

## Use of Calcitonin To Treat Phantom Limb Pain

*Ishwer L. Bharwani, MD, MBBS, MRCP (Ireland), FACP*

*Arthi Rajagopal, MD*

*James B. Ray, PharmD*

**A**mbrose Paré first described phantom limb pain in the mid-16th century,<sup>1</sup> and Mitchell painted a vivid description of this condition in 1866.<sup>2</sup> Because of its intangible, subjective sensation, phantom limb pain has a widely variable incidence.<sup>3</sup> Current studies reveal that 50% to 85% of amputees experience phantom limb pain. However, earlier reports described a very low incidence,<sup>4-13</sup> which may be attributed to the medical and social stigma surrounding patient reports of phantom limb pain. Sherman reported that “. . . amputees are reluctant to divulge their complaints for fear of being labeled insane.”<sup>14</sup> In recent years, society has become more accepting and tolerant of various illnesses and symptoms, affording patients the opportunity to speak openly regarding their health problems and to seek relief from this painful condition.

Surgical procedures as well as physical, pharmacological, and psychological therapies—including transcutaneous electrical nerve stimulation (TENS), opioids, and physical therapy—have been used to treat this condition. Treatment with salmon calcitonin was first reported by Mertz in 1986<sup>15</sup>; later, Kessel and Worz also reported the usefulness of this therapy.<sup>16</sup> In a controlled study by Jaeger and Maier, calcitonin was described as a very effective treatment for phantom limb pain.<sup>17</sup> This article reports the case of a man who experienced phantom limb pain that failed to respond to standard treatments. He was subsequently treated successfully with intravenous administration of salmon calcitonin.

### CASE PRESENTATION

A 71-year-old man with a history of peripheral vascular disease, coronary artery disease, chronic obstructive airway disease, and prostate cancer was admitted to our rehabilitation center for treatment of phantom limb pain. He had seen his physician approximately 2 years earlier because of ulcer-related pain in his right

foot. The patient initially had been resistant to surgery and had been treated conservatively for 12 months, at which time he had elected to undergo an above-the-knee amputation. For a year after surgery, the patient had experienced phantom pain in the tips of the toes of his amputated foot. The pain had been unsuccessfully treated with multiple medications, including codeine, narcotic analgesics, an anticonvulsant agent, and nonsteroidal anti-inflammatory drugs.

After discussing the advantages and risks associated with intravenous calcitonin therapy, the patient provided informed consent and underwent calcitonin treatment. Prochlorperazine (10 mg) was administered orally 1 hour before infusion. Hydrocortisone (100 mg), diphenhydramine hydrochloride (50 mg), and epinephrine (1:1000) were readily available in the event of an allergic reaction. Calcitonin (200 units in 50 mL of normal saline with 5 mL of 25% albumin) was then infused over the course of 30 minutes.<sup>17</sup> A single dose was administered on day 1, day 6, and day 9. The patient experienced a fair response to the first infusion, with the pain moving to the phantom knee. Following administration of the second and third doses, the patient described a telescoping of the phantom limb. The pain was then referred to the stump, and after 12 months, the patient reported no further phantom limb pain.

The patient was very pleased with the results of the calcitonin therapy. He stated that no one had believed he had pain in the toes of his missing foot and commented that he had been afraid to report it because “people might have thought I was crazy.”

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*Dr. Bharwani is the Medical Director, Erie Center on Health and Aging, Erie, PA; and an Attending Physician, Hamot Medical Center, Erie, PA. Dr. Rajagopal is an externship student, Erie Center on Health and Aging, Erie, PA. Dr. Ray is a Clinical Pharmacist, Department of Pharmacy and Drug Information, Hamot Medical Center, Erie, PA.*

## **DISCUSSION**

Limb amputation is most frequently associated with traffic and occupational injuries (especially in the military), peripheral arterial disease, cancer, and congenital malformation. The seeming incongruity of pain in a missing body part, combined with the difficulty of successfully managing this pain, results in severe, chronic pain in the majority of people who undergo amputation. Although documented for centuries, phantom limb pain remains difficult to treat, and no single reliable treatment regimen exists. Sherman reported 60 different treatments for managing phantom limb pain.<sup>14</sup>

### **Description**

Phantom limb pain is commonly described as a sensation of a twisted, absent limb; as a feeling of hyperflexed, absent fingers or toes digging into the palm or plantar surface; or as a burning, cramping, crushing, shooting, or stabbing sensation in a missing body part. The pain is not necessarily of the same strength, location, or duration from one occurrence to the next. The frequency of the episodes often fluctuates with time, and episodes may last for several minutes, hours, or days; episodes may occur occasionally or continuously over a long period of time. In some patients, an episode may be triggered or intensified by unrelated pain or by gentle pressure of the stump, the other limb, or even the head. Urination, defecation, sexual intercourse, or approaching low-pressure weather systems may also act as triggers. Incidence is not associated with the reason for or location of the amputation. Age, gender, socioeconomic status, and psychological disorders are also unrelated to occurrence.

### **Etiology**

Phantom limb pain is such a complicated and widely varying phenomenon that its origins are most likely multicentric. Although research suggests a physiologic basis for the pain, the exact etiology is unknown. Referred pain, initiated by decreased blood flow and microspasms in the residual limb and mediated, in part, by prosthetics, accounts for most of the clinically reported occurrences of phantom pain.

Both the peripheral and the central nervous system play a role in persistent phantom limb pain. The pain and touch sensations are the result of impulses traveling through the thalamus, which relays the information to the cerebral cortex, where the sensations are mapped. Stimulation of the amputated limb end can induce phantom sensation. The hypothesis proposed for this phenomenon is that neuroplasticity changes

the innervation pattern from the limb to the brain. If some type of innervation of the stump of the limb exists, this stimulation can produce reinnervation and, subsequently, a phantom limb.<sup>18</sup>

Another theory is that cortical remapping occurs in response to an amputation.<sup>19,20</sup> This remapping can cause, for example, the cortical region that represents the hand before amputation to become responsive to the stimuli from the facial region, thus causing facial sensation to be felt in the phantom hand. This phenomenon seems to occur because the facial region is adjacent to the hand in the motor cortex homunculus.<sup>21</sup>

A third theory involves the neuromatrix—a massive body of interconnected neurons.<sup>22</sup> The neuromatrix analyzes the sensory information and gives perception of the sensation. If the brain believes that the limb is present, it may instruct the limb to move by stimulating certain neural pathways in the neuromatrix. Because the limb is not present and the brain receives no sensory feedback, it will increase the strength of its stimulation, possibly causing phantom pain.<sup>22,23</sup>

Yet another hypothesis suggests that disruption of the sensory pathway caused by amputation triggers a pain state that is reverberated in the central loop between the hypothalamus and the cortex.<sup>24</sup> Finally, a suggestion has been made that lasting intense preamputation pain may imprint an engram of that pain centrally. The changes in the neural structures caused by this sensory input result in this engram being experienced as pain, rather than as a memory of pain.<sup>25,26</sup>

### **General Treatment Modalities**

Comprehensive evaluation and a multimodality treatment approach comprise the current standard of care for patients experiencing phantom limb pain.<sup>27</sup> However, in geriatric patients with multiple illnesses, drug therapy may be problematic and invasive techniques risky.<sup>28</sup> Also, in a substantial number of cases, phantom leg pain diminishes and even resolves. Treatment with drugs that reduce the functional sodium channels has been successful, as have various neurophysiologic manipulations.<sup>29</sup> When used appropriately, mechanism-based treatments related to specific symptoms can be effective; these include peripheral vasodilators, muscle relaxants, and biofeedback to correct specific problems with blood flow and muscle tension in the residual limb.<sup>30</sup>

Pharmacologic treatment should be combined with TENS,<sup>31,32</sup> sympathetic blockade, and psychotherapy. Currently, pharmacologic treatments include administration of medications such as  $\beta$ -blockers,<sup>33</sup> serotonin

**Table 1.** Published Reports of Phantom Limb Pain Treated with Calcitonin

Source*	Experimental Design	Number of Patients	Results
Kessel and Worz <sup>16</sup> (1987)	Open label, non-randomized	10	No statistical analysis
Jaeger et al <sup>17</sup> (1988)	Open label	12	10 patients were pain free after 24 months; 4 patients experienced a recurrence.
Fiddler and Hindman <sup>48</sup> (1991)	Case history	1	Good response to calcitonin
Jaeger and Maier <sup>17</sup> (1992)	Double-blind crossover	21	Approximately 50% pain relief (on numeric analogue scale) occurred in 19 patients; 16 patients were pain free.

\*Arranged from earliest to latest study.

agonists, tricyclic antidepressants, clonazepam, lidocaine (for regional anesthesia), fluoxetine,<sup>34</sup> buprenorphine (intrathecally), and calcitonin.<sup>25,26,35</sup> New therapeutic strategies (eg, administration of capsaicin, new anticonvulsant agents, N-methyl-D-aspartate antagonists) are now being tested.<sup>28</sup>

Preoperative and postoperative administration of anesthetics has been shown to block pain sensation and spinal cord hyperexcitability associated with nociception.<sup>36</sup> The latest surgical method involves implanting a spinal cord stimulator (the dorsal column stimulation procedure).<sup>3</sup>

### Calcitonin

Calcitonin is a peptide with high a molecular weight and a probable special carrier protein.<sup>37,38</sup> The intravenous route of its administration may be related to its peak concentration.<sup>17</sup> The exact mechanism of action of calcitonin is still unknown. Although this drug increases the production of  $\beta$ -endorphin,<sup>39</sup> the process is independent of the endogenous opioid system.<sup>40–42</sup> Calcitonin may stimulate the serotonergic neurons, which are blocked by methysergide. Binding sites for calcitonin near areas of the brain that are rich in serotonin (eg, hypothalamus, limbic system) further support this hypothesis.<sup>43</sup> Calcitonin also leads to decreased formation of local cytokines and prostaglandin, which both play a role in generating pain. Intraventricular calcium may reverse the analgesic effects of the calcitonin, but no relationship exists between analgesic potency and calcium level in humans.<sup>39</sup>

In the acute state of phantom limb pain, calcitonin infusion and orally administered opioid analgesics have proved helpful; established phantom limb pain may respond to administration of antidepressant agents, anticonvulsant agents, and drugs that mimic or en-

hance  $\gamma$ -aminobutyric acid function. Calcitonin has also been used in the treatment of Paget's disease, osteoporotic collapse of vertebrae, and metastatic carcinoma of the osteoclastic type.<sup>39,44–46</sup>

In those cases in which phantom limb pain is causing disability, intravenous administration of calcitonin should be considered. However, reports of its use are very limited, with single case reports and a few case series with very small numbers of patients (**Table 1**).<sup>16,17,47,48</sup> Large double-blind studies are needed to establish optimal dosing and timing for calcitonin therapy. Although evidence is very limited, 1 or 2 intravenous doses of salmon calcitonin (200 IU) may be an effective treatment for phantom limb pain. The minor adverse effects reported in the literature support the safety of this regimen; however, clinicians should be aware of a rare, but severe, hypersensitivity reaction that may occur with salmon calcitonin. Intranasal administration of calcitonin appears to be similar in efficacy to the parenteral formulation, at least in managing pain associated with vertebral crush fractures.<sup>49</sup> Long-term studies using intravenous administration of calcitonin for relief of phantom leg pain are warranted.

### CONCLUSION

Phantom limb pain presents a challenge that influences the quality of life of affected patients and, therefore, must be treated aggressively. The phantom limb pain reported by the case patient failed to resolve with conventional treatments, but it was treated successfully with intravenous administration of salmon calcitonin. Although evidence is limited, in recalcitrant cases, calcitonin therapy should be considered for treatment of phantom limb pain. More data are needed to assess the efficacy of this modality, and we hope that our observations will promote further research. **HP**

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