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Case Series

Ultrasound Guided Cryoneurolysis for Treating CRPS-Case Report

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Abstract

Complex Regional Pain Syndrome (CRPS) is a relatively rare, challenging condition, that includes a broad spectrum of sensory, autonomic, trophic and motor disorders that predominantly affect extremities after trauma such as fractures, soft tissue injuries, or surgery.

The syndrome can be divided in CRPS type 1 and CRPS type 2, differentiated by the absence or presence of peripheral nerve damage respectively.

CRPS type 1 occurs without a definable nerve damage but with an initiating noxious stimulus, such as a crush or soft tissue injury, or by prolonged immobilization of the affected limb. Approximately 90% of all CRPS patients have type 1.

CRPS type 2 follows a distinct nerve injury.

Keywords: *Complex Regional Pain Syndrome (CRPS); CRPS Type 1; CRPS Type 2*

Introduction

CRPS is characterized by pain, hypersensitivity (allodynia), swelling, limited range of motion, vasomotor instability and skin changes. Factor analysis demonstrates that signs and symptoms of the syndrome cluster into four subgroups: 1) abnormalities in pain processing that cause allodynia, hyperalgesia, and hyperpathia; 2) skin color and temperature change; 3) neurogenic edema, vasomotor, and sudomotor abnormalities; and 4) a movement disorder and trophic changes [1].

CRPS is a multifactorial disorder with complex etiology and pathogenesis, and the symptoms can differ between patients, disappearing or persisting, or moving/spreading to different locations.

Goals of therapy in CRPS should be pain relief, functional restoration and psychological stabilization, but early interventions are needed in order to achieve these objectives.

We report 5 cases of CRPS; one case involved CRPS of the left foot, one case involved bilateral feet CRPS, one case presented with ankle pain, and 2 cases presented with foot pain. All were successfully treated in our pain clinic using ultrasound-guided cryoneurolysis of the involved nerves.

The aim of this review is to report on the treatment of CRPS with ultrasound-guided cryoneurolysis of the affected nerves.

Case 1

In September 2015, a 24 year-old female presented to our clinic with a 7 year history of left foot pain after a sprained ankle injury while roller-skating. No fracture was seen on MRI. She developed persistent pain in the ankle, initially at the lateral malleolus and then spreading to the dorsum of the foot, eventually encompassing the entire foot.

During the years after the injury, she had been treated with anticonvulsants, tricyclics, opioids, Qutenza® (Capsaicin) patch and two ketamine infusions, without any improvement in the intensity of the pain.

She couldn't walk (at that time she had been wheelchair-bound for 6 years). She complained of limitation in ankle range of motion, as well as a sensation of electric shocks, burning, pins and needles, and numbness across the dorsum of the foot. She had no history of chronic or metabolic disease.

At the time of our intervention, she was being treated with methadone and antidepressant medication. On the Visual Analogue Scale (VAS) of 100 mm, she reported a pain intensity of 90 - 100 mm.

On physical examination, she had edema of her left foot, with asymmetry in skin color and temperature. Allodynia and hyperalgesia were present on the left foot up to 10 cm above the ankle in the pattern of the superficial peroneal nerve. She was diagnosed with CRPS-1.

At the first visit in the clinic, the patient received an ultrasound-guided diagnostic injection using 1 mL of 1% lidocaine at the superficial peroneal nerve with dramatic pain reduction. After 3 minutes, the pain on the VAS decreased from 90 - 100 mm to 0 - 10 mm. We could mobilize the patient out of the wheelchair, and the pain relief lasted for 4 hours after the blockade.

We repeated the injections 5 times, with one week in between the treatments, and after every procedure, the pain relief lasted for longer period of time. After this series of injections, we performed one treatment of ultrasound-guided cryoneurolysis on the superficial peroneal nerve, using the 1.3 mm triangular shaped probe, with two 2-minute freezing cycles, followed by 30 seconds of thaw period in between.

The patient noted instant pain relief after the cryoneurolysis, with the VAS decreasing from 90 mm to 10 mm and free movement of the ankle. Patient was advised to perform physiotherapy after the treatment to improve the motor dysfunction.

Patient underwent a follow up 3.5 years later. She is completely pain free, VAS 0, off of the methadone and the antidepressant medicine; she is out of the wheelchair and she feels no need for further treatments.

Case 2

In March 2016, a 21 year-old female presented with pain in both feet for 10 years after a fall from a horse. No fracture was seen on MRI or X-ray During the years after the injury, she has been treated with anticonvulsants, tricyclics and opioids, without a positive effect on the pain.

She reported a pain intensity of 80 mm.

Pain was provoking when touching cold objects with both feet. EMG was consistent with small fiber neuropathy.

On physical exam, both feet were noted to be cyanotic, with swelling, hyperalgesia and allodynia up to the knee level. The pain was present in the pattern of the superficial peroneal nerve bilaterally.

At the first visit to the clinic, the patient received an ultrasound-guided diagnostic injection 1mL of 1% lidocaine at the superficial peroneal nerve, with remarkable effect on the pain. After 2 minutes, the VAS decreased from 80 mm to 0 mm. She could walk on bare feet without pain immediately after the injection. The cold surface was no longer a pain provocateur, and the allodynia and hyperalgesia disappeared. The normal sensation was back on both feet and the patient felt normal muscle strength with normal skin coloration and a warm feeling of the feet. The patient couldn't provoke the pain after the injection.

We repeated the injections 4 times, with one week in between the treatments, and we could notice that the patient became more confident with each procedure and the effect of the blockade lasted longer. After this series of injections, we performed one treatment of ultrasound-guided cryoneurolysis on the superficial peroneal nerves bilaterally, using the 1.3 mm triangular-shaped probe, with two 3-minute freezing cycles, separated by 2 minutes of thaw period in between.

At the follow up visit 6 months after the cryoneuroablation, the patient described a return of a shocking pain in her right foot. We repeated the diagnostic block on the right superficial peroneal nerve, with 0.5mL of 1% lidocaine with good relief of the pain. The shocking pain disappeared for the next 12 hours. The next day, we did an ultrasound- guided cryoneurolysis, with two 3-minute freezing cycles, separated by 2 minutes of thaw cycle.

The shocking pain disappeared just after the treatment and at the 1 year follow up, the pain hasn't returned.

Follow up after 3.5 years confirmed that the patient is completely pain free, VAS 0 and she feels no need for further treatments.

Case 3

In April 2017, a 46 year-old female presented with pain in the left foot for 8 years, after a sprained ankle injury with damage to the ligaments on the left ankle. No fracture was seen on MRI and X-ray After the injury, she was operated on 3 times for ligament repair operations, without relief. During the second operation, there was a surgical injury of the sural nerve, with the development of chronic neuropathic pain after the operation.

In 2013, she underwent a surgical resection of the sural nerve in order to decrease the pain, but, unfortunately, there was no improvement in the intensity of pain. During the years, she has been treated with anticonvulsants, tricyclics, opioids and Qutensa® patch. On the VAS, she reported intensity of pain of 70 mm.

On physical exam, neuropathic pain presented along the pattern of the sural nerve. She was diagnosed with CRPS-2.

At her first visit to the clinic, the patient received an ultrasound-guided diagnostic injection with 0.5 mL of 1% Lidocaine on the sural nerve, with a notable effect on the pain. After 2 minutes, the VAS decreased from 70 mm to 20 mm. The normal sensation was returned to left foot and the neuropathic pain disappeared.

One week after the positive diagnostic injection, the patient was treated with an ultrasound-guided cryoneurolysis of the sural nerve using the 1.3 mm blunt tipped probe, with two 2-minute freezing cycles, followed by 1 minute of thaw period in between.

After the treatment, the patient's VAS decreased from 70 mm to 10 mm.

2.5 years later, the patient is not completely pain free (VAS 20 mm), but she feels no need for further treatments.

Case 4

In August 2018, a 15 year-old young lady presented with pain in her left foot for 4 years, after a sprained ankle injury, with damage to the ligaments of the left ankle. No fracture was seen on MRI and X-ray. After the injury, she underwent 2 -ligament repair operations. After the operations, the patient developed chronic neuropathic pain in the left foot.

Over the years, she had been treated with anticonvulsants, tricyclics and Durogesic® (Fentanyl) patches.

At the physical examination, patient presented with pain along the medial side of the foot, associated with allodynia and hyperalgesia. She was diagnosed with CRPS-2.

Using Ultrasound, we could recognize/visualize 3 neuromas at the site of the previous surgeries. We performed an ultrasound-guided diagnostic injection with 0.5 mL of 1% Lidocaine around each of the neuromas, with remarkable effect on the pain. After 5 minutes, the VAS decreased from 90 mm to 10 mm, and the allodynia and hyperalgesia disappeared.

The injection was repeated 3 times over the next few days. After this series of positive injections, the patient was treated with ultrasound-guided cryoneurolysis of all 3 neuromas, using the 1.3 mm blunt-tipped probe, with two 3-minute freezing cycles, separated by 2 minutes of thaw cycle.

At the follow up visit 1 month after the treatment, patient claimed only shocking pain in part of the medial side of the foot. We repeated the diagnostic injection with 0.5 mL of 1% Lidocaine with instant pain relief.

The next day, we did the ultrasound- guided cryoneurolysis, with two 3-minute freezing cycles, separated by 2 minutes of thaw cycle.

The shocking pain disappeared just after the treatment, and at the 1 year follow up, the pain hadn't returned.

Case 5

In November 2018, a 20-year-old female, presented with pain in left foot for 8 years, after a severe sprained ankle injury; for 6 weeks, a fracture of the lateral malleolus went undiagnosed on MRI and X-ray After the injury, the fracture was conservatively treated with a fracture boot for 6 weeks. During this period, the patient developed chronic neuropathic pain in the left ankle and foot.

Over the years, the patient was treated with anticonvulsants, tricyclics, opioids, Qutenza® patch and several steroid injections with only a short positive effect on the pain. She was eventually diagnosed with CRPS-2.

On physical examination, the left foot and ankle were noted to be cyanotic, with swelling, hyperalgesia and allodynia up to the knee level. The pain was present in the pattern of the superficial peroneal nerve.

During her first visit to the clinic, the patient underwent an ultrasound-guided, diagnostic injection at the superficial peroneal nerve using 0.5 mL of 1% Lidocaine with good relief of the pain. After 10 minutes, the VAS decreased from 80 mm to 0 mm, and the allodynia and hyperalgesia disappeared. The normal sensation returned to the foot and ankle, and the patient felt normal muscle strength with normal skin coloration and warm feeling of the foot. The patient couldn't provoke the pain after the injection.

We repeated the injection 4 times, with one week in between the treatments, and after this series of injections, we performed one treatment of ultrasound-guided cryoneurolysis of the superficial peroneal nerve, using the 1.3 mm triangular-shaped probe, with two 3- minute freezing cycles, separated by 2 minutes of thaw cycle.

Follow up after 6 months found the patient to be completely pain free, VAS 0 and she feels no need for further treatments.

Discussion

Pathophysiology

The pathophysiology of CRPS is not fully understood; it is unclear and controversial.

The exact mechanism of disease onset and progression remains unknown. CRPS appears to be multifactorial with evidence pointing to components of inflammation, autoimmune factors, neuronal plasticity and autonomic dysregulation. Over time, the clinical features spread usually proximally and very rare distally and can even emerge on the opposite or ipsilateral limb.

The diagnosis of CRPS is clinical, but a variety of tests help in the exclusion of other diagnoses. Patients with suspected CRPS should have a neurological examination, and nerve conduction velocity studies and EMG should be performed to confirm nerve lesions.

Treatment for peripheral neuropathic pain has been limited to either treating underlying cause (such as diabetes) or using medication such as tricyclic antidepressants, anticonvulsants and opioids to manage the symptoms.

A wide variety of therapeutic approaches are proposed for treating of CRPS, but all of them are unpredictable and of variable efficacy. Patients in the early phases of CRPS are more likely to respond to sympathetic ganglion blocks, as their symptoms are still sympathetically mediated [2]. Aggressive physical therapy has also been a mainstay of CRPS treatment.

However, these therapies presume that the underlying process of CRPS is sympathetically mediated, rather than that the sympathetic symptoms are the response to the process.

Albrecht., *et al*. [3] in 2006, and Oaklander., *et al*. [4] in 2009, both felt that some form of initial nerve trauma (and the subsequent ischemia) was "an important trigger for the cascade of events leading to CRPS" [5].

Coderre and Bennett [6] proposed that "the fundamental cause of the abnormal pain sensation is ischemia" and hypothesize that the role of the sympathetic nervous system in CRPS I "is a factor that is not fundamentally causative but may have an important contributory role in early-stage disease".

They also suggested that ischemia provides a "unifying idea that relates the pathogenesis of CRPS-I to that of CRPS-II", suggesting that the distinction between the two diagnoses is a matter of degree and not pathology.

Peripheral nerve entrapment, triggered perhaps by the edema of the initiating trauma, has more recently been proposed as the underlying etiology of CRPS. Dellon., *et al*. [7] in 2009 hypothesized that chronic pain input to the spinal cord is misdiagnosed as CRPS I, and that chronic nerve compression and inflammation (i.e. CRPS II) can be the source of these painful CNS inputs. They performed a retrospective review of 100 consecutive patients with the diagnosis of CRPS I based on the following criteria from the International Association for Study of Pain [8]:

- **Absolute:** Pain extending outside the area of trauma, impaired extremity function, and either cold or warm perceptions or temperature changes in the affected extremity.
- **Relative:** Edema, increased or decreased hair or nail growth, hyperalgesia, allodynia, abnormal skin coloring.

Seventy of those 100 patients had documentation of chronic peripheral nerve entrapment based on abnormal sensory testing, a positive Tinel's sign at the site of known anatomic narrowing, and temporary response to a local anesthetic injection (without steroid). They noted "good" to "excellent" relief in 80% of the patients after a surgical release.

Clinical observations support the hypothesis that the initial site of pain reflects the most affected nerve, and treatment of that nerve can significantly decrease the overall pain.

The use of peripheral nerve injections (diagnostic blocks), can diagnose the cause of the painful peripheral neuropathy but the relief is usually only temporary; however, cryoneuroablation may offer significant long- term relief.

Cryoneurolysis

Cryoneurolysis (also called cryoablation or cryoneuroablation) is a technique of precise peripheral neurolysis using cold temperatures. A probe is placed percutaneously on the targeted nerve, using landmarks, ultrasound, and/or the built-in peripheral nerve stimulator. When the probe is in the exact right place, a gas (carbon dioxide or N_2O) travels down the center of the probe, where it passes through a tiny opening; this causes the gas to expand and cool the tissues, creating an ice ball. These cold temperatures (-70ºC) cause ice crystals to form in the tissues, which kill the nerves but leave the endoneurium intact, allowing the nerve to grow back without neuroma formation.

Cryoneurolysis results in a second- degree injury to the peripheral sensory nerve. Treatment in this temperature range cause Wallerian degeneration (axonal and myelin degeneration), which occurs with exposure to temperatures between -20°C and -88°C, causing a reversible degeneration of the axon beginning at the site of treatment and proceeding distally. Concurrently, the myelin sheath undergoes a degeneration phase, and the macrophages and Schwann cells function to clear the cellular debris. Regeneration of the axon follows with the Schwann cells undergoing a proliferation and differentiation phase along the endoneurium to re-form the scaffolding for the axon, to guide the regenerating axon along the previously established path to eventually re-innervate the muscle or sensory receptors. Regeneration occurs at a rate of approximately 1 - 2 mm per day. Cryoneurolysis therefore creates the effect of a prolonged anesthesia, with eventual regeneration of a normal nerve. This provides a window of painless rehabilitation and then the return of full nerve function.

All of our patients were treated with Cryo S-Painless device, produced by Metrum Cryoflex (Warsaw, Poland). The probes were single use, and either triangular or blunt shaped.

Conclusion

In this case series report, we show the successful treatment of patients with CRPS type 1 and CRPS type 2. They had undergone multiple therapies in the many years following their injury. We emphasize that the early use of interventional techniques such as ultrasound-guided cryoneurolysis have important clinical efficacy in order to cut off the process of the three major pathophysiological pathways - aberrant inflammatory mechanisms, vasomotor dysfunction and maladaptive neuroplasticity. However, treatment of the underlying pathology, even years after the initial injury, can result is significant improvement. These techniques should be therefore the cornerstone for effective pain management.

Based on our current experience treating CRPS pain with ultrasound-guided cryoneurolysis, we can conclude that

1. The diagnostic injections should be repeated several times (between two and five times) in order to achieve the best results.
2. The initial site of pain reflects the most likely affected nerve, and
3. Treatment of that nerve can significantly decrease the overall pain.

Cryoneurolysis should be considered a necessary tool in the treatment of this debilitating condition.

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