

LETTER TO THE EDITOR

Perineural Injection Therapy in the Management of Complex Regional Pain Syndrome: A Sweet Solution to Pain

Dear Editor,

Perineural injection therapy (PIT) is one of the latest advancements in regenerative medicine. It targets cutaneous nerves as a potential pain generator. First described by Dr. Paul Pybus and Dr. Roger Wyburn-Mason, PIT targets neurogenic inflammation in subcutaneous nerves that potentially generates pain [1,2]. PIT was further refined by Dr. John Lyftgoft using dextrose injection, which provided substantial pain control in a series of 300 Achilles tendinopathy [3]. However, this treatment approach remains largely unknown; thus we sought to document the effect of PIT in the management of complex regional pain syndrome (CRPS) and its outcome on pain and functional restoration.

Three patients who fulfilled the Budapest Criteria for CRPS were treated with series of PIT. The cutaneous nerves were palpated along its course until tender chronic constrictive injury (CCI) points were encountered. (CCI points are formed by cutaneous nerve swelling proximal to its point of penetration of the fascial layer at the fascial transition zone [FTZ].) Once identified, the CCI points were cleansed with alcohol skin prep; using a 25G hypodermic needle, 2 to 5 mL of 5% dextrose was administered subcutaneously directly at the CCI points. On average, the patients received 1 to 1.3 injections per week to tender CCI points of the cutaneous nerves supplying the dermatomes overlying the affected area or joint.

Table 1 summarizes the clinical features of the PIT recipients. The first patient sustained a left anterior talofibular ligament injury six months prior and presented with recalcitrant ankle pain with left foot and toes swelling, skin changes, and allodynia affecting gait. The second patient presented with left shoulder pain after a fall onto the left shoulder. At presentation six months later, she had limited neck, shoulder, and elbow range of motion and would prevent any handling of the left shoulder and upper limb. The third patient sustained a traumatic amputation of his right fourth and fifth distal interphalangeal joints with severe unrelieved pain at two months post-trauma, with allodynia and edema involving the amputated fingers up to the right elbow, loss of all third finger joints, loss of fourth and fifth metacarpophalangeal and proximal interphalangeal joints' range of motion, and skin changes. Pain was assessed prior to PIT and weekly thereafter; pain score evolution is summarized in Figure 1. Figure 2, A and B, graphically documents the physical findings of the first patient prior

to and upon completion of PIT. Figure 3 depicts the tender CCI palpated and injected in the first case. At the end of the PIT series, all three patients had resolution of their presenting CRPS features and were able to actively participate in therapy.

Neurogenic inflammation plays an important role in the occurrence of CRPS and is the basis of managing CRPS with PIT [4]. Soft tissues are innervated by peptidergic sensory nerves with transient receptor potential vanilloid-type 1 (TRPV-1) receptors. Upregulation of TRPV-1 receptors in response to pro-inflammatory signals from injured tissues leads to production of substance P and calcitonin gene-related peptide (CGRP) by the peptidergic nerves [1]. Substance P is responsible for pain while CGRP causes breakdown of soft tissue structures, neurogenic inflammation, and inflammation of the surrounding tissues. The nerve supply to the nerves called *nervi nervorum* can also release similar neurodegenerative peptides onto the C fibers while in a pathological state [5].

Nerve irritation can happen through repetitive muscular contractions and the sudden change in direction of sensory nerves travelling between muscle and fascial layers, predisposing the TRPV-1 nerves to irritation or trauma. Irritation to a superficial nerve supplying cutaneous sensation over a joint may cause transmission of ectopic impulses in prodromic and antidromic directions. Prodromic transmission leads to pain perception via the somatosensory cortex and generation of reflex muscle spasm through the spinal cord ventral horn cells. The antidromic transmission toward the blood vessels releases substance P [6]. Trauma to the superficial nerve can affect the deeper structures based on Hilton's law, which states that nerves supplying a joint also supply both the muscles moving the joint and the skin covering the articular insertion of those muscles as a result of embryological development [7]. Cutaneous nerve trauma may precipitate nerve edema proximal and distal to the injury. Swelling along the traumatized cutaneous nerve will reach the nerve's fascial penetration points, which will cause strangulation of the affected nerve as it passes through the fascial transition zone, creating a CCI point. These constrictions inhibit the flow of nerve growth factors essential for nerve health and repair [8]. Repetitive muscle dysfunction also changes fascial tension and creates a CCI point [1].

Dextrose binds to presynaptic calcium channels, inhibiting the release of neurodegenerative peptides, thus

Table 1 Clinical parameters of patients receiving perineural injection therapy for CRPS

Budapest Criteria	Case 1		Case 2		Case 3	
	Pre	Post	Pre	Post	Pre	Post
Continuous and disproportionate pain	√	×	√	×	√	×
Sensory	√	×	√	×	√	×
Vasomotor	√	×	√	×	√	×
Sudomotor/oedema	√	×	×	×	√	×
Motor/trophic changes	√	×	√	×	√	×
Impairment	Reduced left ankle aROM	Full left ankle aROM	Reduced neck, left shoulder, and left elbow aROM	Full aROM	Loss of 3rd finger and left elbow aROM	Full left elbow aROM
Functional outcome	TUG: 300sec	TUG: 20 sec	DASH: 91.7	DASH: 5.0	DASH: 99.2	DASH: 4.2
CCI points treated	Left medial and lateral sural cutaneous nerves CCI	Left medial and lateral sural cutaneous nerves CCI	Left medial, intermediate and posterior supraclavicular cutaneous nerves CCI and the left punctus nervosum	Left punctus nervosum	Right medial antebrachial and ulnar nerve CCI	

aROM = active range of motion; CCI = chronic constrictive injury; CRPS = chronic regional pain syndrome; DASH = The Disabilities of the Arm, Shoulder and Hand score; NRS = numerical rating scale; TUG = timed up and go test.

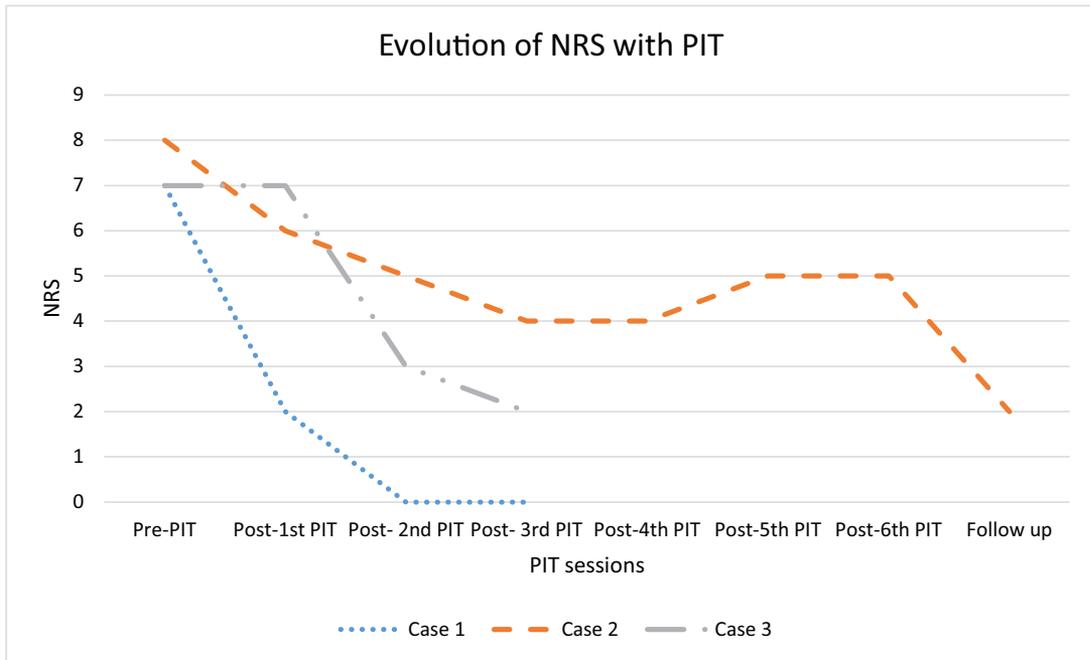


Figure 1 Numeric rating scale evolution during the course of PIT in three recipients with complex regional pain syndrome. NPT = ; NRS = numerical rating scale of pain; PIT = perineural injection therapy.



Figure 2 Patient 1 with complex regional pain syndrome affecting her left foot and ankle. (A) Pre-perineural injection therapy (PIT). (B) Post-PIT.

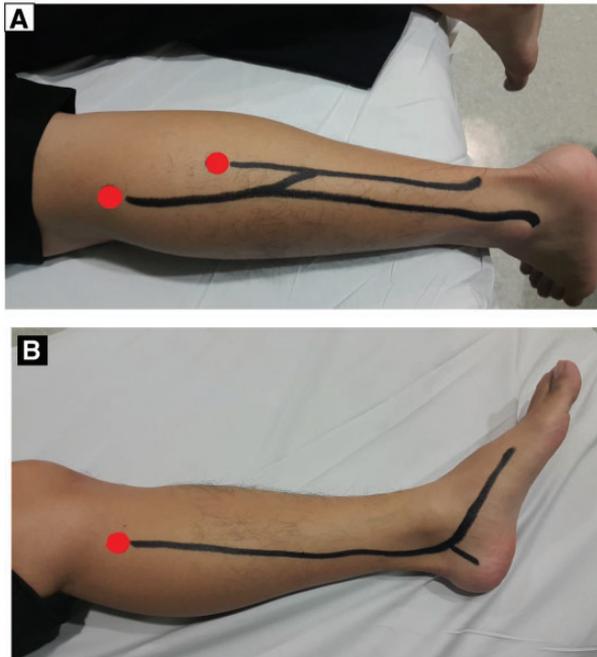


Figure 3 (A) Medial and lateral sural cutaneous nerves. (B) Saphenous cutaneous nerve. Dots indicates the chronic constrictive injury sites, which are injected subcutaneously.

decreasing neurogenic inflammation. This results in pain reduction, regression of soft tissue swelling, and relief of CCI constrictions, restoring normal nerve growth factor flow, facilitating nerve repair, and providing almost instantaneous analgesic effect lasting from hours to days [9]. In our observations, repeated PIT results in a stepwise decrease of pain in patients with CRPS.

We have demonstrated the effectiveness of PIT in managing CRPS and the various mechanisms underlying the therapeutic effects of subcutaneous dextrose injections. The treatment cost was nominal, with minimal setup required in the outpatient clinic. No adverse events were encountered, and the clients' acceptance of the procedure was good. We believe further clinical acceptance and research of this therapeutic modality will help

advance understanding of neurogenic inflammation's role in neuropathic pain conditions. We believe that this therapeutic modality holds promise to more effective pain management.

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References

- 1 Reeves KD, Lyftogt J Prolotherapy: Regenerative Injection Therapy. In: Waldman SD (ed): Pain. Management. Philadelphia; Saunders (Elsevier), 2nd ed; 2011:1027–44.
- 2 Geppetti P, Holzer P. Neurogenic Inflammation. Boca Raton, FL: CRC Press; 1996.
- 3 Lyftogt J. Subcutaneous prolotherapy for achilles tendinopathy: The best solution? *Aust Musculoskeletal Med* 2007;12(2):107–9.
- 4 Birklein F, Schmelz M. Neuropeptides, neurogenic inflammation and complex regional pain syndrome (CRPS). *Neurosci Lett* 2008;437(3):199–202.
- 5 Lyftogt J. Subcutaneous prolotherapy treatment of refractory knee, shoulder and lateral elbow pain. *Aust Musculoskeletal Med* 2007;12(2):110–2.
- 6 Pybus P. Intra-neural injections for rheumatoid arthritis and osteoarthritis. *Arthritis Trust Am* 1989;9–22.
- 7 Hilton J. *On Rest and Pain*, 2nd edition. New York: William Wood & Company; 1879.
- 8 Bennett G, Xie Y. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain* 1988;33(1):87–107.
- 9 Lyftogt J. Neural Prolotherapy Workshop meeting. Ferrara, Italy: The Hackett Hemwall Foundation and the Italian Society for Prolotherapy; 2010.