Chronic Neurogenic Facial Pain: Lack of Response to Intravenous Phentolamine

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Aims: *Chronic neurogenic facial pain is commonly resistant to treatment and is often the source of significant patient morbidity. Adrenergic mechanisms are postulated to play a role in producing this type of pain, and adrenergic blocking agents are frequently used in clinical practice for pain control therapy. The analgesic effectiveness of an adrenergic blocking agent, intravenous phentolamine, was compared to saline and intravenous lidocaine in the present study using a single-blind protocol in patients with chronic neurogenic facial pain.* **Methods:** *Thirty patients were studied whose common clinical features included pain for more than 6 months, unilateral trigeminal distribution, constant dysesthesia, and no evidence of pathology or known etiology. Phentolamine (30 mg), lidocaine (100 mg), and saline were each infused over periods of 5 to 10 minutes. Pain ratings were assessed every 4 minutes throughout each study period using a 10-point pain intensity scale.* **Results:** *No patient reported subjective improvement of pain during or immediately following phentolamine or saline infusions alone. Sixteen of the 30 patients reported decreased pain following lidocaine infusion. In the majority of the patients, the duration of lidocaine analgesia was less than 30 minutes; however, some patients reported decreased pain for a longer time.* **Conclusion:** *The results do not support an adrenergic mechanism for chronic neurogenic facial pain. The response to lidocaine, a nonadrenergic, membrane-stabilizing agent, suggests that it may have clinical effectiveness in certain neurogenic facial pain patients.*
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Key words: facial pain, neurogenic pain, phentolamine, lidocaine

Neurogenic facial pain is a major clinical problem, with significant patient suffering and morbidity.[1–3] However, the neurophysiologic mechanisms that produce and sustain this type of pain remain incompletely understood.[4–8] Traumatic injury to the face results in a series of changes in both the peripheral and central components of the trigeminal system. The persistence of these changes may be responsible for some of the clinically relevant chronic facial pain syndromes. Abnormalities in the normal anatomic and/or neurophysiologic structure and function of the trigeminal system have been suggested as etiologic factors.[9] Earlier researchers thought that after tissue or nerve injury, primarily peripheral mechanisms were involved in the production and continuation of pain. Current research shows that not only peripheral changes but also central changes (plasticity) are involved in chronic pain conditions, although the mechanism for

the production of pain in these conditions is not completely understood.[9–12] Several prior reports argue that chronic pain may be due to an abnormal interaction between damaged trigeminal sensory afferents and sympathetic efferent fibers innervating the face.[13,14] This view is also consistent with the belief that a number of regional autonomic signs and symptoms often accompany chronic facial pain.[15–17]

Consistent with this hypothesis, many authors contend that chronic pain of neurogenic origin can be mediated by sympathetic mechanisms, and therefore for many years the standard of care for patients with clinical neurogenic pain has included the use of sympathetic blocks, surgical sympathectomies, and antisympathetic drugs. Pain relief following sympathetic blockade is frequently considered an essential part of the diagnosis of sympathetically mediated pain.[18,19] The response to sympathetic blockade then often results in a clinical decision regarding surgical sympathectomy or the use of antisympathetic drugs. However, these treatments are often only partially effective, studies of chronic neurogenic pain are rarely placebo-controlled, and the results do not adequately explain the basic neurophysiologic mechanism for the pain.

Sympathetic mechanisms are often proposed as the etiology for some refractory neurogenic facial pain conditions.[20,21] However, facial pain patients who clearly fit the criteria for sympathetically mediated pain are rare, and the complex clinical phenomenology that accompanies many facial pain problems likely adds to diagnostic confusion.[22–27] Many patients lack evidence of sympathetic dysfunction, and few respond consistently to antisympathetic treatments. Despite the interest in sympathetic pain mechanisms, few clinical studies have investigated the role of sympathetic activity in chronic facial pain disorders.[21,27,28] Based on these theoretical mechanisms, many diagnostic and therapeutic procedures are performed and medications are empirically prescribed.

Intravenous infusions of short-acting agents that modulate peripheral sympathetic terminals and receptors provide a way to investigate sympathetic interactions in chronic pain states.[29–35] The present study was designed to use this approach to determine whether phentolamine, an alpha-adrenergic blocking agent, was analgesic in patients with chronic neurogenic facial pain. The response to phentolamine was compared to infusions of saline and lidocaine in the same subjects in a randomized, blinded protocol. Numerous other groups have used both phentolamine and lidocaine diagnostically and therapeutically for treating chronic pain syndromes, yet few studies have compared these agents to placebo for chronic neurogenic facial pain patients.[29–34]

The objectives of this study were: *(1)* to assess the effectiveness of 2 pharmacologic agents (phentolamine and lidocaine) administered intravenously versus placebo (saline) in alleviating chronic neurogenic facial pain, and *(2)* to evaluate the contribution of adrenergic mechanisms in chronic neurogenic facial pain in this study group.

Methods

Patients who presented to the Craniofacial Pain Center at Massachusetts General Hospital with a complaint of facial pain were evaluated for participation in this study. All patients underwent a comprehensive interview; a complete pain history with documentation of the quality, pattern, radiation, severity, and timing of the pain, as well as a mapping of the location of the pain; and a complete physical examination, with special attention to the head and neck neurologic examination. Neurosensory testing of the trigeminal system for an unpleasant altered sensation was performed as described by Zuniga and Essick[36] to characterize and standardize the sensory examination (Fig 1, Table 1). Pain intensity ratings were determined by the use of a 10-point intensity grading system (0 = no pain to 10 = worst pain). Additional evaluations, diagnostic studies, and imaging studies were performed as necessary.

The following criteria, which are consistent with the classifications by the International Headache Society[37] and the American Association of Orofacial Pain,[38] were used to make the clinical diagnosis of chronic neurogenic facial pain:

1. Pain of greater than 6 months' duration
2. Pain within the distribution of the trigeminal system
3. Spontaneous burning pain (dysesthesia), predominantly constant but occasionally piercing or stabbing
4. Hyperalgesia or allodynia
5. No evidence of pathology that might account for the symptoms

All patients included in the study group were given a pre-study and post-study evaluation as described above. Patients also completed our facial pain questionnaire, which consists of the Melzack Multidisciplinary Pain Questionnaire.[39] Patients with significant medical conditions that might

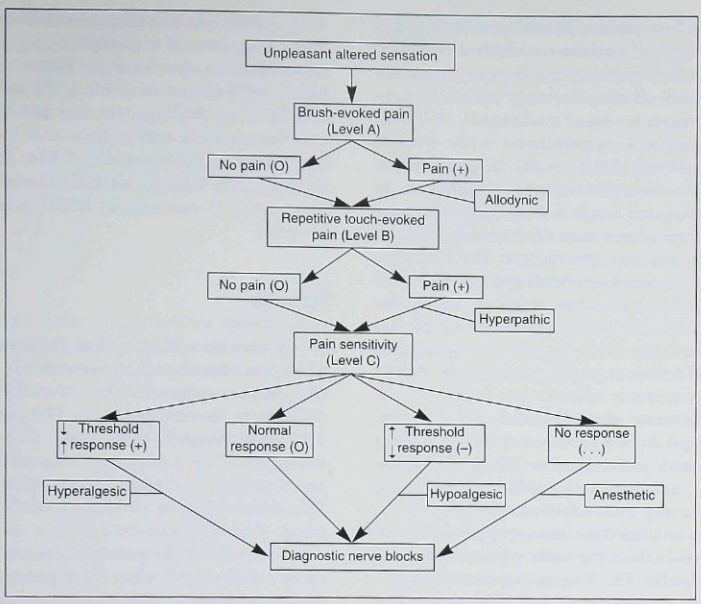

Fig 1 Maxillofacial nerve injury, Step 3: Sensory testing for unpleasant altered sensation, as described by Zuniga and Essick.[36] For details, refer to Table 1. Reprinted with permission of W.B. Saunders Company.

Table 1 Sensory Testing for the Patient with Unpleasant Altered Sensation*

Level A testing: Test for brush-evoked pain

Normal response—patient does not experience pain in response to brush strokes *(go to level B testing).*

Allodynic patient—experiences pain in response to brush strokes *(go to level B testing).*

Level B testing: Test for repetitive touch-evoked pain

Normal response—patient does not experience pain in response to repetitive application of touch/pressure stimulus *(go to level C testing).*

Hyperpathic patient—experiences pain in response to repetitive application of touch/pressure stimulus *(go to level C testing).*

Level C testing: Pain sensitivity

Hyperalgesia patient—exhibits exaggerated response to pin prick, decreased pressure (algometer) pain threshold, or decreased thermal pain threshold on test site.

Normal response—patient exhibits unremarkable response to pin prick, equal pressure (algometer) pain thresholds, and equal thermal pain thresholds on test and control sites.

Hypoalgesia patient—exhibits little response to pin prick, increased pressure (algometer) pain threshold, or increased thermal pain threshold on test site.

Anesthetic patient—exhibits no response to pin prick, noxious pressures, and heat on test site.

*Reprinted from Zuniga and Essick[36] with permission of W. B. Saunders Company.

complicate their general health were excluded from the study. All patients understood the study requirements and gave written consent to participate in the study. During the study period, all nonstudy medications remained unchanged.

The procedures were performed in the Department of Oral and Maxillofacial Surgery Outpatient Unit, Massachusetts General Hospital, in an officially designated Surgical Day Care Operating Room. The procedures were supervised by the unit nurse leader and one investigator. Patients were monitored with an electrocardiogram, continuous automated blood pressure monitor, and pulse oximeter. Peripheral venous access was established in the standard fashion and an infusion was begun with normal saline at a slow, steady rate (KVO) for 12 minutes.

The study was a single-blinded, placebo-controlled design. All patients received the 3 drugs being evaluated: phentolamine (30 mg), lidocaine (100 mg), and normal saline as placebo. Phentolamine and lidocaine were prepared by the unit nurse in unlabeled syringes, with an equal volume of normal saline, the same volume of fluid as the saline placebo. The 3 agents were administered in a standard sequence over 5 to 10 minutes. The patients were blinded as to the agent and to the starting time of the infusions. Patients were advised prior to the start of the drug trial of the potential side effects of the study drugs.

The study drugs were infused in a standard, repetitive fashion (placebo, phentolamine, lidocaine) by one investigator. Each drug was administered over a period of 5 to 10 minutes, with a 12-minute waiting period between each drug infusion. Pain scores were taken every 4 minutes throughout the entire study. At the completion of the 3 infusions, there was another 12-minute waiting period. Patients were questioned and examined for any untoward side effects and were then discharged with an escort and appropriate home care instructions. They were followed up by telephone or in person on the following day and then weekly, for a minimum of 4 weeks, to check for any untoward reactions from the procedure and to evaluate peak pain relief and any extended duration of pain relief.[40]

Data Analysis

The sample size was calculated as though the response was either success (relief of pain) or failure (no relief of pain). A linear analogue scale was followed, which increased the statistical power of the calculations. To account for the fact that there were 2 planned contrasts (lidocaine versus placebo and phentolamine versus placebo), a Bonferroni procedure was performed. Thirty patients will have a 90% chance of rejecting the null hypothesis at a 2-sided 5% significance level, if the true placebo response rate is 10% and 1 of the drugs has a true response rate of 50%. All statistical analyses were carried out in cooperation with the Biostatistics Department at Massachusetts General Hospital.

Results

Thirty patients with a clinical diagnosis of chronic neurogenic facial pain underwent the intravenous drug infusion protocol. There were 25 females and 5 males in the study group. The mean age was 50.3 years (range 32 to 84 years). The right side of the face was more frequently affected than the left, and 6 patients had bilateral facial pain complaints. The mean duration of facial pain was 8.8 years (range 1 to 49 years).

Twenty-six of the patients reported an inciting event for the pain, while in 4 patients there was no history of a precipitating factor. The inciting events were primarily dental surgical procedures: endodontic therapy, extraction, periapical surgery, periodontal flap surgery, or implant placement. There were 2 cases of sinus surgery and 2 cases of maxillofacial trauma with internal fixation as the reported inciting event. Psychologic evaluation revealed that 50% of patients had definable psychologic pathology according to the *Diagnostic and Statistical Manual* criteria.[41] The most common pathologies were anxiety or depression disorders, with 3 patients experiencing opioid dependence and suicidal ideations and 2 patients having attempted suicide. All patients in this study group had previously undergone numerous medical and dental specialist evaluations and treatments, including pharmacologic therapy, local anesthetic blocks, occlusal appliance therapy, dentoalveolar surgery, physical medicine, behavioral medicine, herbal medicine, acupuncture, hypnosis, chiropractic therapy, laser surgery, cryosurgery, and trigeminal radiofrequency thermal rhizotomy.

During drug infusion, no patient experienced a change in their pain in the initial waiting period after intravenous access and saline infusion. After the test infusion protocol had begun, no patient experienced pain relief with the infusion of saline (placebo). No patient experienced pain relief with the infusion of phentolamine, although 2 patients

experienced a transient, mild increase in their pain. During infusion of lidocaine, 16 patients experienced complete pain relief: 12 patients experienced pain relief for 15 to 30 minutes, and 4 patients experienced continued pain relief after the infusion protocol was completed. Two of these patients reported pain relief for 2 to 3 days and 2 reported pain relief for a total of 7 days after the infusion protocol.

Discussion

Neurogenic pain can present with spontaneous burning sensations, hyperalgesia, and evidence of sympathetic dysfunction in the affected region. In 1872, Mitchell et al referred to this condition as "causalgia"[42] (at the suggestion of his friend, Professor Robley Dunglison[43]) because of the persistent burning pain, allodynia, and hyperpathia that accompanied nerve trauma.

After peripheral tissue damage, a variety of cellular, vascular, and neurohumoral changes occur; these may sensitize or excite nociceptors.[44] Nociceptor sensitization alters their physiology such that nociceptors exhibit spontaneous firing activity, lowered thresholds, and increased responsiveness to noxious and nonnoxious stimuli.[15,45] Nerve injury can also lead to increased neuronal activity at the site of injury and in more central regions of the trigeminal system.

It was originally thought that primarily peripheral mechanisms were involved in the production and continuation of pain. Current research indicates that central changes (plasticity) are involved in chronic pain conditions.[9–12,44,46] Changes in the sympathetic nervous system may play a role in sensitization of nociceptive afferent input and may also generate a variety of other regional autonomic signs and symptoms.

Levine et al[47] and Heller et al[48] reported that peripheral tissue injury sets up a cascade of events that produces an intense inflammatory state, which they term "neurogenic inflammation," capable of causing chronic changes in both the peripheral tissues and in more central areas of the trigeminal system. Sessle and colleagues[8,49–51] have shown that with injury to the peripheral nerve endings in teeth, central changes can be found at the level of the trigeminal brain stem complex. These changes can affect the responses of second-order neurons to normal afferent input and induce changes at higher centers involved in the appreciation and interpretation of pain. Abnormalities in the normal inflammatory process following nerve injury have been found, and it has been proposed that this could be a pathologic course of the normal physiologic inflammatory response.[26]

After nerve injury, local burning pain and mechanical sensitivity (primary hyperalgesia) can develop; these are often associated with paresthesia and/or dysesthesia in the distribution of the affected nerve. Experimental studies show that the regenerating tip of a damaged nerve contains numerous small-diameter sprouts of all fiber types.[52] These regenerating axons develop spontaneous discharges, partly as a result of an increase in ionic permeability in the membrane. If the path for normal regeneration becomes blocked by some process, a neuroma can form. Regenerating nerve sprouts within a developing neuroma are sensitive to mechanical and chemical stimulation, and excitation may occur and become sustained by electrical "crosstalk" between bare axons.[53,54] This abnormal activity in damaged axons is a potential source of pain following nerve injury.

Normal axons exhibit little chemical sensitivity, but following experimental nerve injury in rats, the regenerating axon sprouts become sensitive to numerous endogenous substances, especially catecholamines.[15,45] This catecholamine effect appears to be mediated primarily by alpha-adrenergic receptors on the regenerating fibers. The source of this catecholamine response is uncertain; however, in addition to sensory axons, mixed nerves contain large numbers of unmyelinated postganglionic sympathetic efferent fibers that use norepinephrine as a neurotransmitter. In damaged nerves, abnormal coupling may occur between these efferent sympathetic fibers and cutaneous afferents, providing a potential source of chronic sensory activation that is catecholamine-dependent.[7] The concept of such an abnormal synaptic interaction between sympathetic efferents and sensory afferents is consistent with the observation that stimulating the sympathetic efferents to a neuroma produces a discharge in afferent fibers coming out of the neuroma.[20] This abnormal interaction between sympathetic efferents and cutaneous afferents may underlie some types of neurogenic pain following nerve injury and forms the basis for the concept of sympathetically maintained pain (SMP) states.

Neurogenic pain syndromes of this type have recently been redesignated "complex regional pain syndrome" (CRPS) types I (reflex sympathetic dystrophy [RSD]) and II (causalgia).[55] Diagnostic criteria require the presence of regional pain and sensory changes and a varied pattern of associated autonomic, motor, and vascular phenomena.

Sympathetically maintained pain as described by Roberts[4] specified only 2 symptoms: spontaneous pain and allodynia. It was also specified that the pain in the primary lesioned area could be eliminated by sympathetic blockade. Neurogenic pain is found in many disorders, including CRPS types I and II; therefore, neurogenic pain such as SMP may in fact be a clinical descriptor or phenomenon, rather than a disorder or diagnosis.

Sympathetically maintained pain is now classified as the aspect of pain that is maintained by sympathetic nervous system activity. Sympathetically maintained pain may be a component of many different painful conditions but is not a requirement for the diagnosis of any specific pain syndrome. Still, the criteria for differentiating between CRPS and SMP remains incomplete. Sympathetically maintained pain usually exhibits a less complex clinical presentation, with the primary manifestations being spontaneous pain, mechanical allodynia, and hyperalgesia. These sensory symptoms are usually restricted to the territory of the nerve involved. In contrast, the sensory, motor, and autonomic findings in CRPS often extend outside of the affected nerve territory and are more extensive than in SMP. The continued confusion between these entities prompted Ochoa to refer to this complex clinical presentation as the "causalgia-RSD-SMP" syndrome.[56]

There have been several case reports or case series of causalgia-RSD-SMP of the face and head,[22–28,57] with a multitude of presenting signs and symptoms. These reports provide no evidence for the mechanisms involved. Those reports that demonstrate the effectiveness of antisympathetic treatments, either as a diagnostic procedure or as therapy, are poorly documented, not controlled, or have limited follow-up.[22,24–28] Local anesthetic somatic blocks, sympathetic ganglion blocks, skin temperature changes, blood flow measurements, and even sympathectomy do not specifically diagnose anything and are surely not sensitive indicators of pain-producing mechanisms. These modalities, when employed to diagnose or treat causalgia-RSD-SMP of the face, are not randomized or placebo-controlled. The placebo effect for many of these and other invasive procedures is a very real factor in patient response, especially in a group of patients with a chronic pain syndrome.[58]

Phentolamine, an imidazole, is a competitive alpha-adrenergic antagonist that has similar affinities for alpha-1 and alpha-2 receptors. Phentolamine can also block serotonin receptors and causes release of histamine from sensitized mast cells. In addition, phentolamine has been found to block potassium channels in nerve cell membranes. Recent studies have indicated that after nerve injury, there is an increase in adrenergic receptors in the peripheral terminals of C-nociceptors, and mRNA for adrenergic receptors increases in brainstem pathway neurons and in a subset of dorsal root ganglion cells.[30,31,33] With the present theory that sympathetic activity mediates pain states by activating these adrenergic receptors, blockade of these receptors with a sufficient systemic dose of phentolamine should alter these procedures and produce an analgesic effect. In this study, this was not the case.

Lidocaine, an amide local anesthetic, is a membrane-stabilizing agent of nerve cell membranes due to its activity with sodium and potassium channels; it thereby alters the normal physiologic parameters of nerve conduction. Lidocaine has been shown by other studies to be useful in the management of a number of pain disorders.[29]

The present study demonstrates that with a single infusion of phentolamine (30 mg), no patient had an analgesic response; whereas with a single infusion of lidocaine (100 mg), an analgesic response was noted in 16 of 30 patients. This analgesic effect was transient in 12 patients, lasting approximately 15 to 30 minutes; this was most likely related to the serum half-life of the drug. Four patients experienced an analgesic response for more than 30 minutes, with 2 of these patients experiencing pain relief up to 7 days. None of the patients demonstrated an analgesic response to the administration of saline. This response is not surprising in the present study design, since the pharmacologically inactive saline was administered in a blind fashion after an initial baseline waiting period. The response to lidocaine is not likely to be due to a placebo effect, since the patients were unaware of the timing of the drug infusions and had no analgesic response to the saline infusions. Likewise, the fact that no patient responded to phentolamine with this study design suggests that in these patients this dose of phentolamine was not physiologically active to produce a change in whatever mechanism was producing the pain. This does not mean that the pain was not of neurogenic origin or that the dose was not great enough to be effective. Further dose-response evaluations in these patients might shed more light on this issue.

It is possible that some patients could determine the time of active drug administration by minor symptoms (ie, tinnitus or stuffiness) associated with the infusions. All of the possible side effects were described to the patients at the onset of the

procedure, prior to starting any intravenous infusion. The patients were told that they might experience all or none of these side effects from any of the drug infusions. None of the patients experienced side effects with the blinded infusion of saline. Additionally, both phentolamine and lidocaine can potentially produce related side effects that might give a placebo response, but none of the patients reported an analgesic response to the phentolamine infusions, whether or not they experienced any normal drug side effects.

An analgesic response in 16 of 30 patients receiving lidocaine coincides with results from other groups.[29–33] Interestingly, in our group, 14 patients did not experience an analgesic response, and 4 patients experienced a response longer than the conventional serum half-life for lidocaine. This suggests that the diagnosis of neurogenic pain by the criteria in this study might have been incorrect in the nonresponders or that other factors might be involved in producing the pain. It has been well documented that numerous cofactors are associated with chronic facial pain disorders, particularly psychologic factors. Psychologic factors are argued to be prominent in initiating and perpetuating many chronic pain states,[56,59] and patients with these as a primary role in their pain would probably not be expected to respond to lidocaine or phentolamine, especially when administered in a blinded fashion.

The results of this study do not support an adrenergic mechanism for chronic neurogenic facial pain. The response in some patients to lidocaine, a nonadrenergic, membrane-stabilizing agent, suggests that this agent may have clinical effectiveness in certain neurogenic facial pain disorders; it may also give some insight into the potential mechanisms involved in chronic neurogenic facial pain.

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