Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Intravenous infusion of lidocaine enhances the efficacy of conventional treatment of postherpetic neuralgia

This article was published in the following Dove Press journal:
Journal of Pain Research

Xinran Tan[1]
Lulin Ma[1]
Jie Yuan[1,2]
Dexin Zhang[1]
Jie Wang[1]
Wenjing Zhou[2]
Song Cao[1,2]

[1]Department of Pain Medicine, Affiliated Hospital of Zunyi Medical University, Zunyi 563000, People's Republic of China; [2]Guizhou Key Laboratory of Anesthesia and Organ Protection, Zunyi Medical University, Zunyi 563000, People's Republic of China

Background: Postherpetic neuralgia (PHN) is one kind of severe neuropathic pain which currently cannot be effectively cured. Recent researches suggest that intravenous infusion of lidocaine has a therapeutic effect on neuropathic pain such as PHN; however, the optimal dose and frequency of lidocaine infusion and the effectiveness and safety of this treatment in PHN patients still needs more clinical research. The aim of this study was to evaluate the therapeutic effects of daily intravenous lidocaine infusion on the outcome of the routine treatment of PHN.

Methods: Sixty PHN patients were randomly divided into two groups: 1) control group (Control), treated with conventional therapies, such as antiepileptic pills, analgesics, neurotrophic medicines, paravertebral spinal nerve block and physiotherapy; 2) lidocaine group (Lido) received daily infusion of lidocaine (4 mg/kg) besides the conventional treatments. If the pain is not controlled sufficiently, additional tramadol is given and the average consumption of tramadol is calculated. Pain intensity was assessed before and after each infusion, and the number of breakthrough pain in the last 24 hrs were recorded. The incidence of adverse reactions related to intravenous lidocaine infusion was recorded.

Results: For five consecutive days, numeric rating scale (NRS) scores were significantly decreased after 1 hr of intravenous infusion of lidocaine. Compared with Control, the NRS scores and the frequency of breakthrough pain in the Lido were significantly reduced. In addition, the extra tramadol consumption in the Lido was significantly lower than that in the Control, and the average hospital stay of patients in Lido was decreased. However, anxiety and depression scores showed no difference between Lido and Control.

Conclusion: Daily intravenous lidocaine (4 mg/kg for 5 days) enhanced the outcome of PHN treatment, reduced the amount of analgesic medicine and shortened the length of hospital stay with no obvious adverse side effects.

Keywords: postherpetic neuralgia, lidocaine, pain, intravenous infusion

Introduction

Postherpetic neuralgia (PHN) is a neuropathic pain which lasts more than 1 month[1] or 3 months[2,3] following an outbreak of shingles. The pain of PHN is severe and difficult to cure.[4,5] PHN is also an economic burden of the gradually aging society,[6] which affects the quality of life[7] and even increases the risk of anxiety, depression and suicide.[8,9] The mechanisms of neuropathic pain, including PHN, are currently not fully understood,[10,11] and the treatment of PHN is unsatisfactory.[6,12] For refractory PHN, current drug treatment is mainly a combination use of opioids, antiepileptic drugs and antidepressants, which may result in complications such as respiratory

Correspondence: Song Cao
Department of Pain Medicine, Affiliated Hospital of Zunyi Medical University, 149 Dalian Road, Zunyi 563000, Guizhou, People's Republic of China
Tel +86 1 821 217 0434
Email caosong4321@163.com

submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/JPR.S213128

depression, nausea and vomiting, and even addiction. Medicines that are highly effective and with few side effects are needed for PHN treatment.

Lidocaine is a classic and widely used medicine mainly used as an anesthetic for local anesthesia by injection. It is also used intravenously for its antiarrhythmic effect. Current studies reported that intravenous infusion of lidocaine showed analgesic effects and without serious adverse reaction in a variety of chronic pain,[13,14] including PHN.[15,16] Consecutive 3 mg/kg lidocaine infusion (once a week for 4 consecutive weeks) provided effective short-term pain relief in a cohort of neuropathic pain (PHN or CRPS).[17] In another cohort of peripheral nerve injury (PHN or nerve trauma), 5 mg/kg lidocaine infusion induced a significant decrease in ongoing pain for up to 6 hrs and decreased mechanical allodynia and hyperalgesia in these patients.[18] It is reported that lidocaine reduced the amount of opioids use and adverse reactions of the latter.[16,19] Intravenous infusion of 2–5 mg/kg lidocaine has no obvious side effects, and a few patients may report symptoms such as lethargy and dizziness. These reactions are usually mild and transient.[19,20] Patient with chronic pain (mainly neuropathic pain), received 500 mg lidocaine infusion in 30 mins, 41% of them got a long period of pain relief and 60% of them get pain relieved.[20] One study reported that 81 patients with various neuropathic pain syndromes received 3–25 intravenous infusions of lidocaine (5 mg/kg of body weight over 30 mins) and only five patients reported transient dizziness after the infusion, and no additional treatment was needed.[21] These results suggest that lidocaine intravenous infusion is one possible choice for the treatment of PHN.

However, when intravenous infusion of lidocaine is used for PHN treatment, the dose, frequency of infusion, efficacy and safety still require more clinical research to explore. This study was to evaluate the effects of daily intravenous lidocaine infusions on the efficacy of conventional PHN treatment. The short-term efficacy and safety of daily intravenous infusion of 4 mg/kg lidocaine are evaluated in PHN patients.

Methods

Ethics and patients

This study was conducted in accordance with the Declaration of Helsinki. The present study was approved by the Medical Ethics Committee of the Affiliated Hospital of Zunyi Medical University and registered at the Chinese Clinical Trial Registry (ChiCTR1800017762). All patients signed informed consent. The PHN diagnosis was based on the diagnostic criteria of the International Association for the Study of Pain, and only the PHN patients with lesions located in the thoracic or lumbar skin were included. The pain duration of PHN was >1 month, and patients of both genders were enrolled. Inclusion criteria were severe pain (numeric rating scales (NRS) score >5), age >18 years, no other acute or chronic pain, no history of mental illness and no serious cardiovascular and cerebrovascular diseases. Exclusion criteria were any allergy to the medicines listed in the "Treatment" section, any abnormalities reported in the electrocardiogram test, treatments listed in the following section cannot meet the analgesic needs, PHN patients chose other invasive treatments or treatments not listed in the following section, any serious adverse reactions caused by medicines listed in the following section during treatments, patients who request withdrawal from the trial and patients who cannot tell NRS score successfully. A total of 60 PHN patients were enrolled in the trial (see Table 1 for comparisons of clinical data). They were randomly divided into two groups by using the coin tossing method: 28 in Control group and 32 in Lido group.

Treatments

The conventional treatments for PHN patients in this study include the following:

1. Antiepileptic drug: gabapentin 0.3 g, oral administration, 3 times a day.
2. Opioid analgesics: oxycodone/acetaminophen 5 mg/325 mg, oral administration, 3 times a day.
3. Neurotrophic drugs: intravenous vitamin B compound (Vit B_6 30 mg, thiamine nitrate 2 mg, Vit B_{12} 2.5 μg), once a day.
4. Antianxiety drug and antidepressant: flupentixol/melitracen tablet (0.5 mg flupentixol: 10 mg melitracen, Lundbeck, Beijing, China), oral administration, once a day.
5. Paravertebral spinal nerve block: the first block (day 1) used 200 mg lidocaine +1 mg vitamin B_{12}+5 mg betamethasone sodium phosphate (diluted in 20 mL of saline), the 2nd and 3rd blocks (days 3 and 5) used 200 mg lidocaine +1 mg vitamin B_{12} (diluted in 20 mL saline) +20 mL 30 μg/mL ozone (injected after spinal nerve block). Three times for a complete course of treatment.
6. Thermotherapy: wIRA® irradiation thermotherapy (Hydrosun Technology, Beijing, China) of the skin

Table 1 Comparisons of clinical data (mean ± SD)

Parameters	Control (n=28)	Lido (n=32)	Difference
Age (years)	61.5±6.3	60.9±6.2	n.s.
Sex (male/female)	12/16	15/17	n.s.
Pain duration (months)	1.9±0.6	2.1±0.7	n.s.
NRS score	6.7±1.4	6.9±1.2	n.s.
HADS score			
HADS-A	12.3±3.9	12.5±3.5	n.s.
HADS-D	11.3±3.3	10.9±3.1	n.s.

Abbreviations: NRS, numeric rating scales; HADS, Hospital Anxiety and Depression Scale; HADS-A, Hospital Anxiety and Depression Scale (anxiety part); HADS-D, Hospital Anxiety and Depression Scale (depression part); n.s., not significant.

with PHN pain, once a day, continuous 5 days for a complete course of treatment.

Patients in the Control group received conventional treatments. In addition, as a placebo control to the Lido group, 500 mL of saline was intravenously infused every morning during hospitalization (infused in ~1 hr). For patients of the Lido group, in addition to the conventional treatment regimen, 4 mg/kg of lidocaine injection (Southwest Pharmaceutical, Chongqing, China) was mixed with 500 mL saline and infused in ~1 hr at the same time in the morning during hospitalization. If the aforementioned treatments are unable to control the pain sufficiently, tramadol sustained-release capsule (to control persistent pain) or tramadol injection (to control breakthrough pain) were given based on clinical evaluation. Patients were discharged when the pain was relieved (NRS score ≤2).

Lidocaine infusion procedures

The intravenous infusion of lidocaine is conducted in an operating room with rescue facilities and first-aid medicines. Patients' vital signs such as heart rate, blood pressure, electrocardiogram and finger pulse oximetry were monitored. Lidocaine (4 mg/kg) was dissolved in 500 mL saline and infused at a rate of 8–10 drops per minute. Infusions were finished in ~1 hr. Patients were accompanied by doctors and nurses for 30 mins after infusion to ensure safety before returning to their sickbed.

Pain intensity and breakthrough pain evaluation

Pain intensity was assessed using NRS. PHN patients reported pain intensity (including overall pain intensity and breakthrough pain intensity) at the time of admission, before and immediately after infusion of lidocaine (Lido group) or saline (Control group), later after infusion and before discharge. The patients also reported the times of breakthrough pain in the last 24 hrs each day.

Anxiety and depression assessment

Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depression at the time of admission and discharge. The HADS questionnaire consists of two parts, one for anxiety status evaluation and the other for depression evaluation.[22]

Tramadol consumption

If pain is not controlled sufficiently, intramuscular injections of tramadol (mainly used to control breakthrough pain) or tramadol capsules (mainly used to control persistent pain) were given to control pain. The average amount of tramadol used by patients in each group was calculated.

Average hospital stay

Hospital stay was counted from the day of admission to the day of discharge, but the day of discharge is not included in the total number of hospital stay. The average hospital stay for each patient of two groups was calculated, respectively.

Adverse complication observation

The lidocaine infusion-related adverse complications (allergies, chest tightness, dizziness, lethargy, dizziness, palpitations, etc.) were intensively observed and recorded during the lidocaine infusion procedure.

Statistics

Statistical analysis was performed using Prism (v.7.0, GraphPad Software, San Diego, USA). Data were expressed as mean ± SD. The gender composition of the two groups was compared by chi-square test. Comparisons between two groups were performed by independent t-tests. Paired t-tests were used for comparisons in the same cohort of patients

before and after infusion. Statistically, differences of different time points between the Control and Lido group were estimated by the repeated measures two-way analysis of variance. Because data of tramadol consumption did not show normal distribution and variances were not equal between groups, statistical analyses consisted of Mann–Whitney test. $P<0.05$ was considered statistically significant in this study.

Results

Patients and comparisons of clinical data

A total of 60 PHN patients, 28 in Control group and 32 in the Lido group, were enrolled in the study. No difference was found in age, gender, pain duration, pain intensity (NRS score), anxiety and depression status (HADS score, HADS-A for anxiety evaluation, HADS-D for depression) between groups (Table 1). All of the 60 patients completed the trial.

Safety and side effect observation of lidocaine intravenous infusion

All 32 patients in the Lido group received five times or more lidocaine infusions. During and 30 mins after infusions, complains such as somnolence (25% of patients), dry mouth (18.8%), peripheral numbness (9.4%) and so on were recorded (Table 2). The physician assessed the patients' vital signs, which were stable, and the ECG and other monitoring indicators were normal; therefore, the infusions were completed in ~1 hr according to the original plan. All of these adverse effects were not severe.

PHN pain intensity decreased after each lidocaine infusion

There were eight people in the Lido group who were discharged from the hospital on the 6th day; therefore, only 5-day data about the effect of lidocaine infusion on pain scores were analyzed. Patients were infused with 4 mg/kg lidocaine (for Lido patients, dissolved in 500 mL saline) or 500 mL saline (for Control patients) at the same time every morning, and pain was assessed before and after ~1 hr infusion. Data showed that intravenous infusion of lidocaine significantly reduced PHN pain immediately after infusion. In the Control group, although some patients reported pain intensity decreased after the infusion, no significant difference ($P>0.05$) was found compared with NRS scores before infusions (Figure 1).

Intravenous infusion of lidocaine reduced pain intensity and breakthrough pain frequency in PHN patients

The effects of intravenous lidocaine infusion on pain intensity and total number of breakthrough pain in the last 24 hrs during the 5-days hospital stay were evaluated. Patients received 4 mg/kg lidocaine or 500 mL saline each morning. To evaluate the overall analgesic effect of lidocaine, pain intensity was assessed in the afternoon. The NRS scores and breakthrough pain frequency decreased gradually during the hospitalization. In addition, at the same time points, NRS pain scores (Figure 2A) and the numbers of breakthrough pain (Figure 2B) during the last 24 hrs were lower in the lidocaine group from the first day of hospitalization.

Anxiety and depression scores not affected by intravenous infusion of lidocaine

At the time of admission and on the day of discharge, HADS was used to assess the anxiety and depression of patients. Both groups showed lower anxiety (Figure 3A) and depression (Figure 3B) scores at the time of discharge compared with that of the admission day, but no difference was found between the two groups neither at the time of admission nor on the day of discharge.

Lidocaine intravenous infusion reduced tramadol consumption and hospital stay

The amount of tramadol use and the average hospital stay were calculated for Control and Lido groups after PHN

Table 2 Adverse events reported by PHN patients who received lidocaine infusion (n=32)

Adverse events	Number of times	Number of patients (%)
Somnolence	25	8 (25.0%)
Dry mouth	12	6 (18.8%)
Peripheral numbness	8	3 (9.4%)
Dizziness	6	2 (6.3%)
Tinnitus	4	1 (3.1%)
Chest tightness	1	1 (3.1%)

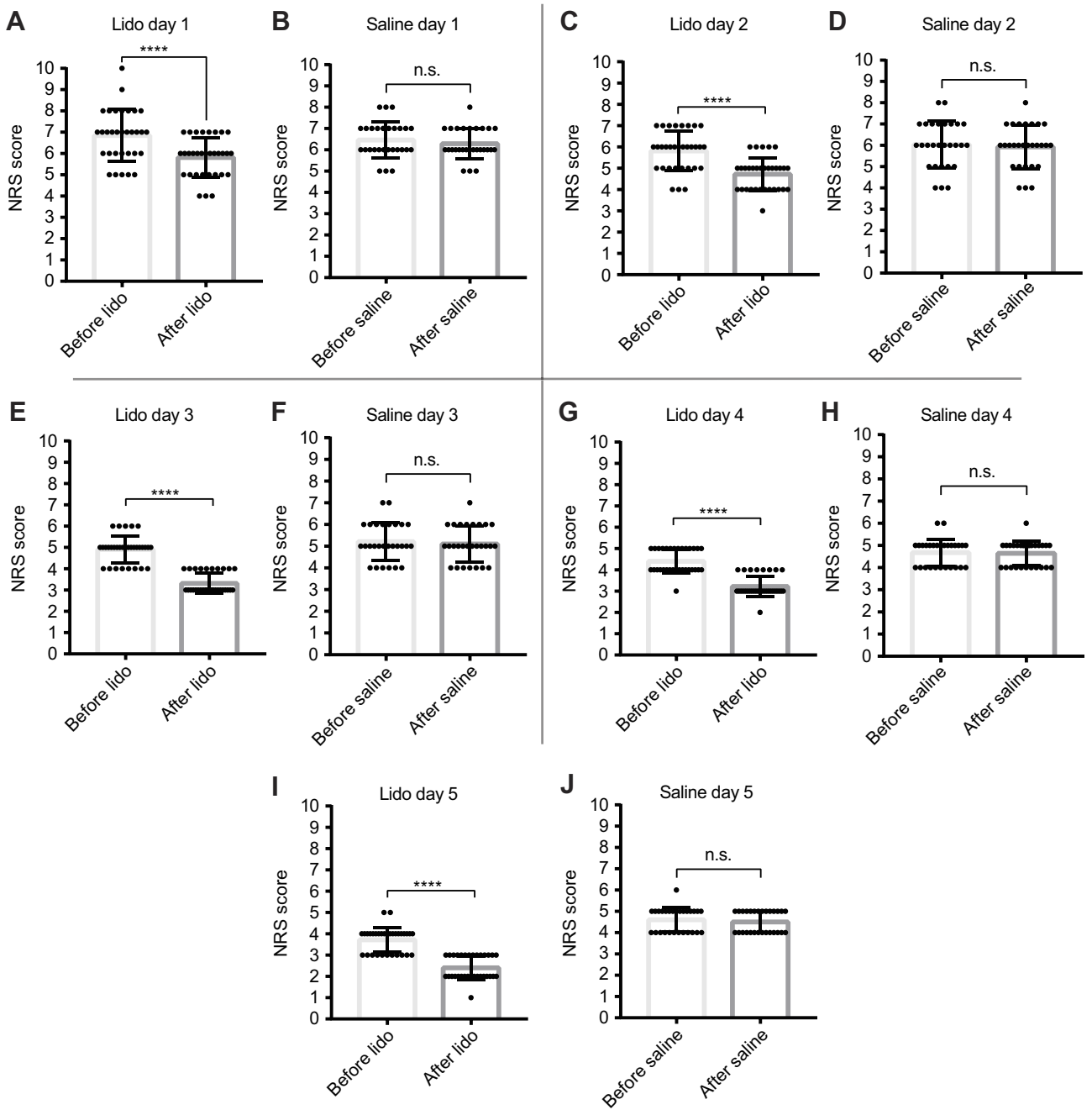

Figure 1 PHN pain intensity decreased after each lidocaine infusion during 5 days of hospitalization. Patients in Lido group were infused with 4 mg/kg lidocaine (dissolved in 500 mL saline) and patients in Control group received 500 mL saline at the same time every morning during hospitalization. Pain was assessed before and immediately after infusion. Intravenous infusion of lidocaine significantly decreased PHN pain intensity after infusion (**A, C, E, G, I**). In the Control group, pain scores of a few patients decreased after the infusion, but no significant difference ($P>0.05$) was found compared with NRS scores before infusions (**B, D, F, H, J**). Data are expressed as mean ± SD, n=28 in Control group and n=32 in Lido group. Statistical analyses consisted of paired t-tests. ****$P<0.0001$.

Abbreviations: n.s., not significant; PHN, postherpetic neuralgia; Lido, lidocaine; NRS, numeric rating scale.

patients were discharged from the hospital. In the Control group, 0.35±0.43 g of tramadol was used per patient, while in Lido group, tramadol consumption was 0.16±0.29 g per patient, which was significantly less than that of Control group (Figure 4A). The average hospital stay for patients of the Control group was 8.8±0.7 days, and it was 6.8±0.6 days for the Lido group, which was significantly shorter compared with that of the Control group (Figure 4B).

Discussion

In this study, we comprehensively observed the short-term therapeutic effects of intravenously infused lidocaine in

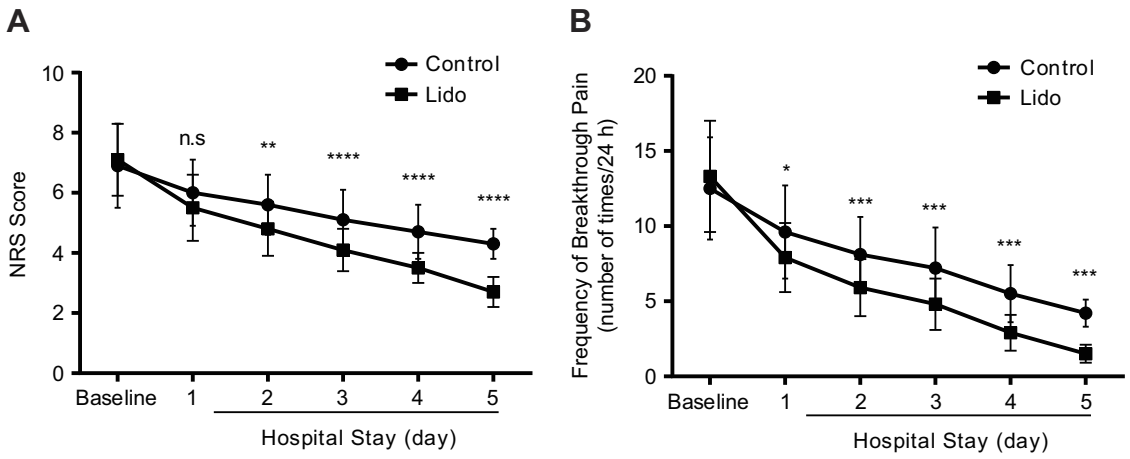

Figure 2 Intravenous infusion of lidocaine reduced pain intensity and frequency of breakthrough pain in PHN patients. The effects of intravenous lidocaine infusion on pain intensity and total number of breakthrough pain in the last 24 hrs during the 5-day hospital stay were evaluated. The NRS scores (**A**) and breakthrough pain frequency (**B**) decreased gradually during the hospitalization. In addition, at the same time points, pain intensity (**A**) and the frequency of breakthrough pain (**B**) during the last 24 hrs were significantly decreased in the lidocaine group from the first day of hospitalization. Data are expressed as mean ± SD, n=28 for Control group and n=32 for Lido group. Statistical analyses consisted of repeated measures two-way ANOVA. **P*<0.05, ***P*<0.01, ****P*<0.001, *****P*<0.0001.
Abbreviations: n.s., not significant; PHN, postherpetic neuralgia; Lido, lidocaine.

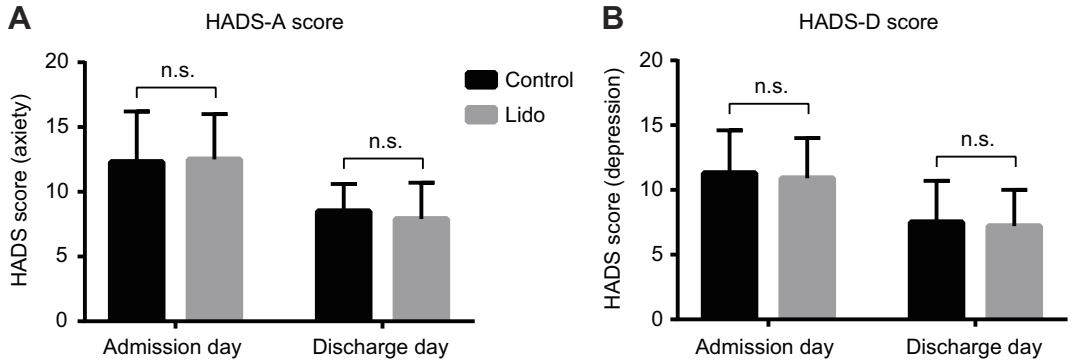

Figure 3 Anxiety and depression scores of HADS were not affected by intravenous infusion of lidocaine. At the time of admission and on the day of discharge, HADS was used to evaluate the anxiety and depression level of PHN patients. The HADS questionnaire consists of two parts, one for anxiety (HADS-A) status evaluation and the other for depression (HADS-D) evaluation.Both groups showed lower anxiety (**A**) and depression (**B**) scores at the time of discharge compared with that of the admission day, but no difference was found between the two groups neither at the time of admission nor on the day of discharge. Data are expressed as mean ± SD, n=28 for Control group and n=32 for Lido group. Statistical analyses consisted of independent t-tests.
Abbreviations: n.s., not significant; HADS, Hospital Anxiety and Depression Scale; PHN, postherpetic neuralgia; Lido, lidocaine.

patients with moderate-to-severe PHN pain. Both the immediate analgesia effect at the completion of infusion and therapeutic effect during hospitalization were evaluated. Intravenous infusion of lidocaine not only enhanced the efficacy of patients with PHN during hospitalization but also reduced the consumption of analgesics and shortened the hospital stay.

A higher frequency of lidocaine infusion was used in this study compared with that reported in patients with chronic pain (once a week[17] or once every 2 days[23]). We strictly set the exclusion criteria and closely observed the changes in vital signs of the patients and infused 4 mg/kg of lidocaine once a day. It is gratifying that no serious side effects were found. Iacob et al infused lidocaine in a fast and massive (1 g/hr in 30 mins, infusion rate of 16.67 mg/mins) way in 233 patients to tailor the tolerance and the dose of intravenous lidocaine infusion for an individual patient with chronic pain (mainly neuropathic pain). This challenge dose determination experiment was continued until complete pain relief, report of side effects or completion of infusion. Of the 233 patients receiving their first lidocaine infusion, 53% reported no side effect and 46% reported mild side effects.[20] Another group used 5 mg/kg lidocaine (infusion finished over 60 min) to test its effect in 20 patients with trigeminal neuralgia. Lidocaine did not change systolic BP, diastolic BP, HR and oxygen saturation, but 32.5% of cases reported side effects such as somnolence or dry mouth although all of these side effects were reported as mild.[23]

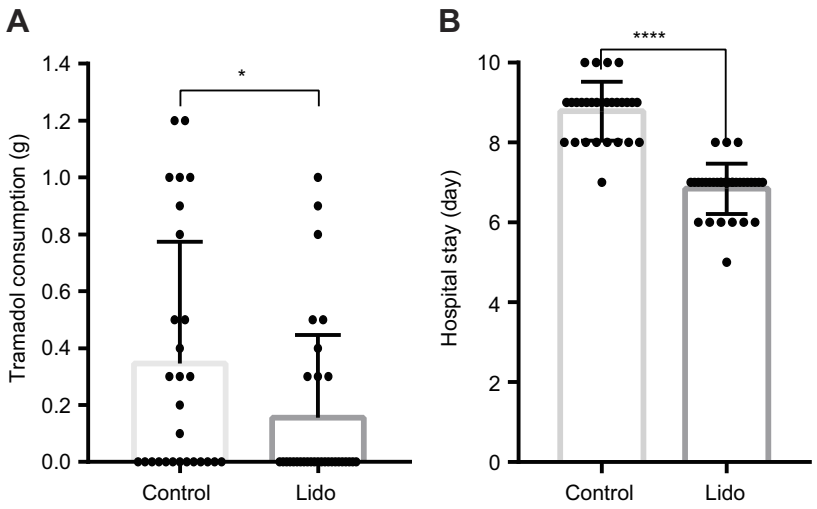

Figure 4 Lidocaine intravenous infusion reduced tramadol consumption and hospital stay. Average tramadol consumption (**A**) and hospital stay (**B**) were calculated for Control and Lido groups when PHN patients were discharged from the hospital. (**A**) In the Control group, 0.35±0.43 g of tramadol was used per patient, while tramadol consumption was 0.16±0.29 g per patient in Lido group, which was significantly shortened compared with that of the Control group. Data did not show normal distribution, and variances were not equal between groups, and statistical analyses consisted of Mann–Whitney test. *P<0.05. (**B**) The average hospital stay for patients of the Control group was 8.8±0.7 days, and it was 6.8±0.6 days for the Lido group, which was significantly lower than that of the Control group. Data are expressed as mean ± SD, n=28 for Control group and n=32 for Lido group. Statistical analyses consisted of independent t-tests. ****P<0.0001.

We speculate that the difference in the ratio of side effects in different studies may be related to patients' physical condition or ethnicity. Taken together, lidocaine intravenous infusion was safe for PHN patients.

Previous studies reported that 3–5 mg/kg lidocaine infusion was used to treat chronic pain.[17,20] Referring to these studies, we used a dose of 4 mg/kg and infused daily. No serious adverse reactions happened in the 60 PHN patients. However, we believe that clinical trial designers such as pain doctors need to be cautious when using intravenous lidocaine infusion therapy. Firstly, lidocaine itself can cause arrhythmia,[24] so it is best to assess whether patients exist arrhythmia or not. Secondly, the infusion speed should be slow, because lidocaine toxicity is dosage-dependent and related to its plasma concentration.[25,26] Thirdly, attention should be paid to the effects of drug accumulation and combined use of medicines on the function of liver and kidney. Other treatments may include lidocaine usage and the total dose need recalculation. In addition, it is necessary to evaluate the liver and kidney function of patients when necessary.

Current PHN treatment guidelines suggest beginning treatment with either alpha-2 delta ligands, tricyclic antidepressants, tramadol or opioids.[27,28] Besides these medicines, nerve block, pulse radiofrequency, physical therapy, etc., are routine treatments for PHN.[29] However, even with the combined use of these strategies, the therapeutic effects are usually poor. Our results show that intravenous infusion of lidocaine significantly enhanced the analgesic efficacy of traditional treatment, the procedure is simple, easy, economical and has no serious side effect. Therefore, it can be considered for clinical use. Recent researches suggest that intravenous infusion of lidocaine has a therapeutic effect in cohorts of patients with neuropathic pain, including PHN.[15,16] In addition, it is reported that lidocaine reduced the amount of use and adverse reactions of opioids.[16,19]

We thought about the possible mechanism by which lidocaine infusion relieves PHN pain in this study. The pain relief at the completion of the infusion may be related to lidocaine's short-term effect – sodium channel blockade,[30] which blocks the sodium channel of the afferent fibers in the pain site and inhibits the transmission of pain signals. While the long-term effect of lidocaine infusion may be related to its anti-inflammatory effects,[31,32] the release of inflammatory cytokines was considered to be one of the causes of neuropathic pain.[33,34] Daykin found that intravenous lidocaine may have an analgesic effect by inhibiting inflammation, and its anti-inflammatory effect can be attributed to the blockade of nerve conduction at the tissue with PHN, leading to attenuation of neurogenic inflammation and initiation of an intrinsic anti-inflammatory pathway. It affected the release of pro-inflammatory and anti-inflammatory cytokines, inhibited peripheral and central sensitization, which resulted in analgesic effects.[16] Some evidence indicated that lidocaine produced analgesic effect through its metabolite N-ethylglycine.[35,36] The therapeutic mechanism of lidocaine for chronic pain needs to be further revealed in blood

and tissue samples with molecular biology, cell biology and animal experiments.

The average HADS scores of the 60 PHN patients enrolled in this study were all more than 10, suggesting the existence of anxiety and depression.[22] Our previous functional magnetic resonance imaging studies suggested that PHN patients had abnormal activities in brain regions related to emotion, anxiety and depression, such as limbic system, temporal lobe and frontal lobe.[37,38] Therefore, we evaluated the effect of lidocaine infusion on anxiety and depression in PHN patients in this study. Results showed that both groups had lower anxiety and depression scores after PHN treatment, but no difference was found between Lido and Control patients on the day of discharge, indicating that lidocaine infusion did not alleviate anxiety and depression in PHN patients. The relief of depression and anxiety may have resulted from the antidepressant flupentixol and melitracen tablets taken by patients of both groups.

Limitation

In this study, only the short-term effects of lidocaine infusion were evaluated, while the long-term data were lacking. According to follow-up results of Kim et al, after 3 mg/kg lidocaine infusion (once a week for 4 consecutive weeks), pain reduction was not detectable at a 4-week follow-up in PHN and CRPS patients.[17] However, the long-term PHN pain relief by daily intravenous infusion of lidocaine (4 mg/kg for 5 consecutive days) will need further research.

Conclusion

Daily intravenous infusion of lidocaine (4 mg/kg for 5 days) enhanced the short-term outcomes of PHN treatment, reduced the amount of analgesic medicine and shortened the length of hospital stay with no serious adverse side effects.

Acknowledgments

The study was supported by the Excellent Young Talents Project (18zy-004) of Zunyi Medical University and a PhD Start-up Fund ((2017)21) of the Affiliated Hospital of Zunyi Medical University.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Schmader K. Postherpetic neuralgia in immunocompetent elderly people. *Vaccine*. 1998;16(18):1768–1770. doi:10.1016/s0264-410x(98)00137-6
2. Cohen JI. Herpes zoster. *N Engl J Med*. 2013;369(3):255–263. doi:10.1056/NEJMcp1302674
3. Keating GM. Shingles (Herpes Zoster) vaccine (Zostavax((R))): a review in the prevention of herpes zoster and postherpetic neuralgia. *Biodrugs*. 2016;30(3):243–254. doi:10.1007/s40259-016-0180-7
4. Makharita MY. Prevention of post-herpetic neuralgia from dream to reality: a ten-step model. *Pain Physician*. 2017;20(2):E209.
5. Pearce J. Post herpetic neuralgia. *N Z Med J*. 2005;76(4):310.
6. Friesen KJ, Falk J, Alessi-Severini S, Chateau D, Bugden S. Price of pain: population-based cohort burden of disease analysis of medication cost of herpes zoster and postherpetic neuralgia. *J Pain Res*. 2016;9:543. doi:10.2147/JPR.S107944
7. Pickering G, Gavazzi G, Gaillat J, Paccalin M, Bloch K, Bouhassira D. Is herpes zoster an additional complication in old age alongside comorbidity and multiple medications? Results of the post hoc analysis of the 12-month longitudinal prospective observational ARIZONA cohort study. *BMJ Open*. 2016;6(2):e009689. doi:10.1136/bmjopen-2015-009689
8. Sah DWY, Ossipo MH, Frank P. Neurotrophic factors as novel therapeutics for neuropathic pain. *Nat Rev Drug Discov*. 2003;2(6):460–472. doi:10.1038/nrd1107
9. Denkinger MD, Lukas A, Nikolaus T, Peter R, Franke S, Group AS. Multisite pain, pain frequency and pain severity are associated with depression in older adults: results from the ActiFE Ulm study. *Age Ageing*. 2014;43(4):510–514. doi:10.1093/ageing/afu013
10. Meacham K, Shepherd A. Neuropathic pain: central vs. peripheral mechanisms. *Curr Pain Headache Rep*. 2017;21(6):28.
11. Colloca L, Ludman T, Bouhassira D, et al. Neuropathic pain. *Nat Rev Dis Primers*. 2017;3:17002. doi:10.1038/nrdp.2017.2
12. Forstenpointner J, Rice ASC, Finnerup NB, Baron R. Up-date on clinical management of postherpetic neuralgia and mechanism-based treatment: new options in therapy. *J Infect Dis*. 2018;218(suppl_2):S120–S126. doi:10.1093/infdis/jiy381
13. Gabriel RA, Swisher MW, Sztain JF, Furnish TJ, Ilfeld BM, Said ET. State of the art opioid-sparing strategies for post-operative pain in adult surgical patients. *Expert Opin Pharmacother*. 2019;20(8):949–961. doi:10.1080/14656566.2019.1583743
14. Khan JS, Hodgson N, Choi S, et al. Perioperative pregabalin and intraoperative lidocaine infusion to reduce persistent neuropathic pain after breast cancer surgery: a multicenter, factorial, randomized, controlled pilot trial. *J Pain*. 2019. doi:10.1016/j.jpain.2019.02.010
15. Yousefshahi F, Predescu O, Francisco Asenjo J. The efficacy of systemic lidocaine in the management of chronic pain: a literature review. *Anesthesiol Pain Med*. 2017;7(3):e44732. doi:10.5812/aapm.
16. Daykin H. The efficacy and safety of intravenous lidocaine for analgesia in the older adult: a literature review. *Br J Pain*. 2017;11(1):23–31. doi:10.1177/2049463716676205
17. Kim YC, Castaneda AM, Lee CS, Jin HS, Park KS, Moon JY. Efficacy and safety of lidocaine infusion treatment for neuropathic pain: a randomized, double-blind, and placebo-controlled study. *Reg Anesth Pain Med*. 2018;43(4):415–424. doi:10.1097/AAP.0000000000000741
18. 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;62(2):218–225. doi:10.1212/01.wnl.0000103237.62009.77
19. Reeves DJ, Foster AE. Continuous intravenous lidocaine infusion for the management of pain uncontrolled by opioid medications. *J Pain Palliat Care Pharmacother*. 2017;31(3–4):198–203. doi:10.1080/15360288.2017.1313356
20. Iacob E, Hagn EE, Sindt J, et al. Tertiary care clinical experience with intravenous lidocaine infusions for the treatment of chronic pain. *Pain Med*. 2018;19(6):1245–1253. doi:10.1093/pm/pnx167

21. Przeklasa-Muszynska A, Kocot-Kepska M, Dobrogowski J, Wiatr M, Mika J. Intravenous lidocaine infusions in a multidirectional model of treatment of neuropathic pain patients. *Pharmacol Rep*. 2016;68 (5):1069–1075. doi:10.1016/j.pharep.2016.06.010
22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361–370.
23. Stavropoulou E, Argyra E, Zis P. The effect of intravenous lidocaine on trigeminal neuralgia: a randomized double blind placebo controlled trial. *ISRN Pain*. 2014;2014:853826.
24. Rahimi M, Elmi M, Hassanian-Moghaddam H, et al. Acute lidocaine toxicity; a case series. *Emergency (Tehran, Iran)*. 2018;6(1):e38.
25. Barash M, Reich KA, Rademaker D. Lidocaine-induced methemoglobinemia: a clinical reminder. *J Am Osteopath Assoc*. 2015;115 (2):94–98. doi:10.7556/jaoa.2015.020
26. Butterworth J, Strichartz GR. Molecular mechanisms of local anesthesia: a review. *Anesthesiology*. 1990;72(4):711–734. doi:10.1097/00000542-199004000-00022
27. Schutzer-Weissmann J, Farquhar-Smith P. Post-herpetic neuralgia - a review of current management and future directions. *Expert Opin Pharmacother*. 2017;18(16):1739–1750. doi:10.1080/14656566.2017.1392508
28. Hadley GR, Gayle JA, Ripoll J, et al. Post-herpetic neuralgia: a review. *Curr Pain Headache Rep*. 2016;20(3):17. doi:10.1007/s11916-016-0548-x
29. Theresa MS, Brett S, Brant JM. Postherpetic neuralgia: epidemiology, pathophysiology, and pain management pharmacology. *J Multidiscip Healthc*. 2016;9:447–454. doi:10.2147/JMDH.S106340
30. Doo AR, Shin YS, Yoo S, Park JK. Radiation-induced neuropathic pain successfully treated with systemic lidocaine administration. *J Pain Res*. 2018;11:545–548. doi:10.2147/JPR.S155070
31. van der Wal SE, van Den Heuvel SA, Radema SA, et al. The in vitro mechanisms and in vivo efficacy of intravenous lidocaine on the neuroinflammatory response in acute and chronic pain. *Eur J Pain*. 2016;20(5):655–674. doi:10.1002/ejp.794
32. Zhang Y, Tao GJ, Hu L, et al. Lidocaine alleviates morphine tolerance via AMPK-SOCS3-dependent neuroinflammation suppression in the spinal cord. *J Neuroinflammation*. 2017;14(1):211. doi:10.1186/s12974-017-0983-6
33. Sommer C, Leinders M, Uceyler N. Inflammation in the pathophysiology of neuropathic pain. *Pain*. 2018;159(3):595–602. doi:10.1097/j.pain.0000000000001122
34. Ji RR, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and central sensitization in chronic and widespread pain. *Anesthesiology*. 2018;129(2):343–366. doi:10.1097/ALN.0000000000002130
35. Werdehausen R, Kremer D, Brandenburger T, et al. Lidocaine metabolites inhibit glycine transporter 1: a novel mechanism for the analgesic action of systemic lidocaine?. *Anesthesiology*. 2012;116 (1):147–158. doi:10.1097/ALN.0b013e31823cf233
36. Werdehausen R, Mittnacht S, Bee LA, et al. The lidocaine metabolite N-ethylglycine has antinociceptive effects in experimental inflammatory and neuropathic pain. *Pain*. 2015;156(9):1647–1659. doi:10.1097/j.pain.0000000000000206
37. Cao S, Song G, Zhang Y, et al. Abnormal local brain activity beyond the pain matrix in postherpetic neuralgia patients: a resting-state functional MRI study. *Pain Physician*. 2017;20(2):E303.
38. Cao S, Li Y, Deng W, et al. Local brain activity differences between herpes zoster and postherpetic neuralgia patients: a resting-state functional MRI study. *Pain Physician*. 2017;20(5):E687.