

Clinical trial

# Cryoanalgesia for post-herpetic neuralgia: a new treatment

Liliana Calandria, MD

From the Dermatology Clinic, José Benito Lamas, Montevideo, Uruguay

**Correspondence**

Liliana Calandria, MD  
Dr. Liliana Calandria  
Luis de la Torre 795  
CP 11300 Montevideo  
Uruguay  
E-mail: dracalandria@gmail.com,  
lbpc@adinet.com.uy

Conflict of interest and disclosure:  
None.

**Abstract**

The existent therapeutic options for post-herpetic neuralgia (PHN) are varied, albeit not sufficiently effective. The aim of this study was to try a new treatment modality for PHN. A spray of liquid nitrogen (LN) was used in 47 patients suffering from PHN as a stimulator of a mechanism not yet completely understood. The LN spray was carefully applied (so as not to freeze the skin surface) along the diseased sensory nerve dermatome, at weekly sessions lasting for 30 s each, with a mean of three applications per patient. The area corresponding to the dermatomes affected by the herpes zoster satisfactorily attenuated the herpetic neuralgia in all patients. Before the sixth treatment session, good or excellent improvement was obtained in 94% of the study patients. Pain was eliminated with one session in nine patients (19%), and with two sessions in eight patients (17%). We conclude that this non-freezing technique is absolutely safe and injury-free, and is very efficient in calming PHN.

**Introduction**

Herpes zoster (HZ) is an infectious, viral, self-limiting disease, restricted to only a few cutaneous dermatomes. It is characterized by an almost always unilateral vesicular eruption associated, or not, to neuropathic pain.<sup>1</sup> The varicella zoster virus that has been dormant in sensory ganglia after recovery from chicken pox (primary infection) may undergo reactivation due to diminished immune competency.<sup>1</sup>

The incidence of HZ is approximately 215 per 100 000 person/years in the USA,<sup>2</sup> and 300 per 100 000 person/years in Europe.<sup>2</sup> In about 50% of cases, the lesions occur in the thoracic dermatomes, particularly the T5 and T6, followed by the trigeminus (20%), especially the ophthalmic branch, and the lumbar and cervical regions (10–20%), the sacral region rarely being affected.<sup>1</sup> Post-herpetic neuralgia (PHN) is a complication of HZ, defined as pain that persists for more than 4 weeks after resolution of the HZ lesions. This neuralgia affects 16% of patients under 60 years old, and about 47% older than 60 years.<sup>3,4</sup> The pain is of the neuralgic type and extends over the cutaneous area innervated by the affected nervous segment. The intensity of the pain may incapacitate the patient in his/her daily activities and even prevent nocturnal rest, thus affecting the patient's psyche, humor and resistance.<sup>1</sup> The duration of the condition is imprecise, as it frequently becomes chronic; it can last for months or even years.<sup>4</sup> The probability of its occurrence is higher in the elderly or in persons with a compromised

immune system, namely transplant and human immunodeficiency virus (HIV)-positive patients and those undergoing cancer chemotherapy.<sup>5</sup>

Medical treatments instituted so far have produced disappointing and frustrating results. The clinical data indicate that tricyclic antidepressants are effective as analgesics in 50% of patients, at 6 weeks of treatment.<sup>6</sup> These act on the endogenous neuromodulation system by inhibiting serotonin and/or noradrenaline reuptake.<sup>4</sup> These drugs have been recommended as first-line treatment for neuropathic pain.<sup>7</sup> The recommended doses are: 10–25 mg/d (amitriptyline) and 40 mg/d (fluoxetine–paroxetine). However, tricyclic antidepressants are often contraindicated due to poor tolerance from elderly patients with PHN, or due to adverse effects (cardiotoxicity, postural hypotension, arrhythmia, syncope, drowsiness, urinary retention, dry mouth, nausea, vomiting and orthostatic hypotension).<sup>8,9</sup> Classically, the use of carbamazepine and opioids<sup>9</sup> obtained variable results. Milder analgesics, anticonvulsant drugs [of the carbamazepine type (300–1200 mg/d in three divided doses), lamictal] and valproic acid (valporate<sup>®</sup>) in patients with carbamazepine intolerance have been tried with good results, achieving up to 75% improvement of the neuralgia with the use of carbamazepine.<sup>5</sup> More recently, gabapentin,<sup>8</sup> a new anticonvulsant, may be considered first-line therapy due to its efficacy<sup>10</sup> and few side-effects (drowsiness). The use of pregabalin is more controversial in view of the doses of up to 600 mg/d (starting with 75 mg/d).<sup>10</sup> On the other hand, the topical use of

lidocaine<sup>11</sup> and capsaicin<sup>9</sup> cause important local side-effects (burns, pruritus, erythema) in up to 50% of cases. Among other reported treatments, intrathecal administration of methylprednisolone<sup>9</sup> seems to produce good results, but it has safety issues that require further investigation. Also described are the use of loco-regional block by neurosurgical procedures, or neuroselective transcutaneous electric stimulation and the use of wide-band UVB in affected dermatomes, starting at 20 mJ/cm<sup>2</sup>, with gradual increases of 10 mJ/cm<sup>2</sup> in each session, to a maximum of 100 mJ/cm<sup>2</sup>, 3 sessions/week.<sup>12</sup>

The cryoanalgesia described to date is a technique that consists of the direct freezing of the nervous fibers, and is used almost exclusively for neuralgias secondary to thoracotomies.<sup>13</sup> Yet, it was questioned whether non-direct cryoanalgesia of the non-exposed nerve would be viable, and if there could be a method that would use “cold” without causing tissue injury.

Here is where the “non-freezing technique” (NFT) claims its place. The technique, completely safe and injury free, uses liquid nitrogen (LN) spray topically applied over the skin, without freezing it, thus calming the PHN.

## Materials and methods

From 1992 to 2007, 47 patients suffering from PHN were treated at the Dermatology Clinic, Montevideo, Uruguay. Of these, 35 were men and 12 were women. Their mean age was 73 years (range: 45–95 years; Table 1). Table 2 shows the diverse topography of the HZ, with a predilection for the thoracic location (51%).

**Table 1** Age of patients

Age (years)	Patients (n = 47)
<50	3
51–60	2
61–70	10
71–80	19
>80	13

Mean age = 73 years.

**Table 2** Anatomical location of the HZ

Location	Patients (n = 47)	%
Cephalic	13	27.7
Cephalic/cervical	3	6.4
Thoracic	24	51.0
Lumbar	2	4.3
Abdominal	4	8.5
Leg	1	2.1

**Table 3** Evolution of the PHN to the acute phase

Duration	Patients (n = 47)
1 week–1 month	19
2 months–1 year	15
>1 year	13

Forty-three patients (91.48%) had previously been, or were being, treated pharmacologically (minor analgesics or opioids, anticonvulsants, antidepressants) at the usually recommended doses.

Evolution of the post-herpetic pain to the acute phase is detailed in Table 3. Although the 19 patients whose evolution leading to the acute phase took between 1 week and 1 month cannot, truly and by definition, be considered as having PHN, they were included in the study on account of their age and intensity of their pain, with the aim of alleviating their suffering. All 47 patients were treated with this new technique.

## Technique

The “NFT” consists of the application of LN spray perpendicularly to the skin, on the dermatome affected by the neuralgia, without allowing it to freeze, forming a nitrogen cloud.<sup>14</sup> The distance between the target skin and the extremity of the device is approximately 15 cm.

A Cry Ac<sup>®</sup> Brymill apparatus with a metal nozzle coupled to its extremity (Figs 1 and 2) was used. To this, another piece (from a variety of pieces with different exit-orifices; Fig. 1) is adapted, to allow for the adequate nitrogen release and cloud formation. In the present study, the piece used was 14G (Abbocath [R] 14G), after having found, in an earlier trial,<sup>15</sup> that this wider diameter (larger exit-orifice) provided the best results. The LN spray was applied several times, with roughly circular



**Figure 1** Abbocath<sup>®</sup> pieces with different calibers and metal adaptors



**Figure 2** Metal adaptor

movements, over the whole affected area, for about 30 s, in a resultant nitrogen cloud and without freezing the skin. As an example, if the neuralgia is located in the chest, the operator's hand guides the device from the front towards the back, in circular movements, and then returns to the front, spraying the entire affected area. Application in this manner, for periods of about 30 s, cools the painful area without freezing it. The procedure is repeated, at weekly intervals, until the pain has improved to an acceptable level. Between one and 20 NFT sessions (mean of 4.8) are required (Table 4).

Assessment of the HZ neuralgic pain is made by the patient, who measures and records its intensity using a scale from 1 (minimum) to 10 (maximum), on a daily basis. Starting at the first appointment, the patient is asked to keep a daily chart detailing the characteristics of the pain (Fig. 3). The chart is evaluated at each appointment for the effects that require improvement, as often enough patients forget the intensity of

**Table 4** Number of NFT sessions performed

No. of sessions	Patients (n = 47)
1	9
2	8
3	5
4	7
5	4
6	5
7	2
8	1
10	1
12	1
14	2
20	2

Mean number of NFT sessions = 5.

Pain chart	Intensity of pain (1–10)	Type of pain	Duration of pain	Analgesics taken	Does the pain wake you up during the night?
Morning					
Midday					
Afternoon					
Evening					

**Figure 3** Chart for patients' daily self-assessment of the pain characteristics

the initial suffering or even the extent of the painful area. This is particularly common for elderly and chronic patients.

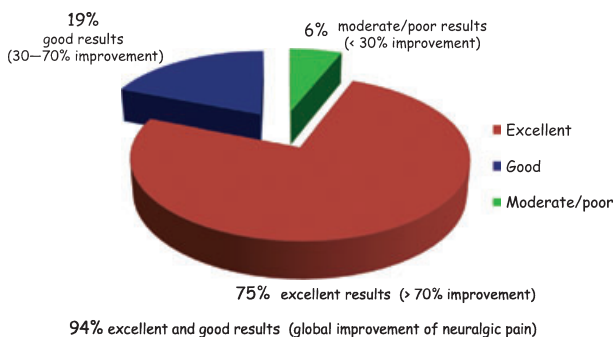
**Results**

Forty-seven cases of PHN have been treated using this "NFT", with very good results.

Immediate improvement of the symptoms is observed, although the intensity is variable. The first signs of improvement, according to the patients, are that they no longer wake up in pain during the night, and that they need to take fewer analgesic drugs as their effect lasts much longer. Many patients report that their pain reaches maximum relief between the third and fourth NFT sessions. In this series, however, the pain was eliminated with one NFT session in nine patients (19%), and with two sessions in eight patients (17%).

Improvement occurs in inverse relation to the number of sessions subsequent to the sixth session; after session no. 6, improvement gets smaller each time. The mean number of NFT sessions was 5.

The results were excellent in 75% of the cases. This was quantified as a reduction in pain greater than 70%; good results (30–70% pain reduction) were obtained in 19%; and moderate or poor results (pain reduction <30%) in only 6% of patients. Considering both the good and excellent results, a global improvement was achieved in 94% of patients (Fig. 4).



**Figure 4** Results of treatment

The chart in Fig. 3 was extremely useful. The advanced age of the majority of patients, their general health or their anxiety concerning the results of the pain management technique often clouded their judgment in the initial appointments when they stated that there had been no improvement in their condition. When evaluating the charts, however, it was obvious that in the majority of patients, from the beginning of treatment, there had been improvement as to the type of pain (the intensity of both sharp and acute pain was reduced); many patients reported that they did not require as much pain medication or that the analgesic drugs' effect lasted much longer; a common report was that they no longer woke up during the night because of the pain. Improvement was effective and stable, although not complete in a few patients.

A particular case of interest is that of a 67-year-old man with a personal history of bilateral myelitis of the lower limbs and a bypass of the right femoral artery. He suffered from PHN affecting the right lumbar, gluteal and testicular regions, and extending to the anterior thigh and right knee. He had been in pain for almost 2 years, and received treatment with gabapentine, amitriptyline, pregabalin and opioids, singly or in combination, without success. Due to the patient's antecedents, nerve block was contraindicated and, as a last resource, he was referred for treatment with the "NFT". This patient came to the Clinic with crutches, walking with great difficulty; he could not drive his car and was profoundly depressed; he described his pain as permanent and very intense. The first NFT session reduced the extent of the painful area, eliminating the thigh pain. After the third session, he could walk up to 1400 m without pain; he assessed his pain as level 3 and suspended the opiates; the pain paroxysms subsided rapidly (<5 min) and the testicular pain ceased. After five sessions, he could walk without the crutches and could drive his car. His treatment was complete with two more sessions (a total of seven), having achieved 95% improvement of the pain and cessation of all medication.

## Discussion

Until now, the multiple therapeutic options available have proven to be insufficient to effectively manage PHN. The "NFT" using a spray of LN as a cytokine stimulant immunomodulator can control PHN pain. Cryonecrosis must not be permitted to occur.

This technique constitutes an efficient tool to improve this often incapacitant pain, particularly in its acute phase, thus permitting the patient's psychological and social rehabilitation. The duration of each application depends on the apparatus used and the intensity of the LN spray released by the device. In the present study, the

piece used was 14G (Abbocath [R] 14G). In a previous trial,<sup>15</sup> various end-pieces with different exit-orifice diameters were tried, and it was found that Abbocath 14G obtained the best results within the shortest period.

It should be stressed that the technique does not involve freezing of the skin, nor does it cause any type of burn or erythema. The mechanism triggered by cooling the affected dermatomes is sufficient to attenuate the pain in all its facets.

## Acknowledgment

The author would like to thank Dr. J.C. Almeida Gonçalves for his thoughtful suggestions and his critique of this manuscript, and particularly for his encouragement to write this article; the late Dr. Gustavo Velazco Paz, with whom the author learned cryosurgery; and Professor Raúl Vignale for his final review and correction of the manuscript.

## References

- 1 Hight AS, Kurtz J. Viral infections. In: Champion RH, Burton JL, Ebling FJG, eds. *Rook's Textbook of Dermatology*, 5th edn. Oxford: Blackwell Scientific Publications, 1992: 888–892.
- 2 Donahue JG, Choo PW, Manson JE, et al. The incidence of herpes zoster. *Arch Intern Med* 1995; 155: 1605–1609.
- 3 Volpi A, Gross G, Hercogova J, et al. Current management of herpes zoster: the European view. *Am J Clin Dermatol* 2005; 6: 317–325.
- 4 Savin JA. Post-herpetic neuralgia. In: Champion RH, Burton JL, Ebling FJG, eds. *Rook's Textbook of Dermatology*, 5th edn, Vol. 4. Oxford: Blackwell Scientific Publications, 1992: 2475.
- 5 Albrecht MA. Clinical features of varicella-zoster virus infection: herpes zoster. Up to date (version 10.3) May 2006. <http://www.uptodate.com/>.
- 6 Lancaster T, McQuay H. Tricyclic antidepressants, capsaicin, gabapentin, and oxycodone are effective for postherpetic neuralgia. *ACP J Club* 2002; 137: 52.
- 7 Sabatowski R, Galvez R, Cherr DA, et al. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomized, placebo-controlled clinical trial. *Pain* 2004; 109: 26.
- 8 Rice AS, Maton S. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. *Pain* 2001; 94: 215–224.
- 9 Hempenstall K, Nurmikko TJ, Johnson RW, et al. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. *PLoS Med* 2005; 2: 628–641.
- 10 Bonezzi C, Demartini L. Treatment options in postherpetic neuralgia. *Acta Neurol Scand (Suppl)* 1999; 173: 25–35.

- 11 Rowbotham MC, Davies PS, Verkempinck C, *et al.* Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. *Pain* 1996; 65: 39–44.
- 12 Jalali MHA, Ansarin H, Soltani-Arabshahi R. Broad-band ultraviolet B phototherapy in zoster patients may reduce the incidence and severity of postherpetic neuralgia. *Photoderm Photoimmun Photomed* 2006; 22 (5): 232–237.
- 13 PAC ANESTESIA-1 C1 laboratorios Abbott (<http://www.drscope.com/pac/anestesia-1/c1/index.htm>).
- 14 Calandria L. Neuralgia post herpética técnica: non freezing technique. In: *Cryomedicine*, Buenos Aires (location): Sociedad Argentina de Criocirugia (publisher) 1996: 143.
- 15 Calandria L. Cómo resolver la neuralgia por herpes zoster. *Tendencias en Medicina* 2005; 27: 117. (<http://www.tendenciasenmedicina.com/tendenciasactual/tendencias27.htm>).