

Case Report

CRYOTHERAPY CAN CAUSE PERMANENT NERVE DAMAGE: A CASE REPORT

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Abstract. Cryotherapy (ice application) and deep cryosurgery are commonly employed for neurological, surgical, and physical therapy. Prolonged and repetitive cryotherapy can result in permanent damage to myelinated nerves which are susceptible to myelin coagulation, axonal destruction, and focal somesthetic nerve dysfunction. The stimulation of microscopic perivascular unmyelinated C-thermoreceptor nerves (CTN) leads to regional sympathetic nerve dysfunction in the form of neuropathic pain, vasoconstriction, and edema. The cryogenic field is not limited to a small microscopic area. The adjacent intact nerves are susceptible to damage as well, leading to a new source of pain. If, from the beginning, cryotherapy aggravates the pre-existing neuropathic pain, it should be discontinued. An illustrative case is presented.

Descriptors. cryosurgery, cryotherapy, C-thermoreceptor nerves, CTN, neuropathic pain, somatic pain

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INTRODUCTION

Cryotherapy and cryosurgery are utilized in multiple disciplines of medicine for pain relief, aesthetic surgery, and cell preservation. Cryotherapy has long been a standard form of physical therapy. However, prolonged and repetitive ice application can cause damage to the myeli-

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nated motor and sensory nerves. The myelin sheath is rich in lipids. Ice application results in solidification and hardening of the myelin lipid, similar to application of ice on melting butter. This can lead to an arrest of motor and sensory nerve conduction. Even brief ice application, lasting no more than 20 minutes, can cause transient paralysis of the motor and sensory nerve fibers, lasting as long as one year (1).

Cryosurgery with application of liquid nitrogen is fraught with a higher risk of nerve damage (2). Ophthalmic and cutaneous cryosurgery procedures are sometimes accompanied by complications such as skin ulcers, immune system dysfunction in the form of edema, bullae formation, scar formation, damage to the lacrimal sys-

tem, wound infection, and vascular headaches (2-4). Moreover, full-thickness skin necrosis, syncope, and sudden death have been reported (5). Chronic repetitive ice application or cryosurgical treatment can also result in nerve tissue injuries. Although theoretically any area of the body can be affected. Only injury of the fingers, angle of the jaw, posterior auricular area, and ulnar nerve injury at the elbow level have been reported in literature (5-10).

Cryotherapy's effect is not limited to the surface of the skin (11). It penetrates through deeper tissues causing both surface and deep nerve fiber coagulation (11). In addition, vascularity of tissues and length of exposure play major roles in the degree of hypothermic effect of cryotherapy (11).

Animal cryogenic experiments on cats, rats, and pigs (12-14) have demonstrated acute damage and vacuolization in muscle cells, acute tissue necrosis, vascular thrombosis; and acute inflammatory manifestations in rats (12). Similar cryogenic experiments (ice application) in pigs have shown inflammatory swelling and injury to soft tissues, obviously including the nerves (13).

Basbaum studied the effects of hypothermia on cats' sciatic (somatic) nerves. She noted reversible total nerve block at 5° C (14). She performed electron microscopic studies showing large myelinated nerve fiber damage after seven days of cryotherapy. Both wallerian degeneration and segmental demyelination were noted (14). However, the unmyelinated nerve fibers were less affected. This research showed the myelin lipid solidification of somatic nerves causing damage to the myelinated nerve fibers. Simply stated, cryotherapy solidifies and destroys myelin lipids as well as the axon nerve fibers.

On the other hand, the microscopic perivascular unmyelinated C-thermoreceptor nerves (CTN) which are practically devoid of myelin lipid, spare the CTN fibers from fatty coagulation, allowing continuation of nerve conduction and perpetration of vasoconstriction. This results in a hypothermic and hypoxic dysfunction of the extremity (15). This phenomenon may explain perpetuation and aggravation of neuropathic pain (7-10,15). In the cited experiments, the hypothermic cooling was at 5° C, allowing nerve fiber regeneration (12-14). How-

ever, if the hypothermia dropped to zero degrees C (freezing) for a few seconds, the nerve degeneration was irreversible (16,17). Moreover, the freezing indiscriminately affected and injured adjacent nerve fibers (18).

Cryotherapy aggravates the tendency for vasoconstriction and coagulates and damages the myelinated nerve fibers. It exacerbates the nerve damage and enlarges the area of mechanoallodynia resulting in bias toward sympathetically independent pain (SIP) rather than sympathetically maintained pain (SMP) (7-10,14). Procedures such as carpal tunnel surgery aimed at relieving inflammation due to complex regional pain syndrome (CRPS), arthroscopy, and exploratory surgical procedures may aggravate the sensory nerve damage and reproduce allodynic pain (14). Michaelis and colleagues have reported rapidly increasing mechanoreceptor activity in damaged nerve fibers. In contrast, somatic nerve stimulation inhibits the aggravation of allodynia (19).

METHODOLOGY

The following a case report of a patient who had undergone repetitive and prolonged cryotherapy (ice), and cryosurgery (cryoablation). The patient's records were reviewed, focusing on the history, neurologic examination, diagnostic tests such as electromyography (EMG), nerve conduction velocity (NCV), infrared thermal imaging (ITI or thermography), and quantitative sensory thermal testing (QST).

CASE REPORT

A 46-year-old physician sustained right knee injury playing softball on 6/8/96. She instantaneously developed edema, dermal erythema, hypothermia, and allodynia. She was diagnosed as having complex regional pain syndrome (CRPS) in November of 1998. Cryotherapy had been initiated at the scene of the accident, and it was repeated 2-3 times daily for almost 5 years (from 6/8/96 till 5/7/01). Prior to referral to our clinic, the patient had already undergone arthroscopy, multiple sympathetic ganglion nerve blocks (which had failed), cryotherapy, and cryosurgery of the right saphenous nerve and vein

which led to neuroinflammation in the form of edema, bulbous lesions, and multiple trophic ulcers over the right knee, hyperthermia, and intractable pain (Figure 1). She also had undergone 12 Bier blocks which caused further exacerbation of signs and symptoms. After the cited procedures, in March of 1999, the patient began to experience multiple skin ulcers on the right knee. By November of 2000, the patient had counted more than 250 ulcers on the right knee.

The patient was first seen in our clinic in May of 2001. Cryotherapy was discontinued. She was found to have marked edema above and below the right knee (Figure 1). Infrared thermal imaging (ITI) showed marked hypothermia on the right patellar region 15 cm in height and 12 cm in width, with a temperature of 22.75° C. This was in contrast to the left knee temperature which was 28° C (DT = 5.25° C), confirming severe vasoconstriction due to CRPS (Figure 2).

TREATMENT

A standard treatment protocol for neuropathic pain was implemented. The edema and bulbous lesions were treated with intravenous mannitol resulting in resolution of the lesions (20,21) (Figure 3). The patient was treated with a standard protocol including (i) discontinuation of cryotherapy; (ii) treatment with analgesic antidepressant trazodone and venlafaxine; (iii) lumbar epidural nerve blocks containing Depo-Medrol®; (iv) physical therapy; (v) tramadol; (vi) butorphanol nasal spray; (vii) Emla and doxepin cream (alternated); and (viii) treatments aimed at reduction of neuroinflammation such as intravenous mannitol, Epsom salt (magnesium sulfate) soaks, and regional nerve blocks. The patient underwent lumbar epidural as well as femoral nerve blocks containing bupivacaine and Depo-Medrol® which provided marked improvement in circulation in the lower extremities.

RESULTS

For the first time since 1996, after 11 days with the treatment described, the patient's knee warmed, the blisters and bullae cleared, and the patient rated her pain at a

two (on the basis of 0-10) (Figure 3). Treatment with trazodone helped suppress the nocturnal pain, and, for the first time in five years, the patient could sleep eight hours a night without interruption. In addition, the epidural and femoral blocks reduced the right knee hypothermia which reversed it to hyperthermia (Figure 3). The nerve blocks dilated the arterioles resulting in further hyperthermia and improved tissue oxygenation.



Figure 1. Five years of daily self-applied cryotherapy resulted in the breakdown of skin, cold blisters, and damage to sensory nerves.



Figure 2. Bilateral thermogram shows marked hypothermia due to vasoconstriction in the cryotherapy area.



Figure 3. Eleven days after discontinuation of cryotherapy, treatment of epidural, regional nerve blocks, and intravenous mannitol, showed marked improvement of the bulbous lesions.

DIAGNOSIS

Early and accurate diagnosis is essential for successful treatment of this condition. The success is achieved by proper clinical and neurophysiological tests.

Clinical. Careful history taking and detailed neurological examination are essential for an accurate diagnosis. The key to early diagnosis is to obtain a detailed history regarding onset and aggravation of pain after ice application. If the pain is aggravated with initial ice application, it is indicative of neuropathic (versus somatic) pain due to dysfunction and excitation of the CTN (15). This nerve excitation is accompanied by immediate aggravation of neuroinflammation (swelling, shiny skin, bulbous skin lesions, and ulcers) (22-27). The neuroinflammation is instigated by T-cell lymphocytes attempting to reduce the destruction of damaged nerves (15).

Electrophysiological tests. After excluding preexisting diseases causing nerve conduction delays (e.g., preexisting diabetic or nutritional neuropathies), nerve conduction velocity studies (NCV) may be quite informative

and diagnostic of somatic nerve dysfunction due to cryotherapy. NCV test measures the function of large-caliber somatic (myelinated) nerve fibers. The test results are abnormal in somatic type cryogenic peripheral nerve palsies such as peroneal nerve palsy. The degree of NCV delay points to the severity of hypothermia ($+5^{\circ}$ to -60° C). The slower the NCV, the slower the recovery time (8).

Quantitative sensory thermal testing (QST). The QST is performed by exposure of the painful area of the skin to a Pelletier thermal source scale, applying controlled ramps of thermal energy (28). The patient is instructed to signal the moment a non-painful cool or warm sensation (somatosensory nerve function) is felt. Then the patient is instructed to signal if he/she feels a painful cold or painful hot sensation (sympathetic nerve function) (28,29). The test is repeated at least 3 times to confirm its reliability (30). This test is quite sensitive in identifying the areas of damage or dysfunction of sympathetic sensory nerves due to CRPS (30-32). The QST also acts as an accurate lie detector due to the fact that conscious manipulation of the test by the patient is impossible and identifies a dishonest intention.

Thermography. Infrared thermal imaging (ITI) measures the thermal changes of the body with the help of an infrared camera. It provides both diagnostic and therapeutic information which identifies the areas of permanent sympathetic nerve damage. Sympathetic nerve damage causes hyperthermia due to loss of vascular tone (vasodilation) as opposed to sympathetic nerve irritation which causes hypothermia due to excess vasoconstriction (33). Obviously, the hyperthermic area should not be treated with regional or sympathetic ganglion blocks because the sympathetic nerves are already partially paralyzed allowing heat leakage and hyperthermia (8). The regional nerve blocks should be applied to areas of hypothermic vasoconstriction (33-35). The test provides a comprehensive picture of the entire body, showing subtle sympathetic nerve dysfunctions (33) (Figure 2). Normally, there maybe a temperature difference (D T) of up to 0.5 to 0.6° C in contralateral body areas (34). Any D T higher than 0.6° C is considered abnormal (34,36).

Scintigraphic triphasic bone scanning. Scintigraphic triphasic bone scanning (SBS) is the most commonly used and least reliable test. The test compares the bilateral radioisotope uptake in bones and joints. Its main limitation is the fact that as the sympathetic dysfunction spreads to the contralateral extremity, both sides show identical concentration of radio-nuclide. This phenomenon artificially leads to a "normal" interpretation of the test. The reliability and sensitivity of this test are reported to be as low as 25% and as high as 55%. Either figure is not statistically significant when compared to controls (37,38).

DISCUSSION

This case is an example of multiple damages from cryosurgery and cryotherapy. The lesson learned from this case report is to discontinue cryotherapy if the patient develops neuropathic pain. This would be an effective preventive measure to avoid permanent chilblain and severe neuropathic pain.

Cryotherapy is useful for treatment of acute pain. However, prolonged and repetitive ice application can cause permanent nerve damage. Cryotherapy stimulates focal vasoconstriction due to excitation of sympathetic system and focal modulation (8). This mechanism is aimed at preventing heat leakage as well as preventing spread of hypothermic tissue damage (39).

Two main aggravating factors influence the pathological changes in cryotherapy - temperature and duration of exposure.

Temperature. The degree of hypothermia is directly related to the extent of nerve damage. Hypothermia progressively slows down the nerve conduction velocity (NCV). Hypothermia down to 10° C (above freezing) temporarily solidifies the myelin and arrests the conductivity of myelinated nerves. This leads to reversible paresis or paralysis of myelinated, somesthetic nerve fibers (e.g., foot-drop) (8,40). If the hypothermia drops to zero or below, permanent nerve damage occurs. Extreme degrees of hypothermia are likely to cause more nerve damage (8).

There are three categories of mechanical and thermal nerve injuries depending on the severity of cryotherapy (41). First degree - *neurapraxia* is a reversible dysfunction of peripheral nerves. Second degree - *axonotmesis* is damage to the axons (wallerian degeneration), and sparing of fibrous anatomy of the perineurium, epineurium and endoneurium with potential regeneration estimated at approximately 1 mm per day (42). Third degree - *neurotmesis* is the anatomical destruction of neuronal and stromal anatomical structures with partial and erratic regeneration after surgical repair (42).

Repetitive cryotherapy may result in further sympathetic nerve dysfunction causing blotching of the skin. Unfortunately, the sympathetic nerve dysfunction in the form of blotching, unstable vasoconstriction, and vasodilation (neurovascular instability) is frequently mistaken for Raynaud's Phenomenon, even if the patient is a male and suffers from severe neuropathic pain. Cryotherapy is contraindicated in such cases (43-45).

The above phenomenon clinically differentiates the intolerable regional neuropathic (sympathetic) pain from the somatic focalized pain. So, if the pain gets worse and the patient adamantly refuses cryotherapy, the procedure should be discontinued, never to be applied again (*Figure 4*). This neuropathic cold sensitivity is also called "cold sensitive syndrome" (43).

This selective development of neuropathic pain and inflammation due to cooling or freezing of CTN fibers is in contrast to the focalized and temporary somatic myelinated nerve fiber anesthesia (8,40). The double-tier hypothermia, at +10° C hypothermia versus at 0° C freezing explains the two different nerve responses - somatic nerve temporary analgesia and paresis at 10° C versus anesthesia following neuropathic pain at 0° C (8,18).

Duration of exposure. Samborski *et al.*, immersed a patient in -150° C whole body cryotherapy (46). The patient had significant analgesia immediately and up to 2 hours after cryotherapy. The length of exposure was quite short, but the extreme cryotherapy, in time, would have been harmful by causing deep hypothermia. The longer the exposure to cryotherapy, the more severe the nerve damage. Prolonged hypothermia is less damaging

if the temperature drops to 5-10° C. In contrast, when the temperature drops to -20° C, then the risk of tissue damage increases without any further therapeutic benefit (18,47).

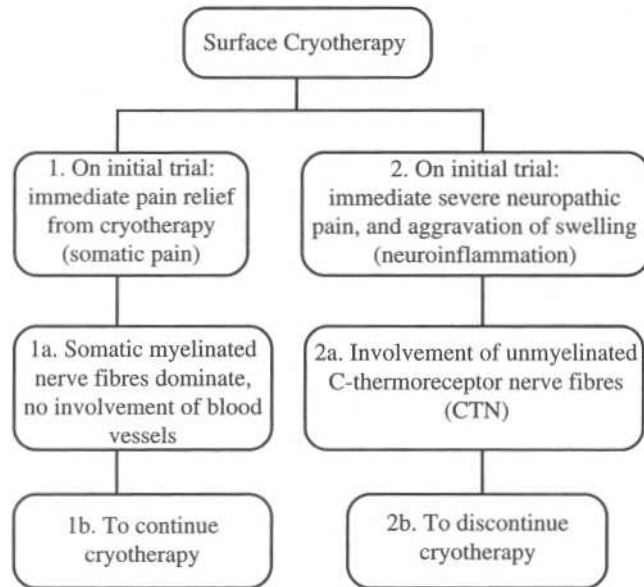


Figure 4. Algorithm for treatment of somatic versus neuropathic pain.

SUMMARY AND CONCLUSION

This case report shows that prolonged (1996-2001) use of cryotherapy can cause permanent somatosensory and thermosensory (sympathetic) nerve damages with contrasting complications of focal somatic myelinated nerve fibers damage and focal pain, versus C-thermoreceptor nerves (CTN) damage causing neuropathic regional pain and inflammation (skin ulcers). Long-term exposure and extreme hypothermia can cause permanent nerve damages.

If from the beginning cryotherapy causes neuropathic pain and aggravation of edema, it should be discontinued. If from the beginning cryotherapy provides pain relief and no vascular changes, it should be continued, but not indefinitely. Prolonged repetitive cryotherapy has the potential of causing permanent nerve damage.

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