not lactating, (13) absence of severe cardiac, hepatic, and renal disease, and (14) be willing to provide a written informed consent to undergo the experimental procedures.

**Procedures:** Each patient participated in four sessions, every 2nd day, receiving two active and two placebo treatments, involving continuous infusion of 1 hour. Active treatment was lidocaine (5 mg per kilogram of body weight) in 250 mL of 5% dextrose solution and placebo treatment was 250 mL of 5% dextrose solution. Subjects were randomly assigned to treatment sequence via a computer-generated randomization list. A randomization list was prepared in sealed envelopes for each patient. Investigator A was responsible for solution preparation according to the randomization list. Investigator B, who was blind to the treatment, was responsible for clinical examination and treatment administration. At the end of each treatment investigator B had to record data and enclose the forms in envelopes

That remained closed until the end of the study. In the morning of each session (08:00) the patients were guided to a calm and separate room where investigator B recorded the pain intensity on VAS before the beginning of the infusion and at the end of it. Moreover, investigator B tested the intensity of (1) mechanical allodynia (pressure of the painful area by an unused pencil), (2) thermal allodynia (application of a thermal roll at 40° C at the painful area), (3) cold allodynia (application of a thermal roll at 26° C at the painful area), (4) pinprick hyperalgesia (feeling excess pain more than usual pain during the pinprick by a needle 26G at the painful area), (5) hot hyperalgesia (application of a thermal roll at 46° C at the of the painful area), and (6) cold hyperalgesia (application of a thermal roll at 20° C at the painful area). During the sessions the patients were monitored continuously by 3- lead electrocardiogram, pulse oximetry, and blood pressure (BP) manometer. Every 15 minutes systolic BP, diastolic BP, oxygen saturation, and heart rate (HR) were recorded. Any side effects, such as somnolence, mental confusion, metal taste, and tingling sensation around the mouth, vision disturbances, tremor, drowsy mouth, tremor, or anything else were also documented. Table 1 shows Characteristics of the study population (= 20), demographic characteristics Male sex (%), Age in years, Clinical characteristics Weight in kg, Location of neuralgia (%), DN4 score at baseline. Finally, at the end of each session the patients were given a "Pain Diary," where they recorded the VAS score at 16:00, 20:00, and 24:00 the same day and at 08:00 the next morning.

**Statistical Analyses:** A database was developed using the Statistical Package for Social Science (version 16.0 for Mac; SPSS). Frequencies and descriptive statistics\ were examined for each variable. Comparisons between patients who received lidocaine and patients who received placebo were made using Student's -tests for normally distributed continuous data and MannWhitney's test for nonnormally distributed data. Allodynia and hyperalgesia were graded according to a Likert scale from 0 to 4 (0 = no pain, 1 = little pain, 2 = moderate pain, 3 = heavy pain, and 4 = unbearable pain). Grading scores in allodynia and hyperalgesia before and after intravenous administration were recorded. Patients who achieved a reduction of at least

1 grading point in the Likert scale were considered to have achieved a reduction of allodynia and hyperalgesia, when patients who either graded the same before and after or showed increase in the Likert scale were considered not to have achieved a reduction. Comparisons between the lidocaine and placebo groups regarding these categorical data were made using the chi-square test. Power analysis demonstrated that a 20% difference in VAS reduction with 80% power could be detected with a sample of 20 patients. A value of < 0.05 was considered to be statistically significant.

## Results

**Study Population:** Between May 2013 and May 2016, 23 individuals fulfilled the above-mentioned inclusion criteria. However, three patients denied continuing after the first session. Therefore, our final study population consisted of twenty patients. Clinical and demographic characteristics of the study total population are summarized in Table 1.

**Table-1: Characteristics of the study population (= 20)**

Demographic characteristics	
Male sex (%)	7 (35)
Age in years (SD )	65.20 (15.28)
Clinical characteristics	
Weight in kg (SD)	73.75 (16.48)
Location of neuralgia (%)	
thoracic region	2 (10)
2nd branch of trigeminal nerve	2 (10)
Cervical region	16 (80)
DN4 score at baseline (SD)	6.25 (0.63)

**DN4:** Douleur Neuropathique 4 Questionnaire; SD: standard deviation.

**Response to Treatment:** Table 2 shows the response regarding intensity of pain, allodynia, and hyperalgesia following lidocaine versus placebo intravenous infusion. ISRN Pain 3 Table 2: Response regarding intensity of pain, allodynia, and hyperalgesia following lidocaine versus placebo intravenous infusion. The study included 20 patients who received twice the active (lidocaine) and twice the placebo drug. Lidocaine Placebo (= 40) (= 40) Effect on intensity of pain VAS score pretreatment (SD) 6.23 (1.56) 5.45 (2.04) 0.060 VAS score post treatment (SD) 1.46 (1.37) 3.33 (2.02) < 0.001). This was maintained for at least 24 hours after treatment as was documented in the

Pain diary. Hence, at 24 hours after treatment lidocaine achieved a reduction of 52% of the pretreatment intensity of pain when patients who received placebo reported a mild increase of 4% of the pretreatment intensity of pain. Similarly, lidocaine reduced mechanical allodynia thermal allodynia, cold allodynia, pinprick hyperalgesia, hot hyperalgesia, and cold hyperalgesia in a statistically significant greater percentage of patients.

**Table-2: Response regarding intensity of pain, allodynia, and hyperalgesia following lidocaine versus placebo intravenous infusion. The study included 20 patients who received twice the active (lidocaine) and twice the placebo drug**

	Lidocaine n = 40	Placebo n =40	P
Effect of intensity of pain			
VAS score pretreatment (SD)	6.23(1.56)	5.45(2.04)	0.060
VAS score post treatment (SD)	1.46(1.37)	3.33(2.02)	<0.001
VAS score at 16: 00 (SD)	1.77(1.61)	4.08(2.33)	<0.001
VAS score at 20: 00 (SD)	2.38( 1.73)	4.45(2.36)	<0.001
VAS score at 24: 00 (SD)	2.33 (1.84)	4.43(2.15)	<0.001
VAS score at 08:00 next morning (SD)	2.95 (1.88)	5.20(2.55)	<0.001
VAS reduction % pre-/post treatment (SD)	76.4 (23.0)	40.1(31.9)	<0.001
VAS reduction % pretreatment—16:00 (SD)	70.5 (27.7)	21.6(45.5)	<0.001
VAS reduction % pretreatment—20:00 (SD)	59.5(30.3)	20.2(42.1)	<0.001
VAS reduction % pretreatment—24:00 (SD)	61.0(32.1)	13.9(39.1)	<0.001
VAS reduction % pretreatment—next day (SD)	52.0(29.6)	-4.0(56.3)	<0.001
Effect on allodynia			
Reduced mechanical allodynia (%)	31(77.5)	20(50)	0.011
Reduced thermal allodynia (%)	18(45.0)	7(17.5)	0.008
Reduced cold allodynia (%)	15(37.5)	5(12.5)	0.010
Effect on hyperalgesia			
Reduced pinprick hyperalgesia (%)	26(65)	14(35)	0.007
Reduced hot hyperalgesia (%)	22(55)	7(17.5)	<0.001
Reduced cold hyperalgesia (%)	20(50)	11(27.5)	0.039

**VAS:** visual analogue scale; SD: standard deviation.

**Adverse Events:** No statistically significant changes regarding systolic BP, diastolic BP, HR, and oxygen saturation were found during the treatment administration between patients who received lidocaine and patients who received placebo. Table 3

Effects were reported as mild. Patients who received lidocaine reported more side effects compared to patients who received placebo. Most common side effect among patients who received lidocaine was somnolence (reported in 32.5% of cases) and most common side effect among patients who received placebo was dry mouth (reported in 5% of cases).

**Table-3: Adverse events reported by patients. The study included 20 patients who received twice the active lidocaine and twice the placebo drug**

	Lidocaine ( n= 40)	Placebo (n=40)
Somnolence	13	1
Dry mouth	5	2
Dizziness	5	0
Headache	3	1
Feeling flushed	2	0
Confusion	1	0
Dysarthria	1	0
Tinnitus	1	0

## Discussion

Intravenous lidocaine infusions are gaining acceptance in a variety of pain-management settings [14]. We find that intravenous lidocaine is superior regarding the reduction of the intensity of pain, the allodynia, and the hyperalgesia compared to placebo. Also lidocaine managed to maintain its therapeutic results during the first 24 hours after intravenous infusion. To our knowledge, this is the first prospective study of the effect of intravenous lidocaine on post herpetic neuralgia compared to placebo. Moreover, in a nonclinical setting not many studies examining the alteration of the evoked pain of PHN by the intravenous administrations of lidocaine exist. An experimental study in neuropathic rats had already shown that intravenous, but not intrathecal or regionally applied, lidocaine produces dose dependent suppression allodynia associated with nerve injury. Interestingly enough, the effects far outlast plasma concentrations of lidocaine; however, the mechanism of these prolonged effects remains unknown [15]. In our study we also observed that lidocaine achieved a decrease of the intensity of pain, as this was measured by VAS, which lasted for 24 hours and this decrease was superior compared to placebo, despite the fact that lidocaine’s half-life is 1.6 hours [16]. Similar to this, TremontLukats et al. reported that the effect of lidocaine in

Patients with neuropathic pain started 4 hours after the onset of treatment and continued for at least 4 hours after the end of the infusion [17]. Moreover, Attal et al. showed that, in patients with central pain, lidocaine decreased VAS for 6 hours after the injection and a subgroup of patients experienced prolonged analgesia for up to 7 days [18]. Until now, the effectiveness of lidocaine in neuropathic pain has been shown through case series. Moreover, Michael et al. have recently published data of nineteen patients with PHN treated with an intravenous infusion of a combination of lidocaine and morphine. The authors concluded that all patients experienced sound pain relief after the combined intravenous infusion therapy [9]. However, as their study was performed in a retrospective way, the authors did not use a control group. The authors explain that because of the very low incidence of intractable PHN it is impractical to perform a randomized placebo controlled trial. As we also had difficulty in identifying a large sample of patients to be recruited in the form of a randomized placebo controlled trial we performed a crossover trial. Thus, each patient participated in four sessions, receiving two active and two placebo treatments. The assignment to treatment sequence was random. This is a very good alternative way to study different drug types and/or doses when the study sample is small. [19]. One other advantage of our study is that we used a standardized dose of lidocaine according to the patients' weight. We chose to use the dose of 5 mg/kg lidocaine over 60 minutes because in this dose lidocaine does not affect the peripheral conduction [20,21] and it, also, acts at hyperexcitable neurons without affecting normal nerve conduction showing, thus, good effects on neuropathic pain [22]. Regarding its safety profile, intravenous lidocaine has been used to relieve several kinds of neuropathic pain without producing major adverse effects [23]. Similarly, in our study, the infusions caused minor side effects and during the infusions all the patients were haemodynamically stable with good oxygen saturation. Moreover, no dropouts were observed because of the occurrence of side effects. Finally, our results should be interpreted with some caution given the fact that we only used a single dose of lidocaine (5 mg/kg). Therefore the effectiveness of different doses remains unstudied. Future clinical research should focus on identifying the least effective dosage of intravenous lidocaine. Interventional procedures, such as the

Role of spinal cord stimulation, deep brain stimulation, and intrathecal medication delivery is inconclusive in PHN [24]. However, such procedures involve the risk of major neurological complications and other less serious adverse effects and their result may not last. Pharmaceutical approach still remains the mainstay of treatment. Although intravenous lidocaine is not a first line treatment, when first line medications fail to help, pain specialists may try it as an add-on treatment.

## Conclusion

Pharmacological treatment of post herpetic neuralgia is the mainstay of treatment. Lidocaine should be consider for refractory pain and further large study needed to define proven role of lidocaine in the management of post herpetic neuralgia.

## Reference

01. Johnson RW, Rice AS. Clinical practice. Postherpetic neuralgia. *N Engl J Med.* 2014 Oct 16; 371(16):1526-33. doi: 10.1056/NEJMcp1403062.
02. Yawn BP, Gilden D. The global epidemiology of herpes zoster. *Neurology.* 2013 Sep 3; 81(10):928-30. doi: 10.1212/WNL.0b013e3182a3516e.
03. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. *BMJ Open.* 2014 Jun 10; 4(6):e004833. doi: 10.1136/bmjopen-2014-004833.
04. Haanpaa M, Rice ASC, Rowbotham MC. Pain Clinical updates. 2015 May; 23(4).
05. GILBERT CR, HANSON IR, BROWN AB, HINGSON RA. Intravenous use of xylocaine. *Curr Res Anesth Analg.* 1951 Nov-Dec; 30(6):301-13.
06. DE CLIVE-LOWE SG, DESMOND J, NORTH J. Intravenous lignocaine anaesthesia. *Anaesthesia.* 1958 Apr; 13(2):138-46.
07. BARTLETT EE, HUTSERANI O. Xylocaine for the relief of postoperative pain. *Anesth Analg.* 1961 MayJun; 40:296-304.
08. Rowbotham MC, Reisner-Keller

01. LA, Fields HL. Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia. *Neurology*. 1991 Jul; 41(7):1024-8.
02. Khaliq W, Alam S, Puri N. Topical lidocaine for the treatment of postherpetic neuralgia. *Cochrane Database Syst Rev*. 2007 Apr 18 ;(2):CD004846.
03. Nagaro T, Shimizu C, Inoue H, Fujitani T, Adachi N, Amakawa K, Kimura S, Arai T, Watanabe T, Oka S. [The efficacy of intravenous lidocaine on various types of neuropathic pain]. *Masui*. 1995 Jun; 44(6):862-7.
04. Mao J, Chen LL. Systemic lidocaine for neuropathic pain relief. *Pain*. 2000 Jul; 87(1):7-17.
05. Tanelian DL and Brose WG. Neuropathic pain can be relieved by drugs that are use-dependent sodium channel blockers: lidocaine, carbamazepine, and mexiletine. *Anesthesiology* 1991; 74(5):949-51.
06. Lauretti GR. Mechanisms of analgesia of intravenous lidocaine. *Rev Bras Anesthesiol*. 2008 MayJun; 58(3):280-6.
07. Vadalouca A, Raptis E, Moka E, Zis P, Sykioti P, Sifaka I. Pharmacological treatment of neuropathic cancer pain: a comprehensive review of the current literature. *Pain Pract*. 2012 Mar; 12(3):219-51. doi: 10.1111/j.1533-2500.2011.00485.x. Epub 2011 Jul 29.
08. Chaplan SR, Bach FW, Shafer SL, Yaksh TL. Prolonged alleviation of tactile allodynia by intravenous lidocaine in neuropathic rats. *Anesthesiology*. 1995 Oct; 83(4):775-85.
09. Thomson PD, Melmon KL, Richardson JA et al. Lidocaine pharmacokinetics in advanced heart failure, liver disease, and renal failure in humans. *Ann Intern Med* 1973; 78(4):499-508.
10. Tremont-Lukats IW, Hutson PR and Backonja MM. A randomized, double-masked, placebocontrolled pilot trial of extended IV lidocaine infusion for relief of ongoing neuropathic pain. *Clin J Pain* 2006 Mar - Apr; 22(3): 266-71.
11. Attal N, Rouaud J, Brasseur L, Chauvin M, Bouhassira D. Systemic lidocaine in pain due to peripheral nerve injury and predictors of response. *Neurology*. 2004 Jan 27; 62(2):218-25.
01. Jones B and Kenward MG. Design and Analysis of Cross over Trials. CRC Press 2003; 98:727-28.
02. Attal N, Gaudé V, Brasseur L, Dupuy M, Guirimand F, Parker F, Bouhassira D. Intravenous lidocaine in central pain: a double-blind, placebocontrolled, psychophysical study. *Neurology*. 2000 Feb 8; 54(3):564-74.
03. Bach FW, Jensen TS, Kastrup J, Stigsby B, Dejgård A. The effect of intravenous lidocaine on nociceptive processing in diabetic neuropathy. *Pain*. 1990 Jan; 40(1):29-34.
04. Ferrante FM, Paggioli J, Cherukuri S, Arthur GR. The analgesic response to intravenous lidocaine in the treatment of neuropathic pain. *Anesth Analg*. 1996 Jan; 82(1):91-7.
05. Tremont-Lukats IW, Challapalli V, McNicol ED, Lau J and Carr DB. Systemic administration of local anesthetics to relieve neuropathic pain: a systematic review and metaanalysis. *Anesth Analg* 2005; 101(6):1738- 49.
06. Dworkin RH, O'Connor AB, Kent J, Mackey SC, Raja SN, Stacey BR, Levy RM, Backonja M, Baron R, Harke H, Loeser JD, Treede RD, Turk DC, Wells CD; International Association for the Study of Pain Neuropathic Pain Special Interest Group. Interventional management of neuropathic pain: NeuPSIG recommendations. *Pain*. 2013 Nov; 154(11):2249-61. doi: 10.1016/j.pain.2013.06.004. Epub 2013 Jun 6.
07. Priya S, Lisa AD, David PM; Mayo Clin Proc. 2009 Mar; s84 (3): 274-280.