CLINICAL REPORT

Treatment of Phantom Limb Pain by Cryoneurolysis of the Amputated Nerve

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■ **Abstract:** The pathophysiology of phantom limb pain (PLP) is multifactorial. It probably starts in the periphery and is amplified and modified in the central nervous system. A small group of patients with PLP were questioned as to the portion of the phantom limb affected by pain (eg, "great toe," "thumb"). In the stump, the corresponding amputated nerve was located with a nerve stimulator. With correct placement and stimulation, the PLP could then be reproduced or exacerbated. A small dose of local anesthesia was then injected, resulting in the disappearance of the PLP. If a peripheral nerve injection gave temporary relief, our final treatment was cryoanalgesia at this location. Evaluation of 5 patients, followed for at least 2.5 years, yielded the following results: 3 patients had excellent results (100%, 95%, and 90% decrease in complaints, respectively), 1 patient had an acceptable result (40% decrease), and 1 patient had only a 20% decrease in pain. Although both central and peripheral components are likely involved in PLP, treatment of a peripheral pain locus with cryoanalgesia should be considered. We propose the identification of a peripheral etiology may help match patients to an appropriate therapy, and cryoanalgesia may result in long-term relief of PLP. ■

Key Words: phantom limb pain, cryoneuroablation, cryoneurolysis

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INTRODUCTION

History and Clinical Characteristics

Phantom limb pain (PLP), painful sensations perceived in the missing part of an amputated limb, was first described by Ambroise Paré in 1552. He postulated that peripheral factors, as well as a central pain memory, might cause this "paine like to convulsions."[1] PLP was named by Silas Weir Mitchell, the civil war surgeon who also described causalgia.[2] PLP is common after limb amputation, with 50% to 80% of patients reporting pain in the missing body part.[3–5] In 2005, there were an estimated 1.6 million individuals living with lost limbs, primarily due to trauma and peripheral vascular disease (PVD). This number is expected to double by 2050.[6]

Phantom limb pain is relatively easy to recognize and diagnose, although it should be distinguished from postoperative pain, residual limb pain (RLP, that is, stump pain), and nonpainful phantom sensations (the sense that the limb is still there). It is often described as a sharp, burning, cramping, shocking, shooting, or pins and needles sensation. PLP is more common in patients with pre-amputation pain, intense acute pain after amputation, and/or RLP.[7,8] It is also more common after upper extremity than lower extremity amputations[9]. There is no gender difference in the presence or intensity of PLP or RLP, although women amputees have more generalized pain and greater biopsychosocial distress.[10] Its precise cause remains unclear, and therefore, it is often difficult to manage successfully.[11] This perceived difficulty in treatment may lead to the undertreatment of PLP; a survey by Hanley et al.[12] found

53% of patients with PLP and 38% with severe PLP had never been treated for the disorder.

Peripheral and Central Pathophysiology

Current understanding of the pathophysiology of PLP involves complex interactions between the peripheral and central nervous systems.[4,5,13–15] Axotomy results in complete disruption of normal peripheral motor and sensory nerve architecture, leading to sensory neuron hyperexcitability due to inflammatory mediators released by macrophages, Schwann cells, and mast cells,[16] as well as changes in sodium channels[17] and gene expression.[15] Subsequent neuroma formation may also play a role, although it has been noted that PLP frequently occurs before there has been sufficient time for a neuroma to appear.[5] Changes in neuronal excitability may be amplified by changes in dorsal root ganglia and the sympathetic nervous system.[4,15] Traumatic injury to the nerves may cause abnormal ectopic discharges that are perceived as pain at levels below the severed nerves. Regional or spinal anesthesia eliminates phantom pain in some patients,[18,19] has no effect on others,[18] and may increase pain in a few.[19]

Changes also occur in the spinal cord and brain following amputation. Injuries to peripheral nerves can result in increased synaptic responsiveness in the dorsal horn of the spinal cord[4,15] and changes in the brainstem, thalamus, and several areas of the cortex.[14] Changes in cortical somatosensory representation can happen very quickly, as evidenced by the phantom sensations that occur during a regional anesthetic due to the changes in peripheral input.[18] During a regional anesthetic, patients may continue to feel the limb to be in the position last sensed, a "proprioceptive phantom."[20] Patients with painful phantom sensations have increased cortical changes compared with those with nonpainful limb sensations.[14] However, it is unclear whether these changes are involved in the causation of PLP or are secondary to it.[14] Cortical changes are sometimes reversible with regional anesthesia, implying that, at least in some patients, peripheral pathology maintains the central changes.[14,18]

Treatment

No single intervention has been successful in treating PLP, although many therapies targeting peripheral and central mechanisms have been tried.[11,12,21–23] This report addresses the role of peripheral nerves in maintaining PLP and the use of cryoanalgesia for long-term relief.

CRYOANALGESIA

Cryoanalgesia, also known as cryoneuroablation or cryoneurolysis, is a specialized interventional technique able to provide long-term relief in some patients with chronic pain[24–26] and has been reported as an alternative to phenol or alcohol injection in the treatment of postamputation neuromas.[27] The application of cold to nerves creates a conduction block similar to the effect of local anesthetics. Long-term pain relief from nerve freezing occurs because ice crystals damage the *vasa nervorum*, leading to severe endoneural edema and Wallerian degeneration of the nerve.[16,28] In this way, freezing disrupts nerve conduction but leaves the basal lamina of Schwann cells intact; histologic studies have confirmed axonal regeneration and the complete restoration of function of the nerve without neuroma formation.[29]

METHODS

We reviewed the records of all patients treated for phantom pain over a 10-year period, from 2000 through 2009, from which 5 patients were identified. Patients with stump pain were excluded, as were those patients treated with epidural steroids. All patients had burning pain and sensations of movement in the affected amputated limb. The patients were questioned as to the location of the phantom pain, and the remaining proximal portion of the corresponding nerve was identified by palpation on the distal portion of the stump. For instance, "great toe pain" was traced to the distal remnant of the saphenous nerve, "bottom of the foot pain" to the sciatic remnant, or "thumb pain" to the most distal portion of the radial nerve. A diagnostic injection in the amputation stump was then performed; the most distal portion of the remaining nerve was located with a nerve stimulator, using neurostimulation at 0.5 V to reproduce or exacerbate the PLP, and a small dose (< 2 ccs) of local anesthetic was injected. Correct location was confirmed by complete resolution of the phantom pain. If the stimulator-directed local anesthetic injection did not lead to temporary relief of the PLP, the patient did not undergo cryoneuroablation treatment.

Cryoanalgesia was performed at this same location, using 2 cycles of 3-minute freezing to −70°C, separated

by a 2-minute defrost. The cryoanalgesia probe was placed parallel to the nerve, and the built-in stimulator was used to again reproduce or exacerbate the PLP. During the first 30 seconds of the freezing process, there was a replication and then disappearance of the PLP distally, which then progressively replicated and then disappeared proximally, with complete relief within 45 to 60 seconds. For instance, for a great toe PLP, freezing the saphenous remnant would replicate the toe pain, which would then become "numb," followed by the patient noting a medial ankle pain and then ankle "numbness," followed by calf pain and then calf "numbness," and then medial knee pain and then complete phantom limb "numbness." Interestingly, the phantom limb sensations never resolved. Patients were followed in our pain clinic for a minimum of 3 months and every 6 months thereafter, and therapeutic effect was maintained throughout the follow-up period.

RESULTS

The records of 5 patients were reviewed (1 patient in 2000, 2 patients in 2003, 1 patient in 2004, and 1 patient in 2009). All were male, with 2 requiring arm amputation for trauma and 3 with leg amputation for severe PVD. Three patients had excellent outcomes, with 90% to 100% decrease in pain. One patient had an acceptable 40% decrease, and one had only a 20% decrease in pain (Table 1). Patient 1 was still pain-free after 2.5 years. Patients 2 and 5 reported 90% to 95% improvement at 5 years. Patients 3 and 4 died after 5 months, with pain relief until they died. Functionally, elimination of pain allowed 3 of the patients (1, 2, and 5) to use their prostheses, while the remaining 2 enjoyed at least some symptomatic relief until their deaths. All patients had at least some decrease in visual analog pain score and analgesic use (Table 2).

DISCUSSION

Limb amputation produces the ultimate peripheral nerve injury: complete transection with no possibility of the re-coupling with target receptors that could reverse the changes along the neuraxis set in motion by axotomy.[15] Deafferentation, whether transient (regional anesthesia) or permanent (amputation), results in reorganization of sensory and motor components of the adult central nervous system.[14,18,30] There have been reports that regional anesthesia could trigger transient PLP in patients with a prior limb amputation, although Tessler and Kleiman showed it to be a rare occurrence and therefore not a contraindication[19]. Plastic changes and PLP are more extensive when pain precedes the amputation, whether it is performed for PVD or trauma.[7,8] Intense acute RLP also independently predicts problematic PLP.[8] The contribution of preoperative pain is most likely due to cortical reorganization resulting in increased implicit pain memories.[4,14] In

Table 1. Phantom Limb Pain Patients Treated with Cryoneurolysis

Patient	Age (years)	Site of Amputation	Indication for Amputation	Time Between Amputation and Cryoneurolysis	Success at Follow-up	Length of Follow-up
1	62	Arm	Trauma	7 years	100%	2.5 years
2	37	Arm	Trauma	6 years	90%	5 years
3	71	Leg	PVD	1 year	20%	5 months (died)
4	68	Leg	PVD	3 months	40%	5 months (died)
5	71	Leg	PVD	7 years	95%	5 years

PVD, Peripheral vascular disease.

Table 2. Pain Scores and Analgesic Use Before and After Cryoneurolysis

	VAS		Morphine (mg/24 hour)		Gabapentin (mg/24 hour)		Amitriptyline (mg/24 hour)	
Patient	Initial	Post Cryo	Initial	Post Cryo	Initial	Post Cryo	Initial	Post Cryo
1	10	0	0	0	0	0	×	×
2	9	1	0	0	0	0	0	0
3	7	5	60	30	1200	300	45	25
4	7	3	30	30	1800	0	25	25
5	10	0.5	0	0	×	0	×	0

VAS, visual analog pain score; ×, patient refused; Cryo, cryoneurolysis.

addition, development of abnormal neural structures, such as neuromas, can lead to increased pain.[31] Decreased noxious input into the CNS can lead to improvements in deleterious CNS changes.[18,19]

Twenty years ago, observation of phantom sensations during spinal anesthesia led one author (AT) to focus on peripheral contributions to PLP. Patients questioned during spinal anesthesia noted that, if the anesthetic took effect while the leg was in the air during preparation for surgery, they had a phantom sensation of the leg in the air (despite actually seeing it in a different position) that remained until the local anesthetic wore off.[20] More recently, investigators have studied the limb position prior to anesthesia necessary to evoke a phantom sensation during ischemic anesthesia, observing that body image depends on afferent activity immediately before the anesthetic.[32,33] It was this "phantom sensation" observation that lead to the authors' exploration of peripheral nerve involvement in the treatment of PLP. What seems remarkable is that 2 of these authors (AM and AT) developed nearly identical approaches to the same problem independently, despite practices on 2 different continents.

Some PLP treatments have targeted the peripheral nerve in the amputation stump. Injection of drugs such as lidocaine in the neuroma has been successful for some patients.[34] Neuroma resection may ameliorate PLP[35], even in patients who have failed prior excision.[31] However, some authors state that pharmacological and surgical interventions are not clinically useful.[21] There is little evidence-based support for any particular intervention,[11] perhaps because of inadequate clarification of etiologies.

Modern cryoanalgesia began in 1961 when Cooper used a hollow tube insulated at the tip to deliver liquid nitrogen and achieved a temperature of −190°C.[26] Clinical application of cryoanalgesia for pain treatment dates from 1976 when Lloyd, Barnard, and Glyn published their use of a new cryosurgical probe to freeze peripheral nerves and thereby relieve intractable pain.[24] In that study, 64 patients were treated, 52 of which obtained relief of pain. The authors stated that cryoanalgesia is superior to other methods of peripheral nerve destruction, such as alcohol injection or surgical lesions, because it is not followed by neuritis.[24] Because of the likelihood of anatomic disorganization at the site of amputation, the importance of careful diagnostic blocks and nerve stimulator localization of the cryotherapy site cannot be overemphasized. Cryoanalgesia has reduced acute[29] and chronic[24–26] neuropathic pain in some patients, with little or a negative effect in others,[36] perhaps because of inappropriate diagnosis.

In animals, the effects of cryoanalgesia depend on the temperature at which the lesion was induced[37] and the duration of exposure,[16] with differential effects on nerve and connective tissue. Of note is that cryoneurolysis has been used to create and evaluate models of neuropathic pain, with results most closely resembling those seen after nerve crush injury.[16,38] Incomplete freeze injury may be due to insufficient contact time,[16] inadequate temperature, or inaccurate probe placement and may contribute to the variability of results after cryoanalgesia. It is unfortunate that cryoneuroablation is not taught more often in pain training programs, for it provides a unique technique for addressing neuromas and myelinated nerve entrapments. It is also unfortunate that PLP patients are rarely sent to interventional pain clinics, perhaps because of the mistaken impression that the treatment is by medications only. This article attempts to spark an interest in both the identification and treatment of a peripheral cause of PLP.

In the past, little attention has been given to the role of the peripheral nerve in the generation and maintenance of PLP. Searching for peripheral triggers for phantom pain symptoms can be guided by the nerve pattern of the phantom pain, tracing the known path of the nerve proximally, and examining for proximal tender regions. Low-volume nerve injections (ideally with a peripheral nerve stimulator) with depo-steroid can be both diagnostic and therapeutic; if only temporary relief is obtained, cryoanalgesia may offer long-term relief. Although central and peripheral sites are involved in PLP, treatment by cryoanalgesia of the peripheral pain trigger should be considered for patients who have a substantial peripheral contribution to their PLP.[8] Diagnostic injections should help predict those patients most likely to respond to cryoneuroablation. Cryoanalgesia is most likely to be successful in the context of combined physical,[12] pharmacologic, and behavioral therapies targeted at changes along the neuraxis.

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