

Intravenous Lidocaine for Refractory Chronic Orofacial Pain

Two case reports and a literature review

Abdulaziz Almahrezi,¹ Louise Lamb,² Mark A Ware,² Yoram Shir,² *Ibrahim Al-Zakwani³

الليدوكين الوريدي لعلاج الألم الفموي الوجهي المزمن والمستعصي تقرير حالتين ومراجعة للأدبيات

عبد العزيز المحرزي، لويز لامب، مارك.أ. وير، يورام شير، إبراهيم الزكواني

الملخص: يستعرض التقرير نتائج علاج مريضين بالغين يعانيان من آلام فموية وجهية مستعصية عن طريق حقن الليدوكين الوريدي في مركز علاج الألم في مستشفى مونتريال العام. حقن الليدوكين المتكررة (1 مليجرام لكل كيلو جرام كدفعة واحدة ثم 4 مليجرام لكل كيلو جرام كحقنة على مدار ساعة واحدة) أدت إلى تخفيف الألم بدرجة مقبولة لكلا المريضين. ولم يعاني أي منهما من أي آثار جانبية. الليدوكين الوريدي ربما يكون مفيداً في علاج الآلام الفموية الوجهية المستعصية. هناك حاجة لمزيد من البحوث في هذا المجال.
مفتاح الكلمات: آلام الوجه، الليدوكين، العلاج، البشر، مراجعة، أدبيات، تقرير حالة، كندا.

ABSTRACT This report presents the results of treatment of two adults, at the Pain Center of Montreal General Hospital, Canada, with intravenous lidocaine for intractable orofacial pain. Repeated lidocaine infusions (1mg/kg in a bolus, followed by 4mg/kg infused over 1 hour) resulted in satisfactory pain relief in both patients, and the drug was well tolerated. Intravenous lidocaine therapy may be considered for intractable orofacial pain; further research is warranted.

Keywords: Facial pain; Lidocaine; Therapeutics; Humans; Review; Literature; Case reports; Canada

CHRONIC OROFACIAL PAIN INCLUDES A group of disorders with diverse etiologies affecting approximately 10 % of the adult population and 50 % of the elderly¹ of whom at least 50% seek medical treatment.² Diagnosis is difficult due to lack of a clear diagnostic classification³ and routine treatment modalities are often not effective.⁴ Surgery may be considered in selected cases; however, current international guidelines recommend multi-modal approaches for the management of orofacial pain. These include pharmacological, nerve blocks, physiotherapy and psychological therapies.^{5,6}

Intravenous lidocaine has been used in a variety of neuropathic pain syndromes such as diabetic neuropathy⁷ and post herpetic neuralgia.⁸ To date, few published reports exist on the therapeutic role

for intravenous lidocaine in chronic orofacial pain.⁹ Here we describe two patients, who presented at the Pain Center, Montreal General Hospital, Canada with features of a mixed nociceptive-neuropathic pain syndrome, but with a primarily nociceptive etiology. They both experienced long-term pain relief after repeated lidocaine infusions.

CASE 1

This 46-year old female presented with a long history of pain in the area of both temporomandibular joints (TMJ). The pain was constant and sharp in nature and woke the patient up to 2-3 times per night. The average pain was 8 out of 10 on a visual analogue scale (VAS), a measure of pain intensity expressed on a zero to ten score. In addition, the patient described severe

¹Department of Family Medicine and Public Health, College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman; ²McGill University Health Centre, Pain Centre, Montreal General Hospital, Montreal, Quebec, Canada; ³Department of Pharmacy, Sultan Qaboos University Hospital, Muscat, Oman

*To whom correspondence should be addressed. Email: ial_zakwani@yahoo.com

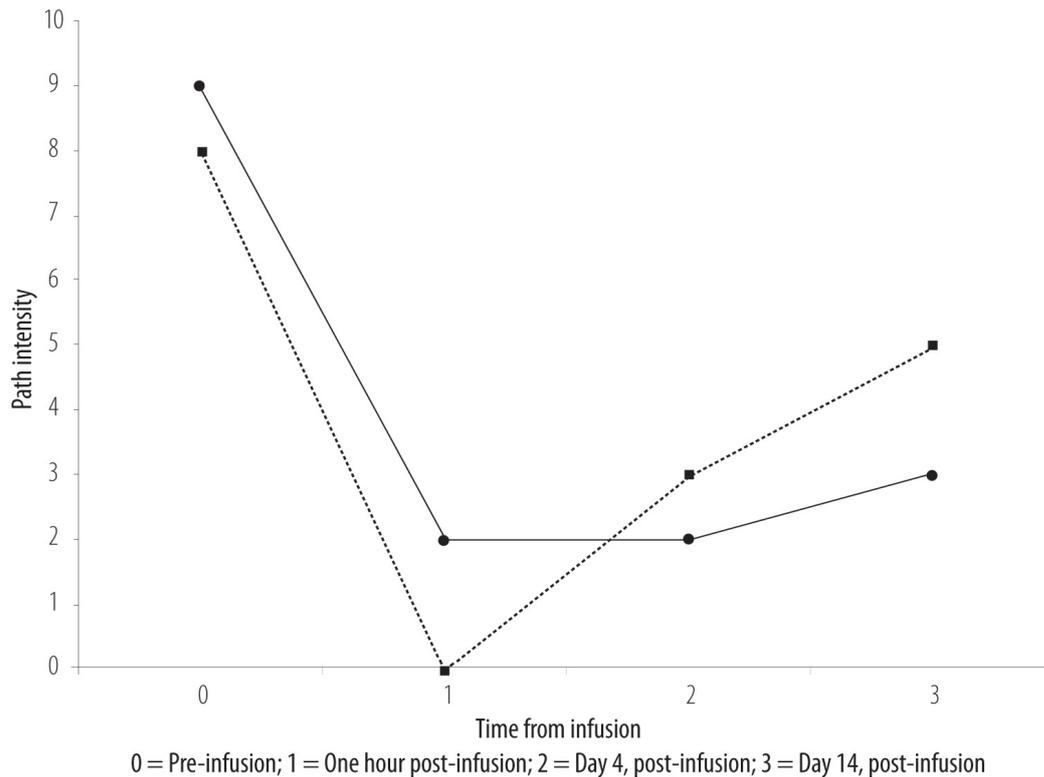


Figure 1: (Patient 1) Pain intensity scores recorded over two weeks following the first intravenous lidocaine infusion (0=no pain; 10=the most intense pain sensation imaginable).

attacks of intermittent ‘pulling-like’ pain, lasting for 30 to 60 minutes. The pain was provoked by chewing solid foods and exposure to humid weather. Mild pain relief was obtained with local ice packs and rest. She had undertaken five surgical procedures on both TMJs, including a prosthesis on the right and an osteotomy on the left.

Apart from a small area of dysaesthesia in the distribution of the mandibular division of the right trigeminal nerve, the rest of the neurological examination yielded no pathologies. In particular, the patient had no evidence of facial muscles atrophy, weakness or allodynia. However, tenderness bilaterally over the TMJs was noted. The patient was diagnosed with a mixed nociceptive-neuropathic pain syndrome and she was treated with the following medications sequentially: amitriptyline, 25mg/day, gabapentin, up to 900mg/day and sustained release oxycodone up to 20mg/day. Trials with each of these medications had to be abandoned prematurely due intolerable side effects experienced by the patient despite a very slow and careful titration. In view of the patient’s poor tolerance, further trials with other oral medications were not initiated. Nerve blocks were not offered. Further-

more, a trial of physiotherapy which included transcutaneous electrical nerve stimulation (TENS) did not yield any significant result.

As an alternative, the patient was given a trial of intravenous lidocaine, using 1 mg/kg in a bolus followed by an infusion of 4 mg/kg over 1 hour. Response to treatment was recorded using both the VAS and the Neuropathic Pain Scale (NPS)¹⁰: pre-infusion and at 1 hour, 4 days and 14 days post-infusion. During the infusion, and for 14 days thereafter, the patient’s pain decreased by more than 70% [Figure 1]. She reported no pain while chewing, and was able to have a solid meal for the first time in years. The patient received four lidocaine infusions during a period of four months with ongoing pain relief. Since beginning lidocaine treatment the patient has not been taking any other pain medications.

CASE 2

This 51 year old female presented with chronic pain over the right mandible. The patient had a history of a benign right mandibular cyst for which she had mandibular condyle and disc removal with graft reconstruction. The pain was refractory to botulinum toxin

injections, sympathetic ganglion blocks, and various oral medications including opioids and anti-convulsants. The patient underwent replacement of the right TMJ; however, despite significant improvement in function, the pain persisted. The pain was described as constant, deep, with numbness and tingling at the painful area and was triggered by eating and speaking.

On examination, she had difficulty opening her mouth and moving her chin from side to side. The patient had no facial weakness or asymmetry. Tactile and cold hyperalgaesia was detected over the lower part of the right face. The remainder of the neurological assessment including cranial nerves, motor, sensory, and cerebellar examination was normal. At the time of referral, she was taking amitriptyline 75mg/day, gabapentin 1800mg/day, lorazepam 1.5mg/day, and ketorolac 10 mg as necessary. Further titration of the doses of both amitriptyline and gabapentin had previously failed due to the development of intolerable side effects. Her average VAS daily pain score was 8 out of 10.

The patient was diagnosed with a mixed nociceptive-neuropathic chronic post-surgical pain. A trial of low dose methadone had to be stopped due to an allergic reaction. The patient was given a trial of intravenous lidocaine, 1 mg/kg in a bolus followed by an infusion of 4 mg/kg over 1 hour. One hour after the treatment the patient experienced total pain relief [Figure 1]. Pain levels increased during the ensuing two weeks, but remained low compared to the pre-infusion period. The patient subsequently received nine infusions in eight months, with ongoing pain relief and improved function, and has decreased her pain medications by 20-30%.

DISCUSSION

Lidocaine, an amide local anesthetic and an anti-arrhythmic agent, possesses analgesic properties when given systemically particularly in chronic neuropathic pain conditions,^{7, 8, 11, 12} cancer pain,¹³ fibromyalgia,¹⁴ and chronic daily headaches.¹⁵

Findings from experimental models of neuropathic pain suggest that lidocaine acts by suppression of abnormal ectopic discharges which are generated by damaged primary afferents or dorsal root ganglion neurons.¹⁶ Intravenous lidocaine was also shown to produce suppression of mechanical allodynia^{17, 18} and hyperalgaesia.¹⁶ The postulated mechanism of action

was thought to be peripheral in origin; however, this view was later challenged with several lines of evidence suggesting that lidocaine may also have central effects. Some of these observations include: suppression of polysynaptic C-fibre evoked flexor responses without evidence of conduction block at the periphery;¹⁹ suppression of the activity of dorsal horn neurons evoked by ionophoretically administered glutamate;²⁰ and selective inhibition of a nociceptive response in the isolated rat spinal cord.²¹ Clinical studies^{23, 24} and human experimental models^{25, 26} have reached similar conclusions as to the action of intravenous lidocaine on mechanical allodynia and hyperalgaesia. In one study on healthy volunteers using the heat/capsaicin sensitisation model, intravenous lidocaine (5 mg/kg) was shown to have a selective effect on secondary hyperalgaesia.²⁵

Several well-designed studies have documented the effectiveness of intravenous lidocaine. A randomised double-blind cross-over study showed that intravenous lidocaine (5mg/kg over 30 minutes), but not saline, reduced symptoms of pain, dysaesthesia, paraesthesia and nightly pain exacerbation as well as sleep disturbance in patients with chronic painful diabetic neuropathy for a period of 3-21 days.⁷ According to VAS, 11 out of 15 patients had a significant reduction (a reduction of greater than 15 millimetres on the VAS) in pain for a period of 3 days and no reported side effects.⁷ Another similarly designed study investigated the effect of two different doses (1 mg/kg and 5 mg/kg over 2 hours) of intravenous lidocaine on 24 patients of postherpetic neuralgia.¹¹ The investigators reported a significant reduction in VAS for evoked pain and a decline in the area of allodynia for up to 120 minutes following treatment with intravenous lidocaine.¹¹ Circumoral paraesthesia was the only side effect reported by patients who received the higher dose.¹¹ In a similar study investigating the effects of intravenous lidocaine (5 mg/kg over 30 minutes) on neuropathic central pain, a significant reduction (VAS score decreased by 50% or more) in spontaneous pain was reported.¹² This response was achieved by 10 out of 16 patients.¹² The period of observation in this study was for 45 minutes after the infusion. Investigators, using quantitative sensory testing, also reported a reduction in the intensity of mechanical allodynia and hyperalgaesia.¹² Side effects were reported as moderate and consisted mainly of lightheadedness, somnolence, nausea and dysarthria.¹² Sorenson et al studied

11 fibromyalgia patients who were randomised to lidocaine (5 mg/kg over 30 minutes) and saline in a double-blind and crossed-over design trial.¹⁴ Four patients were reported as responders (a reduction of 16 millimetres or greater on the VAS).¹⁴ Three of the responders had a reduction in pain for 4-7 days. Side effects were mild and included nausea, perioral numbness, drowsiness, dysarthria and tremor.¹⁴ In another study of postamputation pain, intravenous lidocaine (1 mg/kg bolus + 4 mg/kg over 40 minutes), but not the placebo (diphenhydramine) decreased stump pain until 30 minutes after the infusion.²⁶ No side effects were reported.

Both of our patients had reported nausea and light-headedness during the period of the infusion. This is consistent with previously mentioned studies which documented only mild and transient adverse effects; however, serious side effects such as arrhythmias and pulmonary edema can occur with high doses.²⁷ Close monitoring of the patient while receiving the infusion is therefore recommended. This is usually performed by means of a continuous electrocardiogram (ECG) and a regular check-up of blood pressure and heart rate.

Besides side effects, other problems associated with the use of intravenous lidocaine include: invasiveness and the inconvenience of the intravenous route. Possible alternatives to intravenous lidocaine are transdermal lidocaine and oral congeners such as mexilitine. A lidocaine patch has been shown to be effective in a randomised controlled trial in postherpetic neuralgia;²⁸ however, patients may find it inconvenient to apply a patch on the face. Furthermore, it is not known if a good response to intravenous lidocaine would predict a similar response to transdermal lidocaine since the concentration of plasma lidocaine would be much lower with local administration. Mexilitine has been suggested as an alternative particularly in patients who respond negatively to intravenous lidocaine;²⁹ however, the use of this drug is associated with frequent side effects which limit its usefulness.²³

In randomised controlled trials of chronic pain, the doses of intravenous lidocaine used ranged between 1 to 5 mg/kg. However, we elected to use a total dose of 5 mg/kg since this dose seems to be the best documented effective dose according to a systematic review of these trials.³⁰

The significance of our case reports is twofold: first, they provide the first evidence of the usefulness

of intravenous lidocaine as a therapeutic option in the management of chronic orofacial pain. Second, these reports raise the likelihood that intravenous lidocaine is not only effective in pure neuropathic pain syndromes, as the current literature suggests, but may also be effective in mixed nociceptive and neuropathic pain conditions that are primarily nociceptive in origin. The observations that lidocaine is effective in non-neuropathic pain conditions such as burns³¹ and fibromyalgia,¹⁴ together with the variable effect of lidocaine in peripheral or central neuropathic pain conditions³² and its effect beyond the pharmacological half-life, are all supportive of this latter conclusion.

CONCLUSION

In summary, based on this experience, intravenous lidocaine was a powerful and successful treatment option after several insufficient therapeutic attempts that included oral pharmacotherapy, nerve blocks and surgery. A trial of intravenous lidocaine should be considered much earlier, even if a multimodal management approach is used. Moreover, intravenous lidocaine should also be tried in pain syndromes of nociceptive origin rather than reserving it only for patients with pure neuropathic pain conditions. However, further research is needed to determine the exact role of intravenous lidocaine in the treatment of orofacial pain.

REFERENCES

1. Shinal RM, Fillingim RB. Overview of orofacial pain: epidemiology and gender differences in orofacial pain. *Dent Clin North Am* 2007; 51:1-18.
2. Riley JL 3rd, Gilbert GH, Heft MW. Health care utilization by older adults in response to painful orofacial symptoms. *Pain* 1999; 81:67-75.
3. Sarlani E, Balciunas BA, Grace EG. Orofacial pain - Part I: Assessment and management of musculoskeletal and neuropathic causes. *AACN Clin Issues* 2005; 16:333-346.
4. Wirz S, Wartenberg HC, Nadstawek J. Pain management procedures used by dental and maxillofacial surgeons: an investigation with special regard to odontology. *Head Face Med* 2005; 1:14.
5. Türp JC, Hugger A, Nilges P, Hugger S, Siegert J, Busche E et al. Recommendations for the standardized evaluation and classification of painful temporomandibular disorders: an update. *Schmerz* 2006; 20:481-489.
6. Okeson JP. Orofacial Pain: Guidelines for Assessment, Diagnosis, and Management. 4th ed. Chicago: Quintessence Publishing, 1996.
7. Kastrup J, Angelo H, Petersen P, Dejgard A, Hilsted J.

- Treatment of chronic painful diabetic neuropathy with intravenous lidocaine infusion. *Br Med J* 1986; 292:173.
8. Rowbotham MC, Reisner-Keller LA, Fields HL. Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia. *Neurology* 1991; 41:1024-1028.
 9. Scrivani SJ, Chaudry A, Maciewicz RJ, Keith DA. Chronic neurogenic facial pain: lack of response to intravenous phentolamine. *J Orofac Pain* 1999; 13:89-96.
 10. Galer BS, Jensen MP. Development and preliminary validation of a pain measure specific to neuropathic pain: The neuropathic pain scale. *Neurology* 1997; 48:332-338.
 11. Baranowski, AP, De Courcey J, Bonello E. A trial of intravenous lidocaine on the pain and allodynia of postherpetic neuralgia. *J Pain Symptom Manage* 1999; 17:429-433.
 12. Attal N, Gaude V, Brasseur L, Dupuy M, Guirimand F, Parker F. Intravenous lidocaine in central pain: A double-blind, placebo-controlled, psychophysical study. *Neurology* 2000; 54:564-74.
 13. Brose WG, Cousins MJ. Subcutaneous lidocaine for treatment of neuropathic cancer pain. *Pain* 1991; 45:145-148.
 14. Sorensen J, Bengtsson A, Ahlner J, Henriksson KG, Ekselius L, Bengtsson M. Fibromyalgia - are there different mechanisms in the processing of pain? A double blind crossover comparison of analgesic drugs. *J Rheumatol* 1997; 24:1615-1621.
 15. Hand PJ, Stark RJ. Intravenous lignocaine infusions for severe chronic daily headache. *Med J Aust* 2000; 172:157-159.
 16. Abram SE, Yaksh TL. Systemic lidocaine blocks nerve injury-induced hyperalgesia and nociceptor-driven spinal sensitization in the rat. *Anesthesiology* 1994; 80:383-391.
 17. Abdi S, Lee DH, Chung JM. The anti-allodynic effects of amitriptyline, gabapentin, and lidocaine in a rat model of neuropathic pain. *Anesth Analg* 1998; 87:1360-1366.
 18. Chaplan SR, Bach FW, Shafer SL, Yaksh TL. Prolonged alleviation of tactile allodynia by intravenous lidocaine in neuropathic rats. *Anesthesiology* 1995; 83:775-785.
 19. Woolf CJ, Wiesenfeld-Hallin Z. The systemic administration of local anaesthetics produces a selective depression of C-afferent fibre evoked activity in the spinal cord. *Pain* 1985; 23:361-374.
 20. Biella G, Sotgiu ML. Central effects of systemic lidocaine mediated by glycine spinal receptors: an iontophoretic study in the rat spinal cord. *Brain Res* 1993; 603:201-206.
 21. Jaffe RA, Rowe MA. Subanesthetic concentrations of lidocaine selectively inhibit a nociceptive response in the isolated rat spinal cord. *Pain* 1995; 60:167-174.
 22. Wallace MS, Dyck JB, Rossi SS, Yaksh TL. Computer-controlled lidocaine infusion for the evaluation of neuropathic pain after peripheral nerve injury. *Pain* 1996; 66:69-77.
 23. 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; 62:218-225.
 24. Wallace MS, Laitin S, Licht D, Yaksh TL. Concentration-effect relations for intravenous lidocaine infusions in human volunteers: effects on acute sensory thresholds and capsaicin-evoked hyperpathia. *Anesthesiology* 1997; 86:1262-1272.
 25. Dirks J, Fabricius P, Petersen KL, Rowbotham MC, Dahl JB. The effect of systemic lidocaine on pain and secondary hyperalgesia associated with the heat/capsaicin sensitization model in healthy volunteers. *Anesth Analg* 2000; 91:967-972.
 26. Wu CL, Tella P, Staats PS, Vaslav R, Kazim DA, Wesselmann U et al. Analgesic effects of intravenous lidocaine and morphine on postamputation pain: a randomized double-blind, active placebo-controlled, crossover trial. *Anesthesiology* 2002; 96:841-8.
 27. Raphael JH, Southall JL, Treharne GJ, Kitas GD. Efficacy and adverse effects of intravenous lignocaine therapy in fibromyalgia syndrome. *BMC Musculoskelet Disord* 2002; 3:21.
 28. Galer BS, Rowbotham MC, Perander J, Friedman E. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain* 1999; 80:533-538.
 29. Galer BS, Harle J, Rowbotham MC. Response to intravenous lidocaine infusion predicts subsequent response to oral mexiletine: a prospective study. *J Pain Symptom Manage* 1996; 12:161-167.
 30. Kalso E, Tramer MR, McQuay HJ, Moore RA. Systemic local-anaesthetic-type drugs in chronic pain: a systematic review. *Eur J Pain* 1998; 2:3-14.
 31. Jonsson A, Cassuto J, Hanson B. Inhibition of burn pain by intravenous lignocaine infusion. *Lancet* 1991; 338:151-152.
 32. Galer BS, Miller KV and Rowbotham MC. Response to intravenous lidocaine infusion differs based on clinical diagnosis and site of nervous system injury. *Neurology* 1993; 43:1233-1235.