Use of calcitonin in recalcitrant phantom limb pain complicated by heterotopic ossification

Ricardo Viana MD FRCPC, Michael WC Payne MD FRCPC

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BACKGROUND: Phantom limb pain (PLP) is a common complication after amputation, affecting up to 80% of the amputee population. However, only 5% to 10% of amputees have severe PLP impacting daily function. The present report details the management of severe, treatment-resistant PLP in a 72-year-old man with a traumatic left transradial amputation and a comorbid complication of heterotopic ossification (HO).
OBJECTIVE: To describe a case of PLP with HO and the possible role of calcitonin in the treatment of both conditions.
METHODS: A systematic review of the literature regarding the management of PLP.
RESULTS: Seventeen articles that directly addressed PLP were identified; 11 were randomized controlled trials. All involved small samples and follow-up ranged from 6 h to one year, with the majority limited to six weeks.
DISCUSSION: In the present case, medication management was limited by side effects, lack of response and the patient's desire to avoid long-term medication. Investigations revealed HO, which was suspected to envelop the median nerve in the proximal forearm. After several unsuccessful medication trials, the literature was reviewed in search of common variables between HO formation and persistent PLP. Ultimately, the biochemical effects associated with nerve injury were identified to be a possible factor in both HO and PLP development. Calcitonin's proposed mechanisms of action may help to manage HO and PLP at multiple stages of disease development and maintenance. In the present case, a four-week trial of intranasal calcitonin was successful, with pain control lasting at least 18 months.
CONCLUSION: The present case report provided a review of the current literature in PLP pharmacological management and the current understanding of the etiology of PLP and HO, as well as how the two may coexist. It also provided an opportunity to discuss the proposed mechanisms of action of calcitonin in the management of PLP and HO.

Key Words: *Adult upper limb amputation; Calcitonin; Heterotopic ossification; Phantom limb pain; Post-traumatic*

L'utilisation de la calcitonine pour soulager des douleurs fantômes récalcitrantes compliquées par une ossification hétérotopique

HISTORIQUE : Les douleurs fantômes (DF) sont une complication courante de l'amputation, qui touchent jusqu'à 80 % des amputés. Cependant, de 5 % à 10 % d'entre eux éprouvent de graves DF qui nuisent à leur fonction quotidienne. Le présent rapport expose la prise en charge des graves DF récalcitrantes chez un homme de 72 ans après une amputation traumatique du bras gauche et de l'artère radiale et présentant une complication comorbide d'ossification hétérotopique (OH).
OBJECTIF : Décrire un cas de DF associée à une OH et le rôle possible de la calcitonine pour traiter ces deux affections.
MÉTHODOLOGIE : Analyse bibliographique systématique sur la prise en charge des DF.
RÉSULTATS : Les chercheurs ont trouvé 17 articles portant directement sur les DF, dont 11 essais aléatoires et contrôlés. Tous portaient sur de petits échantillons, et le suivi se situait entre six heures et un an, la majorité se limitant à six semaines.
EXPOSÉ : Dans le présent cas, l'administration de médicaments était limitée par les effets secondaires, l'absence de réponse et le désir du patient d'éviter une médicothérapie prolongée. Les examens ont révélé une OH, soupçonnée envelopper le nerf médian de l'avant-bras proximal. Après plusieurs essais de médicaments infructueux, les chercheurs ont analysé les publications scientifiques pour trouver des variables communes entre la formation de l'OH et les DF persistantes. Ils ont fini par déterminer que les effets biochimiques associés à la lésion nerveuse avaient peut-être contribué à l'évolution de l'OH et des DF. Les mécanismes d'action proposés de la calcitonine peuvent contribuer à traiter l'OH et les DF à diverses étapes de l'évolution et de l'entretien de la maladie. Dans le présent cas, un essai de calcitonine intranasale pendant quatre semaines s'est révélé concluant, et le contrôle de la douleur a persisté au moins 18 mois.
CONCLUSION : Le présent rapport de cas a permis d'analyser les publications à jour sur la prise en charge pharmacologique des DF, sur les connaissances actuelles de l'étiologie des DF et de l'OH, ainsi que sur leur mode de coexistence. Il a également permis de discuter des mécanismes d'action proposés de la calcitonine pour traiter les DF et l'OH.

Phantom limb pain (PLP) is a common complication after an amputation, impacting up to 80% of the amputee population. However, only 5% to 10% of amputees have severe PLP with an impact on daily function (1-3). Current management of PLP is limited due to an incomplete understanding of the pathophysiology of PLP and the limited number of studies addressing pharmacological and nonpharmacological management. As a result, most clinicians treat PLP using the same algorithm used for other neuropathic pain syndromes (1).

The patient in the present case report did not respond to the 'standard' treatments for PLP and requested avoidance of any pharmacological intervention that would require daily use for more than a few weeks. The medical team was faced with treatment-resistant PLP and a desire to respect patient autonomy and avoid daily use medication, which prompted a review of the literature on PLP and its treatment as well as further investigations. These investigations identified the presence of heterotopic ossification (HO), an uncommon entity in the adult amputee population, as a possible mechanism for exacerbated PLP.

The objective of the present report was to present a summary of the current understanding of PLP pathophysiology and the evidence for pharmacological management of PLP. Also summarized is the proposed pathophysiology of HO development and its possible link to peripheral nerve injury. Finally, a link between the respective pathophysiological mechanisms and how they can coexist is discussed as well as a

Department of Physical Medicine and Rehabilitation, Western University; Parkwood Institute, St Joseph's Health Care, London, Ontario
Correspondence: Dr Ricardo Viana, 550 Wellington Road, London, Ontario N6C 0A7. Telephone 519-685-4559, fax 519-685-4023, e-mail ricardo.viana@sjch.london.on.ca

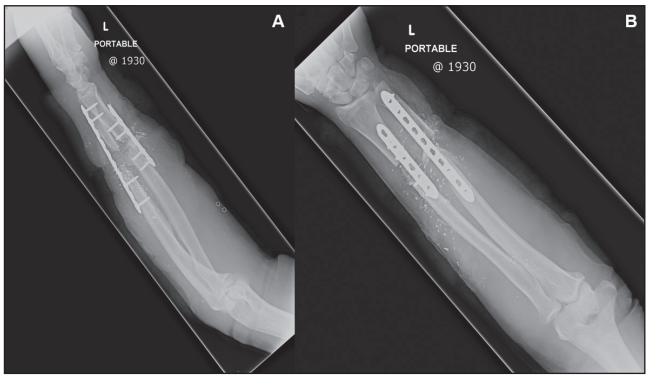

Figure 1) *Preoperative x-ray images after return to home hospital.* **A** *Lateral x-ray image demonstrating adequate alignment achieved with plate and screw fixation. There is significant debris, bone fragments and soft tissue swelling.* **B** *Anterior-posterior x-ray image of the left forearm, demonstrating adequate alignment with plate and screw fixation of the distal radius and ulna. Also apparent are significant debris, bone fragments and soft tissue swelling*

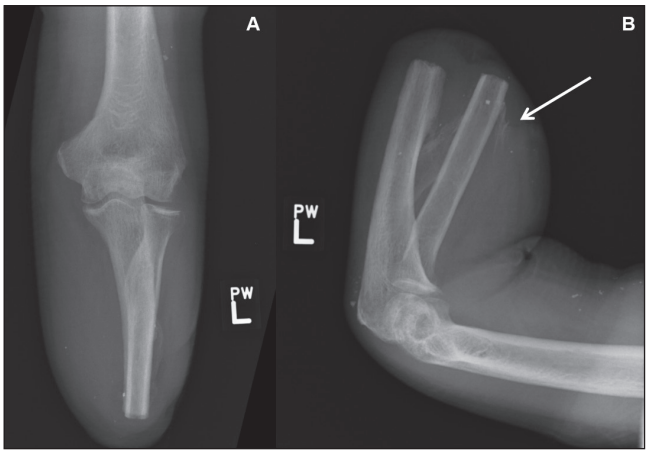

Figure 2) *X-ray image of the left residual limb.* **A** *Anterior-posterior image with no soft tissue abnormality, and evidence of bony growth between the proximal ulna and radius.* **B** *Lateral x-ray image displaying a bony bridge between the proximal ulna and radius as well as osseous growth adjacent to the radius in the soft tissue indicative of heterotopic ossification (arrow)*

review of the possible role of calcitonin in PLP and HO management. This discussion is framed around a single case. Ethics approval was granted from the local university review board and informed consent was obtained.

CASE PRESENTATION

A 72-year-old, right-hand dominant retired mechanic presented with PLP. His medical history was significant for left shoulder remote rotator cuff injury with adhesive capsulitis, aneurysmal dilation of the ascending aorta and mild aortic insufficiency. His injury occured while travelling in another country, where he sustained a crush injury to the left forearm and hand, as well as rib fractures and a pneumohemothorax. He received acute treatment of his injuries in a local trauma centre. Four days postinjury, he was transferred to his home hospital.

On arrival to his home hospital, he was admitted to the intensive care unit with symptoms of sepsis; his left upper extremity appeared to be infected. Arrangements were made for imaging and surgical exploration. The preoperative x-ray revealed adequate alignment of the radius and ulna with plate and screw fixation, along with significant debris, bone fragments and soft tissue swelling (Figure 1).

On postoperative day (POD) 5, he underwent a second surgery. After extensive debridement and lavage for deep infection, the flexor carpi radialis, all hand intrinsic muscles, long flexors and extensors were determined to be nonviable. The wound was packed and the surgery was ended to discuss the role of limb salvage versus a transradial amputation with the patient and family. On POD 7, the patient returned to the operating room for a short transradial below-elbow amputation of the left forearm. On POD 19, he underwent debridement of the amputation site and split-thickness skin grafting from the right thigh to the left forearm amputation site.

The patient recovered well and was soon discharged home and a referral was made for consideration of prosthetic fitting and training. Rehabilitation and prosthetic fitting were impaired by PLP, which he described as an intense sensation of flexion and cramping of digits 1 to 3.

The patient agreed to short-term trials of medication but wished to avoid long-term daily medication use. Nonpharmacological management included multiple modifications to the socket, desensitization therapy, compressive stump covers (shrinker type and Farabloc [Farabloc Development Corporation, USA] [4]), mirror therapy and, ultimately, discontinuation of prosthesis use. None of these had any impact on the PLP. Pharmacological management trials included: gabapentin titrated to a dose of 600 mg three times daily (not tolerated due to severe lightheadedness); pregabalin titrated to a dose of 150 mg twice daily (no effect and lightheadedness); tramadol (immediate release) 37.5 mg, one to two tablets every 6 h as needed (no effect); hydromorphone (immediate release), 1 mg to 2 mg every 4 h as needed (no effect); and two local injections of xylocaine to point of maximal tenderness (no effect). After repeated trials of pharmacological and nonpharmacological interventions, the patient's pain remained severe and limited the use of the prosthesis.

Further investigations included an x-ray of the residual limb (Figure 2), which identified local HO in close anatomical proximity to the median nerve's expected location in the proximal forearm. This was significant given that the phantom pain consisted of flexion and cramping of the lateral three digits of the hand, which are innervated by the median nerve. Management options were reviewed with the patient including the use of daily bisphosphonates for a minimum of six months with the goal of slowing HO development as well as analgesic effects; however, the patient refused any long-term daily treatments. Returning to the literature, calcitonin was identified as a possible treatment option for PLP and a possible aid in HO management. This was explained to the patient and he agreed to a two-week trial and then an extension to a total of four weeks of intranasal calcitonin, 200 units into alternating nostrils once daily.

At one month, the patient reported a significant reduction in both frequency and intensity of PLP and had discontinued all other scheduled and as-needed analgesic medication, but had not returned to using the prosthesis. At the three-month follow-up, pain was at a minimum and a repeat x-ray showed no progression of the HO. At the six-month follow-up, the patient returned to prosthesis use and at the 18-month follow-up the patient continued to report minimal phantom pain and continued prosthesis use with no desire to pursue surgical management with HO excision.

DISCUSSION

PLP

Phantom sensation (ie, feeling the absent limb), is a well-recognized phenomenon after amputation, with 100% of amputees reporting phantom sensation at some point post amputation (1,3). PLP, pain in the absent limb, is also fairly common with up to 80% of amputees experiencing PLP (1-3); however, only 5% to 10% experience severe PLP with an impact on daily function (3). Symptoms include sensations of burning, tingling, sharp-shooting pain, prickling, throbbing or crushing, or the sensation of sustained digit flexion or painful posturing of the absent limb (1-3).

The etiology of PLP is poorly understood and believed to involve a mix of peripheral and central mechanisms. Nikolajsen (3) and Knotkova et al (2) propose the following possible mechanisms:

TABLE 1
Condensed summary of the literature evidence supporting the use of selected pharmacological agents

Medication class	Agent	Studies available	(–/+) Support of use (duration of follow-up)
Nonsteroidal anti-inflammatory drug		No studies available	
Antidepressant	Amitriptyline	Robinson et al, 2004 (5)	(–) (6-week follow-up)
	Duloxetine	Spiegel et al, 2010 (6) (case report)	(+) (14 days)
Anticonvulsant	Gabapentin	Bone et al, 2002 (7)	(+/–) (6-week follow-up)
		Smith et al, 2005 (8)	
	Pregabalin	Spiegel et al, 2010 (6) (case report)	(+) (14 days)
Opioids	Morphine	Huse et al, 2001 (9) (crossover with placebo)	(+) (every week × 4 weeks) (30 min postinfusion)
		Wu et al, 2002 (10) (crossover with lidocaine)	
	Methadone	Bergmans et al, 2002 (11) (case report)	(+) (2–4 months)
	Buprenorphine	Casale et al, 2009 (12) (crossover with placebo)	(+) (1 h postinjection)
	Tramadol	Wilder-Smith et al, 2005 (13)	(+) (1 month)
Injection therapy	Bupivacaine	Casale et al, 2009 (12) (crossover with placebo)	(+) (1 h postinjection)
Infusion therapy	NMDA receptor antagonist	Memantine versus placebo	(–) (3–4 week follow-up)
		Maier et al, 2003 (14)	
		Schwenkreis et al, 2003 (15)	
		Wiech et al, 2004 (16)	
		Dexromethorphan versus placebo	(+) (10 day follow-up)
		Abraham et al, 2003 (17)	
		Ketamine versus placebo	(+) (45 min post treatment)
		Nikolajsen 1996 (3)	
		Ketamine ± calcitonin	(+) (48 h post treatment)
		Eichenberger et al, 2008 (18)	
	Lidocaine	Wu et al, 2002 (10) (cross-over with lidocaine versus morphine)	(–) (30 min post infusion)
Other	Calcitonin	Kessel and Worz, 1987 (19) (case series)	(+) (6 h) (24 h and 1 year) (48 h after single infusion)
		Jaeger and Maier, 1992 (20)	
		Eichenberger et al, 2008 (18)	

Study design for the included studies was randomized controlled trial unless otherwise specified. Current evidence for selected pharmacological agents commonly used in the management of phantom limb pain. Also indicated are whether the studies were positive (+) or negative (–), as well as the length of follow-up, which ranged from 30 min to 6 weeks post-treatment. NMDA N-methyl-D-aspartate

1. Injured, axotomized, afferent fibres exhibit spontaneous and abnormal activity. This may present with the development of a neuroma (benign growth of nerve tissue) or with partial retrograde degeneration of the nerve ending. Both entities are associated with pain due to either local mechanical or chemical irritation.
2. Heightened activity of the dorsal horn of the spinal cord from the irritated nerve remnant as well as ectopic activity from the dorsal root ganglion increases the overall load of abnormal afferent input. This continuous pain sensation leads to spinal cord level sensitization, which, in turn, results in a reduction of local intersegmental inhibitory mechanisms and increased *N*-methyl-D-aspartate receptor systems. These changes function to prime these local sensory systems so that less stimulation is needed to produce greater pain sensation.
3. Centrally, neuroplastic alterations at the somatosensory cortex and thalamus results in changes in somatotopic organization as seen on functional magnetic resonance imaging. Reversal of this somatotopic reorganization is found when individuals are provided with adequate pain control.

Table 1 lists the current evidence regarding commonly used agents in the management of PLP. Included are 11 clinical trials, three crossover studies, one case series and two case reports. The main limitations common to all the studies are small sample size, inconsistent use of objective measures of pain intensity and limited follow-up. Close review of the literature reveals that many of the positive studies are those with very short study follow-ups (hours to days) while the majority of studies with three to six week follow-up show mixed or negative outcomes for PLP control. Even with such limited evidence, many of these agents, including amitriptyline, gabapentin and pregabalin, continue to be the standard of care for long-term management of PLP.

HO in the amputee population

HO is the formation of mature trabecular bone in the soft tissue outside the confines of the periosteum (21). HO is believed to develop in response to inflammatory or mechanical stimuli often associated with musculoskeletal trauma, central nervous system injury, surgery, burns and orthopedic procedures (ie, arthroplasty). The actual pathophysiology of HO development is largely unknown. Salisbuty et al (21) provide a summary of the current understanding and the potential role of sensory nerves in HO development. HO develops as a result of activation of pluripotent mesenchymal cells in soft tissue to osteoprogenitor cells under the influence of bone morphogenic proteins, substance P and prostaglandins. Salisbuty et al (21) discovered that bone morphogenic proteins also play a prominent role in the stimulation and maintained release of neuroinflammatory markers (substance P and calcitonin gene-related peptide) from sensory peripheral nerves. These markers are key to developing and maintaining an environment favouring the development of HO.

HO is rarely reported in the adult amputee population and is believed to be more common in the post-traumatic population (22-24). The largest studies in this area are by Potter et al (23,24) who performed a chart review of 330 patients with 373 traumatic, combat-related (mainly blast injury) amputations. The authors identified HO in 63% of available images. An incidence of 63% is impressive for the adult amputee population because, before these studies, HO was considered to be a rare entity (22). However, a limitation of the studies is that the authors did not identify how many, if any, of the individuals who developed post-traumatic HO also had comorbid traumatic brain injury or spinal cord injury. This is important because HO development in the traumatic brain injury and spinal cord injury populations is common, with an incidence reported to be

as high as 77% (25,26). The unusually high incidence in the combat-related adult post-traumatic amputee may have been primarily due to a comorbid etiology and not the amputation.

Management of HO includes identification and monitoring development with a triple-phase bone scan. The bone scan can detect HO as early as two to four weeks after symptom onset, well before it is present on x-ray. Indomethacin is used in the acute phase (before presence on x-ray) with the goal of reducing the inflammatory environment. Bisphosphonates, specifically etidronate (27), can be used throughout HO development to expedite maturation, minimize size and manage pain. If the HO continues to be symptomatic, ie, pain or range of motion restriction, surgical excision may be considered once the lesion has matured and is no longer active on bone scan.

In the presented case, the HO was believed to be in the proximity of the median nerve in the forearm. The PLP experienced by this individual involved extreme flexion and cramping of the digits innervated by the median nerve. The HO may have developed at the site of the transected median nerve, with the nerve itself creating a pro-inflammatory environment conducive to HO development.

Calcitonin in PLP and HO

There are only three studies investigating the use of calcitonin in PLP (18-20) (Table 1), and only Jaeger and Maier (20) had long-term follow-up at one year, but all three studies reported a positive effect on pain control. The action of calcitonin in the treatment of PLP is not fully understood and currently there are four postulated mechanisms focusing on both peripheral and central sites of action (18-20,28,29):

1. Calcitonin leads to increased concentration of β endorphins, which will act on μ receptors improving pain control analogous to opioid mechanism of action.
2. Stimulation of descending serotonergic inhibitory neurons to improve centrally mediated pain signal modulation at the level of the spinal cord, which would lessen centrally directed pain signalling.
3. At the site of injury, calcitonin is believed to reduce the production of prostaglandins and other proinflammatory cytokines, which would lessen local, chemical irritation of the injured sensory nerve.
4. Modulate activity of voltage-gated Ca^{2+} channels on nociceptive neurons resulting in hyperpolarization, making action potential generation more difficult, which would lessen the frequency and intensity of pain impulses directed centrally from the injured peripheral nerve.

Regarding the management of HO, there is only one animal study available in the literature (30). Günal et al (30) implanted demineralized bone matrix in two groups of rats; group 1 received calcitonin and group 2 did not. The group treated with calcitonin had a net decrease in implant weight with no new bone formation while group 2 had a net increase in bone mass. No mechanism to explain the finding was provided by the authors. However, our current understanding of HO development points to the need for a proinflammatory environment and calcitonin is believed to work, in part, by reducing the production of inflammatory cytokines. A possible explanation is that calcitonin works by creating an environment less conducive to HO formation.

In the present case, the HO identified was in the territory of the median nerve and it is possible that the injured nerve was contributing to a proinflammatory environment facilitating HO development as well as chemical irritation of the nerve. In time, the HO may also have contributed to mechanical irritation of the median nerve, creating a positive feedback loop. The calcitonin may have helped by modulating pain through its μ receptor activity and/or the descending serotonergic inhibitory neurons; however, by reducing local prostaglandin production, the calcitonin may have reduced the chemical irritation on the median nerve and helped to stop HO progressing by reducing the amount of inflammation in the soft tissue.

CONCLUSION

It appears that the etiology of PLP is multimodal, with involvement of the injured peripheral nerve, cord level signal modulation and central somatosensory processing areas. This degree of complexity may be one of the reasons why persistent PLP is so difficult to manage and often requires a multimodal treatment plan. In the present paper, the mechanism of action of calcitonin was explored and the overlap between the calcitonin therapeutic targets and the PLP multimodal etiology was discussed. Theoretically, calcitonin targets the various proposed pain generators associated with PLP, which identifies it as a possible treatment option. This was true in the treatment-resistant case discussed in the present report. Also of interest is the possibility of comorbid HO in PLP mainly due to the proinflammatory environment created by the injured peripheral nerve. Interestingly, calcitonin's mechanism of action peripherally may be effective at limiting HO progression in this scenario because it reduces the release of proinflammatory cytokines from the injured peripheral nerve.

Calcitonin should be considered in the management of treatment-resistant PLP and more reports regarding its use are needed. Calcitonin may also provide a unique advantage over other analgesic medication in the management of PLP with comorbid HO.

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