Continuous Dentoalveolar Neuropathic Pain Response to Repeated Intravenous Ketamine Infusions: A Case Report

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This article describes a case of continuous dentoalveolar neuropathic pain in which relief was obtained following repeated administration of intravenous infusions of a subanesthetic dose of ketamine. A 50-year-old female presented in 2006 with a 1-year history of constant sharp pain in the gingiva surrounding the maxillary left second premolar and second molar rated as 10/10 on a pain intensity scale. After multiple systemic medications failed to adequately manage the patient's pain, partial pain reduction was obtained (4/10) with daily use of methadone 50 mg in combination with application of a topical compound including lidocaine, amitriptyline, and carbamazepine to the affected area as needed. In July 2012, for reasons unrelated to the neuropathic pain condition, the patient underwent extraction of the maxillary right second premolar under intravenous sedation. Initially, a subanesthetic dose of ketamine was added to the sedation regimen for postoperative pain management; however, due to subsequent improvement of the dentoalveolar neuropathic pain, repeated intravenous infusions were recommended for further pain management. The patient's neuropathic pain condition was successfully managed by a total of five intravenous ketamine infusions repeated over a 4-year period of time. The patient's daily use of methadone was progressively reduced and finally discontinued. This case suggests a possible role for intravenous infusions of subanesthetic doses of ketamine as an adjuvant management option in patients suffering from intractable dentoalveolar continuous neuropathic pain conditions.
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Chronic neuropathic pain conditions remain a clinical challenge not only due to limited patient response to the currently available treatments,[1] but also because of the impact of suffering and disability on the patient's quality of life. These conditions also carry a significant economic burden for society.[2] Epidemiologic studies conducted in the general population have estimated that the prevalence of neuropathic pain varies between 6.9% and 10%.[3] The International Association for the Study of Pain defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system."[4] It can be classified as peripheral or central and can be categorized by its temporal features (ie, episodic or continuous).[5,6]

Continuous dentoalveolar neuropathic pain describes a painful neuropathy felt in the oral cavity. Traditionally, it has been described as atypical odontalgia or phantom toothache. In 2013, the International Headache Society (IHS) proposed the term painful traumatic trigeminal neuropathy (PTTN) to describe pain felt in the trigeminal distribution associated with sensory disturbances and related to a traumatic event.[7] However, as described in this case report, in many cases it is complicated to determine whether the neuropathic pain was experienced prior to the trauma or secondary to the dental treatment. In most cases, by the time patients are diagnosed with neuropathic pain, they have already received some type of dental treatment.[8]

In a systematic review performed by Nixdorf et al,[9] nonodontogenic toothache was estimated to occur in 3.4% of patients after endodontic procedures. In a mailed survey performed by Klasser et al,[10] an estimated 7% of patients were calculated to have continuous neuropathic pain after nonsurgical root canal treatment. Nevertheless, data regarding prevalence and incidence are still missing due in part to lack of consensus on the diagnostic criteria for continuous dentoalveolar neuropathic pain.

Despite the fact that the pathophysiology of this condition is not fully understood, it appears to present similar clinical characteristics to deafferentation pains secondary to nerve injury.[11] Neuropathic pain is not only characterized by spontaneous pain, but also by positive symptoms such as hyperalgesia and allodynia and can occasionally also present negative signs (ie, sensory deficits).[12] The clinical presence of hyperalgesia and allodynia suggests that a phenomenon of neuroplasticity of the nociceptive pathways is involved, leading to peripheral and central sensitization of pain-signaling neural structures.[13] This neural hyperexcitability involves the release of amino acids, primarily glutamate.[14] Proposed mechanisms of central sensitization include the activation of the N-methyl-D-aspartate glutamate receptor (NMDAR) on postsynaptic neural terminals at the spinal cord or at the caudal portion of the trigeminal brainstem nuclear complex in orofacial pain conditions.[14–16] Therefore, the use of drugs capable of reducing NMDAR activity has been proposed to treat neuropathic pain.

Among the NMDA antagonists available, ketamine (2-[2-chlorophenyl]-2-[methylammino]-cyclohexanone) was first synthesized and introduced in the 1960s in the United States as a safer general anesthetic alternative to phencyclidine (PCP).[17] Ketamine has proven antihyperalgesic effects due to the noncompetitive NMDAR antagonism.[18] Hence, in the last decades, ketamine has been largely studied as an adjuvant agent to control peri- and postoperative pain at subanesthetic levels.[19–26] At low doses, ketamine has also demonstrated antinociceptive effects through activation of the monoaminergic descending inhibitory system and opioid receptors[18] in addition to its antidepressant effect.[27,28] Furthermore, immunomodulatory effects have also been attributed recently to ketamine in inflammatory processes.[28,29]

Despite the evidence of the multiple mechanisms of action of ketamine and its potential role in pain, clinical research on ketamine in chronic pain conditions remains scarce.[17,30] This article describes a case of chronic continuous neuropathic pain located in the dentoalveolar region that was refractory to conventional pharmacotherapy but responded favorably to repeated infusions of subanesthetic doses of ketamine.

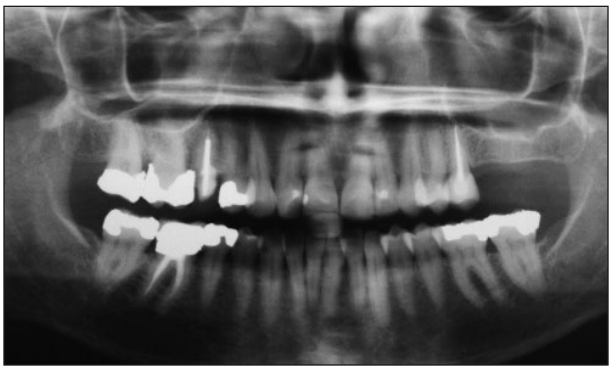

Fig 1 Panoramic radiograph taken in a follow-up appointment in 2006.

Case Report

A 50-year-old Caucasian female presented in 2006 to the Orofacial Pain Center of the University of Kentucky College of Dentistry with a 1-year history of constant sharp pain located in the gingiva surrounding the maxillary left second premolar and second molar. The patient rated the pain as having an intensity of 10/10 on a visual analog scale (VAS), and it was aggravated by talking and eating. She reported that the pain started in August 2005 in the upper left quadrant with no evident precipitating factor. The pain prompted a root canal treatment on the maxillary left first molar, which unfortunately exacerbated the patient's symptoms. The patient's dentist attempted to manage this persistent pain by performing a second root canal therapy on the maxillary left second premolar, then extracting the maxillary left second molar followed 3 days later by extraction of the maxillary left first molar. Neither of the latter treatments reduced the pain. During the following months, several medications, including carbamazepine, oxcarbazepine, and gabapentin, were tried, but the patient could not tolerate them due to side effects.

By the time of the patient's initial evaluation at the Orofacial Pain Center, her pain experience had dramatically changed her life, limiting and interfering with basic daily activities such as eating and sleeping, significantly reducing her quality of life, and leading to negative effects on mood. Suicidal ideations were reported, but without intent or plan to follow through. Clinical examination revealed allodynia upon palpation of the area of the extracted teeth. This allodynia was partially and temporarily alleviated by topical application of benzocaine 20%. A panoramic radiograph revealed no evidence of local pathology (Fig 1).

Over a 1-year period, multiple systemic medications failed to adequately manage the patient's pain, including by order of trial amitriptyline up to 60 mg;

baclofen up to 40 mg and then combined with tizanidine 2 mg at bedtime; pregabalin up to 300 mg in combination with baclofen 40 mg and hydrocodone 5 mg/acetaminophen 300 mg or tramadol 37.5 mg/acetaminophen 325 mg to breakthrough pain; topiramate up to 100 mg (discontinued due to side effects); and oxycodone 7.5 mg/acetaminophen 500 mg. Decreased transient pain relief was obtained (VAS: 6–8/10), but the pain would ultimately return.

In January 2007, after a neuropsychological assessment, a narcotic contract was obtained and the patient was started on a daily use of methadone, slowly titrated up to 50 mg, that decreased her pain intensity to an average of 4/10. Periodic electrocardiograms were ordered to monitor for potential cardiovascular side effects. A topical compound of 5% lidocaine, 2% amitriptyline, and 5% carbamazepine in orabase was introduced (instead of benzocaine 20%) to use as needed.

In July 2012, the patient underwent extraction of the maxillary left second premolar for reasons unrelated to the neuropathic pain. This procedure was performed under intravenous sedation using 100 µg of fentanyl. A subanesthetic dose of 20 mg of ketamine in combination with 7.5 mg of diazepam was added to this intravenous regimen for better management of postoperative pain and as a preemptive treatment for exacerbation of the patient's neuropathic pain. The procedure took 15 minutes and was well tolerated. The patient was encouraged to keep a pain diary to monitor postoperative pain.

Interestingly, during the 6 months following the dental procedure under intravenous sedation, the patient noted experiencing a total of only 9 days of pain on the gingiva surrounding the left maxillary second premolar and second molar, whereas prior to extraction the pain was constant. Consequently, she was able to reduce her daily methadone dose to 20 mg, and occasional pain flare-ups were well managed with short-duration use of tizanidine, alprazolam, and topical medication.

Six months later, a second intravenous sedation was performed specifically for management of the neuropathic pain, and the dosage of ketamine was increased to 50 mg in combination with 4 mg of midazolam and 50 µg fentanyl. The sedation took place without complications and was again followed by an extended period of reduction in overall pain.

At the 1-year follow-up appointment (ie, 1 year after the initial intravenous sedation), the patient reported infrequent pain episodes and dysesthesia in the affected area, which were well managed by topical medication. Daily methadone dose was continued at 20 mg per day and occasionally increased to 30 mg if needed. The patient reported a dramatic improvement in quality of life, and she was able to return to work.

In November 2013, the patient underwent another dental extraction by her dentist, and a third intravenous infusion that included 30 mg of ketamine, 7 mg of diazepam, and 100 µg fentanyl was administered. In the following year, the patient reported 1 to 7 days of pain per month that lasted for a few hours. She continued her 20 mg of methadone daily, with a low dose of alprazolam included as needed if pain increased.

In December 2014, intravenous infusion with no surgical intervention was repeated with 50 mg of ketamine, 4 mg of midazolam, and 50 µg fentanyl. In July 2016, after routine dental treatment, a flare-up in pain was reported and a fifth intravenous infusion was delivered. At 3 months, the patient reported that pain was successfully managed (0/10) with tramadol 50 mg twice a day, and the daily use of methadone was at last discontinued after 10 years. At the time of this writing, the patient continues to enjoy pain relief and an improved quality of life, managing her neuropathic condition with only tramadol 50 mg twice a day.

Discussion

Despite the wide variety of treatment options available for neuropathic pain conditions, the overall clinical success is usually modest and patients rarely achieve adequate pain relief.[1] A 7-year follow-up naturalistic study showed that two-thirds of patients diagnosed with persistent dentoalveolar pain were refractory to standard treatment and only a third improved, with low intensity of pain as a predictor for a good prognosis.[31] Hence, new management strategies should be explored.

The management options for neuropathic pain are divided according to the level of evidence and safety into first-line treatments (anticonvulsants and antidepressants), second-line treatments (topical medications [ie, lidocaine or capsaicin patches] and tramadol), and third-line treatments (botulinum toxin A and strong opioids).[1,32] Strong opioids, such as long-acting methadone, are not recommended as a first-line option due to potential abuse and other adverse effects, particularly at high doses in long-term use. In addition to its moderate effectiveness, opioid therapy is also frequently complicated by analgesic tolerance and an increased sensitization of NMDAR by the treatment. As demonstrated in a study in rats, the coadministration of ketamine with fentanyl prevented the delayed fentanyl-induced hyperalgesia and at the same time enhanced its earlier postoperative analgesic effect.[33]

In light of this evidence, in the present case, a subanesthetic dose of ketamine (30 mg) was initially added to the standard fentanyl protocol for tooth extraction under sedation per the patient's request to

prevent aggravation of the pre-existing chronic pain condition and management of postoperative pain.[20,34] Surprisingly, the patient not only reported no postoperative pain but also improvement of the neuropathic pain condition, which was successfully managed by 50% of what the methadone dose had been prior to the surgery. The improvement lasted for approximately 6 months before the pain started to progressively return to baseline. This dramatic and extended pain reduction allowed the patient to return to work, and her daily activities were no longer limited by her chronic pain condition.

The use of ketamine in pain management is not a novel idea.[35,36] Nowadays, there is a growing interest and a great deal of recent evidence for the uses of ketamine in pain medicine,[37–43] but the number of trials investigating the use of ketamine in chronic pain conditions is still limited.[44] Studies have proven the efficacy of ketamine in decreasing pain intensity in cancer-related neuropathic pain,[45] hence reducing the opioid consumption in cancer pain.[46,47] Several studies have been performed in different chronic conditions, such as complex regional pain syndrome (CRPS),[48–50] postherpetic neuralgia,[51] and chronic peripheral and central neuropathic conditions,[49,52,53] and have demonstrated that pain scores and dysesthesias were decreased in up to two-thirds of the patient population. More recently, Patil et al[54] demonstrated that ketamine infusions reduced VAS pain intensity in patients suffering from different chronic neuropathic pain conditions, including CRPS, refractory headaches, and back pain. Unexpectedly, this decrease in pain lasted up to 3 weeks. This intriguing observation that analgesia can persist after the ketamine infusions was also noted by Prommer in 2012.[30]

Quinlan[55] reported that 3 out of 11 patients suffering from different chronic pain conditions refractory to opioid treatment experienced a significant improvement of their pain intensity after a single intravenous infusion of ketamine along with complete cessation of their opioid intake 6 months later. Similar results were observed in the present case, where the patient experienced progressively prolonged pain-free periods (6 months after the first infusion, 10 months after the second infusion, 12 months after the third infusion, and 1.5 years after the last infusion) and was therefore able to reduce opioid intake.

Even though ketamine has been proven to be useful for pain management, it is feared mostly due to its psychomimetic side effects.[19] It is classified as a dissociative anesthetic, since it causes a dissociation between the thalamus and limbic system and produces feelings of detachment or dissociation from the environment and self. Side effects display a range of manifestations, including a "drug high," hallucinations, or fear/panic attacks, which are dose dependent, ranging from 300 to 500 mg. Other adverse effects that are also dose dependent include gastrointestinal effects such as nausea/vomiting, anorexia, and cardiovascular effects such as hypertension, tachycardia, and increased cardiac output. Thus, caution is warranted when treating patients who have cardiovascular disease.[56] However, at subanesthetic levels such as the ones utilized in the present case, the most common side effects involve the central nervous system (sedation, vertigo), and the cardiovascular and gastrointestinal side effects are infrequent.[30] In order to mitigate the potential psychotropic effects in awake or sedated patients, concomitant administration of a benzodiazepine[19,30] or haloperidol[30] is recommended. In the present case, in an effort to keep the patient comfortable, a benzodiazepeine (7 to 7.5 mg of diazepam or 4 mg midazolam) was added to the ketamine infusion, which could have also provided additional analgesia.[46,57,58]

The variety of dosing protocols and administration routes has also been discussed in the literature.[59,60] Subanesthetic doses (< 1 mg/kg) are effective for pain management with fewer side effects. It has been suggested to initially administer a test dose of 5 mg intravenously or 20 mg orally in combination with prophylactic benzodiazepine or haloperidol, which could be used as a predictor for treatment response.[30] If pain relief is obtained and side effects are well tolerated, the recommended intravenous infusion dose ranges between 0.1 mg/kg and 0.8 mg/kg, with a starting dose of 0.5 mg/kg. In the present case, the weight-based dosing bolus was calculated between 8 and 61 mg. The repeated subanesthetic doses of ketamine ranged between 20 and 50 mg, and the patient tolerated the procedures, reporting no side effects. Other administration routes of ketamine for analgesia described in the literature include transdermal patch, subcutaneous, intramuscular, oral, nasal, and rectal. However, the evidence for the most effective method of ketamine administration is still scarce.[35]

Regarding the orofacial pain literature, only a few studies have been published with a limited number of cases. In 1995, a pilot study with seven cases was published where ketamine given intravenously or intramuscularly was used for the management of chronic trigeminal neuropathic pain. Three of the seven cases described constant pain localized in the dentoalveolar area that responded to the ketamine treatment with a pain-free period lasting from 24 hours up to 2 to 3 days. The remaining four cases did not respond to the treatment with ketamine; however, two of these cases presented with paroxysmal pain, one was central poststroke pain, and the last was secondary to orthognathic surgery.[56]

Similar results were found in an open study performed in a subset of 43 patients suffering from continuous neuropathic orofacial pain. Ketamine was administered intramuscularly at 0.4 mg/kg as a test dose and 1 week later at 4 mg/kg orally. One-third of the sample obtained pain reduction after the use of ketamine that lasted for several hours, another third experienced transient pain relief (less than an hour), and the remaining patients did not experience any relief. Patients who responded positively to the intramuscular dose obtained the same repeated improvement with the oral formulation. Thus, it has been suggested that in some patients NMDAR activation plays a more important role in the maintenance of the neuropathic pain condition than others, influencing the response to ketamine.[61,62] Douglas et al[63] found differences in micro-RNA between responders and nonresponders that could predict which patients benefit from treatment with ketamine.

The use of intraoral topical ketamine has also been suggested in the literature. Direct application to the postextraction socket reduced postoperative pain after third molar extraction.[64] Topical ketamine (40 mg in 30 mL normal saline) applied to the oropharyngeal tissues for 30 seconds prior to endotracheal intubation diminished the incidence and severity of the postoperative throat pain after extubation.[65] In the present case report, a topical compound composed of 5% lidocaine, 2% amitriptyline, and 5% carbamazepine in orabase was introduced as a palliative approach. Moreover, the addition of ketamine to this topical compound could be considered, and, if needed, a neurostent could be fabricated to facilitate the application of the topical medication.[8]

In contrast to a single intravenous administration, five intravenous infusions of subanesthetic doses in the present case were administered over a 4-year period. Similar results have been published in another case report, where 21 intravenous infusions were given over a period of 4 months.[66]

Therefore, further research is needed to more fully develop specific treatment protocols for the use of ketamine as a viable adjunctive treatment for certain subsets of chronic orofacial pain sufferers in whom NMDRA hyperactivity may be playing a crucial role in pain maintenance.

Conclusions

This finding suggests that drugs capable of reducing the activity of NMDA receptors, such as ketamine, may lessen dentoalveolar continuous neuropathic pain conditions and could be used as a coadjuvant treatment in a subset of refractory patients.

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