Techniques in Regional Anesthesia and Pain Management 18 (2014) 145–149

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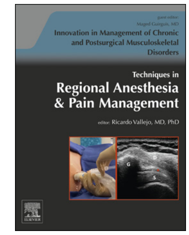

An ancient treatment for present-day surgery: Percutaneously freezing sensory nerves for treatment of postsurgical knee pain

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ARTICLE INFO

Keywords:
Knee pain
Knee arthritis
Pain
Arthritis
Total knee arthroplasty
Total knee repacement
Knee anatomy
Cryotherapy

ABSTRACT

The analgesic properties of cold therapy have been well known for many centuries. Cryoneurolysis of sensory peripheral nerves, in which the epineurium and perineurium resist freeze damage, allowing the structural scaffold to remain intact for normal axonal regeneration and remyelination to occur, has been used to treat pain for many decades. Chronic knee pain due to osteoarthritis is a common condition associated with significant disability among the elderly. Because no single treatment modality has been shown to be effective for treatment of knee pain secondary to osteoarthritis, treatment usually involves a combination of nonpharmacologic (including total knee arthroscopy) and pharmacologic therapies. Given the paucity of effective nonsurgical options for the treatment of knee pain, cryoneurolysis of the sensory nerves surrounding the knee may be a novel effective treatment strategy. Because cutaneous innervation of the knee is highly variable and complex, additional research is needed to understand which sensory nerves should be targeted for cryoneurolysis to maximize effectiveness. Recent advances in cryoneurolysis technology have allowed for the creation of more precise cold zones using smaller gauge needles that cause less pain when puncturing the skin. Emerging evidence suggests that this technology has clinical utility when used as part of a multimodal pain regimen for total knee arthroplasty. In addition to its potential to treat chronic knee pain, cryoneurolysis of sensory nerves has shown efficacy for the temporary relief of pain caused by numerous conditions.

History of cold therapy

Cold has been used for medical therapy for centuries as far back as 460 BC, when Hippocrates described its analgesic and anti-inflammatory purposes.[1,2] In the mid-19th century, Arnott[3] described uses of cold therapy (mixtures of ice and salt), which he advocated for treatment of certain cancers and nerve pain. Cryotherapy continued to be practiced into the late 1800s with the use of prepared refrigerants, such as ethyl chloride spray for topical anesthesia, which allowed the

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http://dx.doi.org/10.1053/j.trap.2015.10.014
1084-208X/

achievement of lower tissue temperatures.[2,4] More recent advancements in cryotherapy include the development of technology using nitrous oxide as a cryogen,[5] which has enabled reversible treatment of peripheral nerves. In 1913, Dr Irving Cooper, a neurosurgeon, developed a liquid nitrogen probe to treat movement disorders, such as Parkinson's disease, by freezing the thalamus and also used the device to treat previously inoperable brain tumors.[2] Dermatologists currently use cryotherapy to treat benign and cancerous skin lesions, such as viral warts, premalignant solar keratosis, and Bowen's disease.[2] In addition, many surgical specialties (eg, ophthalmology, gynecology, general surgery, and orthopedics) use different types of cold therapy in their practices.

Science of cold and effect on nerves

Cryoneurolysis, freezing of sensory peripheral nerves, a particular form of cryotherapy, has been used for many decades for the treatment of chronic pain.[1] Randomized controlled trials have shown that cryoneurolysis significantly reduces postoperative pain or opiate requirements or both following thoracotomy[6] and tonsillectomy.[7] In noncontrolled studies, cryoneurolysis has effectively relieved pain in patients with postherpetic neuralgia,[8,9] neuroma,[10] and intractable facial,[11-15] temporomandibular joint,[16] postthoracotomy,[17] intercostals,[18] and perineal pain.[19] These reports have demonstrated pain relief ranging from a few months to years.[12,14]

The Table summarizes the forms and degrees of nerve injury that occur because of exposure to various temperatures.[20-22] Temporary inactivation of the nerve (neurapraxia) begins near +10°C, and temperatures slightly colder than −5°C can produce a conduction block lasting from several hours to days.[23,24] This temporary conduction block is likely due to the disruption of the channels or pumps involved in the transfer of sodium and potassium ions across the cell membrane or both. Cooling of nerves to low temperatures (−20°C to approximately −100°C) produces a second-degree nerve injury (axonotmesis) and leads to axonal and myelin degeneration, also known as Wallerian degeneration.[25] The nature of Wallerian degeneration contrasts with the damage that occurs in response to traumatic nerve injuries, such as transection or thermal heat lesion, which disrupt structural proteins and can lead to neuroma formation.[25] In the case of cryoneurolysis, the epineurium and perineurium resist freeze damage, allowing the structural scaffold to remain intact for normal axonal regeneration and remyelination to occur.[26]

Research into the behavioral, electrophysiological, and pathologic recovery of peripheral nerves following cryogenic injury has been conducted using a variety of animal models.[27-29] Data from longitudinal cohort studies suggest that peripheral nerves recover their structure and function within a period of months following direct contact with a cryoprobe delivering temperatures as low as −120°C.[11,15] At temperatures of −100°C-180°C, histologic analyses show extended damage to the basal membrane and collagen proliferations, indicating endoneurial and perineurial damage with the epineurium appearing to remain intact.[21] Lower temperatures also result in a longer duration of electrophysiological and functional disruption compared with temperatures larger than −60°C.[21,22] These findings demonstrate that lower temperatures (<−100°C) create a third-degree nerve injury (neurotmesis) and can result in a longer-term pain attenuation compared with milder freezing temperatures. However, the acellular structure damage of the endoneurium and perineurium caused by third-degree nerve injuries has a risk of neuroma formation and reduced sensory function of the target tissue.

The mechanism of action for tissues treated with temperatures as low as −196°C (the temperature of liquid nitrogen) is based on both the final freezing temperature and the rate of cooling.[30] For this reason, multiple proposed modalities of injury, including physical cell damage by intracellular ice formation, may occur during cooling at a high rate. If cooling occurs at a slow rate, an increase in extracellular solute concentration during the freezing process can cause the cells in the tissues to dehydrate, thereby damaging cytoplasmic proteins.[31] In addition to these mechanisms of action, low temperatures may also cause ischemic injury due to vascular damage.[32,31]

Current treatment of chronic knee pain

Chronic knee pain due to osteoarthritis (OA) is a common yet difficult-to-treat condition. Nearly 80% of the US population

Table – Types and degrees of nerve injuries resulting from temperature exposure.

Reversible	
1st Degree	
Neuropraxia—interruption of conduction; short recovery time	+10°C to −20°C
2nd Degree	
Axonotmesis—loss of continuity of the axon; Wallerian degeneration; preservation of endo-, peri-, and epineurium	−20°C to −100°C
Nonreversible	
3rd or 4th Degree	
Neurotmesis—loss of continuity; some loss of continuity of epineurium and perineurium; endoneurium may or may not be disrupted	−140°C and colder
5th Degree	
Transection (severe neurotmesis)—gross loss of continuity	Not possible with cryoneurolysis