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REVIEW

Novel cryoneurolysis device for the treatment of sensory and motor peripheral nerves

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ABSTRACT

Introduction: Cryoneurolysis is the direct application of low temperatures to reversibly ablate peripheral nerves to provide pain relief. Recent development of a handheld cryoneurolysis device with small gauge probes and an integrated skin warmer broadens the clinical applications to include treatment of superficial nerves, further enabling treatments for pre-operative pain, post-surgical pain, chronic pain, and muscle movement disorders.

Areas covered: Cryoneurolysis is the direct application of cold temperatures to a peripheral nerve, resulting in reversible ablation due to Wallerian degeneration and nerve regeneration. Use over the last 50 years attests to a very low incidence of complications and adverse effects. Cryoprobes have traditionally been applied through a surgical incision; but, recent technical advances allow percutaneous administration. A new hand-held device is now approved for use within the United States. Cryoneurolysis has been used to treat postoperative and chronic pain states as well as spasticity.

Expert commentary: Changes in the US healthcare system such as a push for the reduction of opioid use and the incorporation of Diagnostic Related Group codes, as well as recent technological advances including a handheld unit that allows for treatment of superficial nerves while protecting the skin from damage, may contribute to the resurgence of cryoneurolysis for the treatment of peripheral nerves.

1. Introduction

The local application of low temperatures for medical therapy has been used for centuries and is documented as far back as Hippocrates in 460 BC when he described the use of cold for its analgesic and anti-inflammatory properties [1]. Since then, advancements in cryosurgical technology have allowed for the use of much colder temperatures (as cold as −196°C) for tissue ablation. In addition, the development of technology that uses nitrous oxide or carbon dioxide as a cryogen (a substance used to produce very low temperatures) [2] has enabled reversible destruction of nerves, also known as cryoneurolysis. These technologies employ an established mechanism of action and have been used commercially since the early 1960s [3].

Recently, a new generation of cryoneurolysis devices have been developed that have the potential to expand the clinical applications of this technology. The iovera° system (Myoscience, Inc., Fremont, CA, USA) is a class II medical device cleared by the US FDA with indications for tissue destruction during surgical procedures and cryoanalgesia of peripheral nerves to provide long-term pain relief. This handheld device utilizes compressed liquid nitrous oxide to cool peripheral nerves via small-gauge closed-end needles, creating a localized, reversible nerve destruction that prevents nerve signaling. The purpose of this article is to review the mechanisms of action, discuss the current state of the technology and describe how these recent significant advances can result in

reductions in pain, unwanted muscle movement, and opioid use.

2. Background

2.1. Nerve anatomy

Peripheral nerves allow communication between the spinal cord and the tissues/organs of the body. The innermost part of the nerve is the axon, which conducts signals between the brain and tissues (Figure 1). In myelinated nerves, these axons are surrounded by a myelin sheath composed of concentric layers of Schwann cells which function to increase neuronal signaling speeds. The endoneurium is a layer of loose connective tissue that surrounds each axon. The axons are grouped together into bundles called fascicles, which extend the length of the nerve. Surrounding and holding together each fascicle is a sheath of perineurium. This covering is concentrically laminated with flattened perineurial cells, basement membranes, and collagen fibers. Epineurium, a layer of dense connective tissue, covers and holds together these bundles to create the outer surface of nerves (Figure 1).

2.2. Nerve injury scales

Characterization and classification of nerve injuries have been well established for many decades. Sir Herbert Seddon first
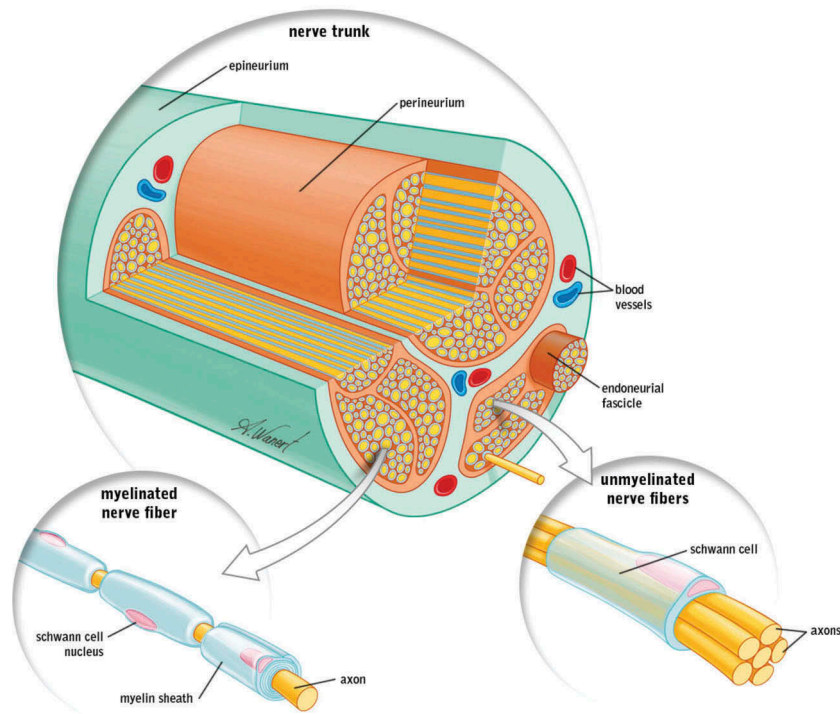
Figure 1. Peripheral nerve anatomy (image courtesy of Myoscience).

published a 3-point nerve injury scale in 1943 [4], and in 1951, Sir Sydney Sunderland published a 5-point scale which gave more resolution to Seddon's scale (Table 1) [5]. These scales classify nerve injury as a function of temperature [6,7]:

- *First-degree* nerve injury (neuropraxia) is the mildest form of nerve injury and is characterized by a disruption of the nerve's ability to transmit an action potential along the axon. Damaged myelin sheath localized at the injury site may occur, but the entirety of the nerve structure and the axon largely remains intact and unchanged. Full functional recovery from neuropraxia can range from minutes to a few weeks.
- *Second-degree* nerve injury is characterized by a reversible degeneration process of the axon, also known as Wallerian degeneration. Degeneration of the axon and myelin sheath occurs initially at the injury site, shortly

followed by degeneration of the remaining distal portions of the axon and associated myelin sheath. The retrograde degeneration of the axon is limited to injury site while the nerve body remains unchanged. Wallerian degeneration results in a longer duration of functional loss as compared to neuropraxia. Functional recovery relies on the time it takes for the axon to regenerate and reinnervate the target organ. Depending on the distance from the axon injury site to the target site, the disruption of signaling can last from weeks to months.
- *Third-degree* injury similarly involves Wallerian degeneration of the axon, but also includes damage to the endoneurium. Studies have shown axon regeneration will deviate from the disrupted endoneurial tube and into the intrafasicular structure, which could lead to a potential neuroma formation [8]. Functional, but not complete, reinnervation of the target site can occur over a period of months to year(s) [5,6,8].
- *Fourth-degree* injury involves Wallerian degeneration and damage to the endoneurium, but adds damage to the perineurium and epineurium as well. The severity of this injury allows the regenerating axon to grow into the extrafasicular structure, resulting in growth termination [9] and can result in the promotion of neuroma formation [5]. Surgical repair can improve chances of useful functional recovery, but with incomplete reinnervation of the target tissue [10].
- *Fifth-degree* injury describes a total transection of the nerve. The result – without surgical repair – is a total lack of functional recovery with scar and neuroma formation. Due to the lack of the nerve scaffolding, axons regenerate aberrantly at the injury site and are not be able to continue regrowth to the distal nerve stump [11].

Table 1. Nerve injury as a function of cold [5,7].

Reversible	
First degree	+10 to −20°C
Neuropraxia – interruption of conduction; short recovery time	
Second degree	−20°C to −100°C
Axonotmesis – Loss of axon continuity; Wallerian degeneration; preservation of endoneurium, perineurium and epineurium	
Nonreversible	
Third/Fourth degree	−140°C and colder
Neurotmesis – loss of axon continuity; some loss of continuity of endoneurium and perineurium	
Fifth degree	Not possible with cryoneurolysis
Transection (severe neurotmesis) – gross loss of continuity	

Additionally, spontaneous and aberrant signaling from the injured sensory nerve results in neuropathic pain symptoms, commonly observed in postamputation residual limb pain [12,13].

In general, the degree of nerve injury determines the ability for the nerve to regenerate over time. The milder forms of nerve injury (i.e. neuropraxia and axonotmesis) allow for normal nerve regeneration, since the minimal structural changes to the scaffolding of the nerve allows for more complete regeneration of the axon. More severe injuries (i.e. axonotmesis with structural damage or neurotmesis) result in disruption of the nerve path, which makes it more difficult or impossible to functionally regenerate of the nerve.

3. Mechanism of action

3.1. Cryoneurolysis, Wallerian degeneration, and nerve regeneration

Cryoneurolysis is the direct application of cold temperatures, resulting in a second-degree injury to the peripheral sensory nerve [7]. Treatment in this temperature range causes a reversible degeneration of the axon beginning at the site of treatment and proceeding distally [8]. Wallerian degeneration (axonal and myelin degeneration) occurs when the nerve is exposed to temperatures below −20°C [7]. Upon injury, the axon begins a degeneration process at the injury site and progresses distally. Morphologically, this process is characterized by a beading appearance followed by granular disintegration of the axons at, and distal to, the site of exposure [14]. 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 to re-form the scaffolding for the axon. Various cell [3] signaling factors occur between the neuron, Schwann cells, macrophages, and the surrounding environment, which promote the regeneration, remyelination, elongation, and guidance of the regenerating axon [3,8,15–19]

These structures act as a scaffold to guide the regenerating axon for optimal recovery, and the reliability of axon regeneration relies on the integrity of the surrounding endoneurial, perineurial, and epineurial structures. Signaling factors promote the axon regeneration. Therefore, the nerve axon is able to regenerate along the previously established path to eventually reinnervate the muscle or sensory receptor [6,20–22]. Regeneration occurs at a rate of approximately 1–2 mm per day.

In contrast, third-, fourth-, and fifth-degree injuries (which occur at temperatures colder than −100°C, transection, or thermal heat lesions) cause irreversible nerve injury, disrupting the acellular nerve structures, and sometimes causing neuroma formation and aberrant axon regeneration [7,23].

Research into the behavioral, electrophysiological, and pathological recovery of peripheral nerves following cryogenic injury has been conducted using a variety of animal models [24–26]. Historical data has indicated that peripheral nerves recover their structure and function within a period of months following direct contact with a cryoprobe delivering temperatures as cold as −120°C [27,28]. A recent preclinical study of a cryoneurolytic device applied to one tibial nerve of adult female Sprague–Dawley rats (n = 27) demonstrated similar histologic results as seen with historical studies using various freezing temperatures [29,30]. Wallerian degeneration was indicated by the loss of axons observed in both hematoxylin and eosin staining (Figure 2) and immunofluorescence (Figure 3). Histological analyses revealed demyelination and axonal degeneration by 2 weeks posttreatment and suggested that the axons and Schwann cells became disrupted while the injury left the epineurium and perineurium intact. Immunofluorescence staining demonstrated the gradual axon regeneration and remyelination. Axonal regeneration and remyelination was complete at 16 weeks and axon density measurements showed a return to normal levels in this study. Low-temperature treatment on motor nerves did not result in any permanent or long-term changes to the
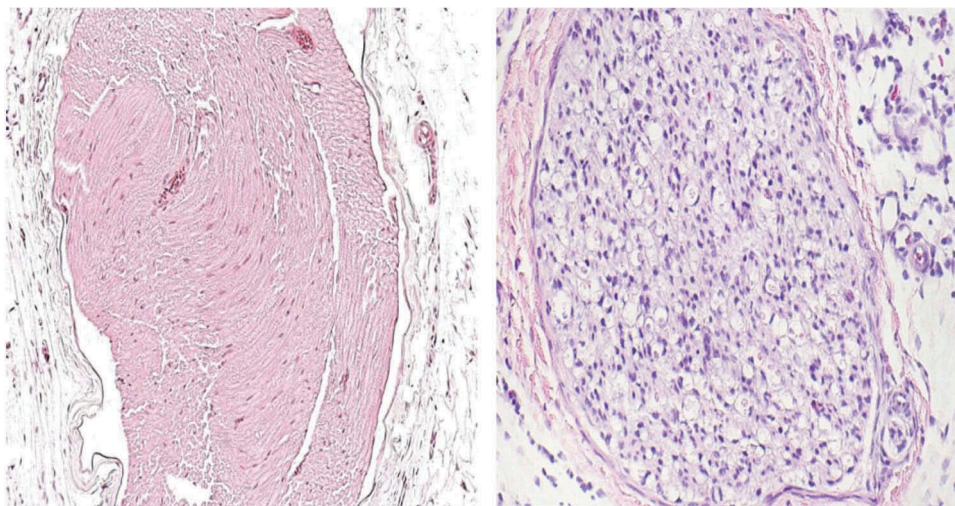

Figure 2. Hematoxylin and eosin (H&E) staining before and after cryoneurolysis (image courtesy of Myoscience).
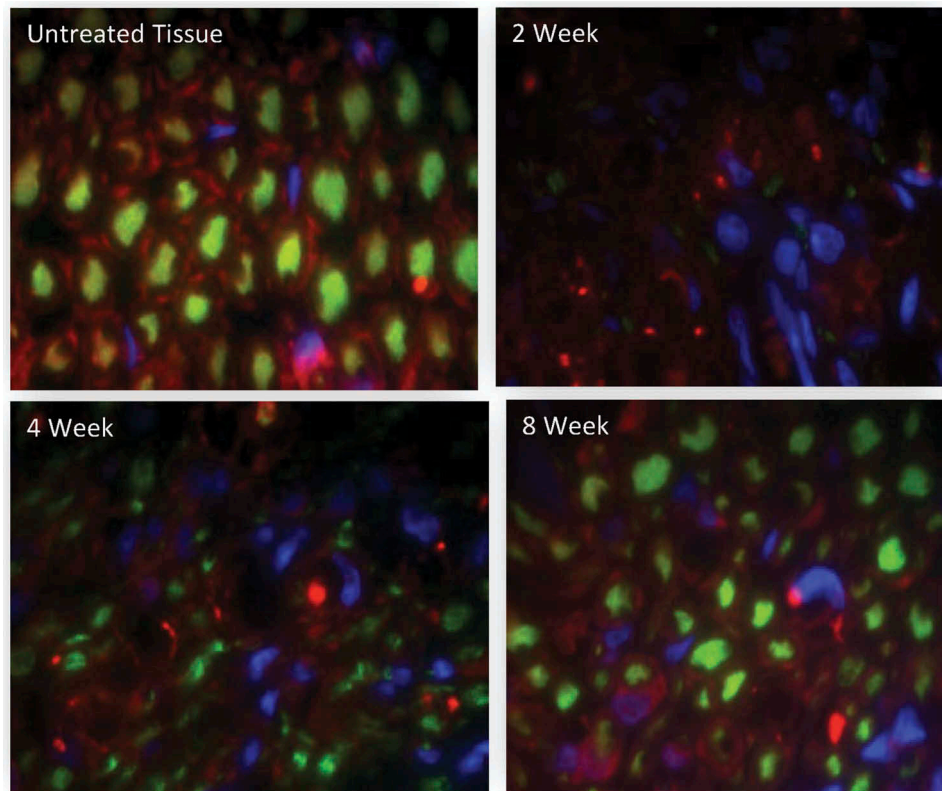
Figure 3. Immunofluorescence staining of tissue before and after cryoneurolysis (image courtesy of Myoscience).

function and structure of the nerves. The temporary loss of axons was reflected in the functional motor loss of the treated hind limb, which resulted in a completely reversible deficit in toe spread function and walking gait.

Cryoneurolysis that results in Wallerian degeneration of specific sensory and motor peripheral nerves could alleviate pain and motor dysfunction caused by any number of medical conditions without damaging surrounding tissue.

3.2. Treatment repeatability

A recent animal study evaluated the effects of long-term and repeated cryoneurolytic treatments of the sciatic nerve through assessments of physiological function and histological analysis [31]. Measured physiological function demonstrated consistent weakening in toe spread ability and motor function following each treatment with gradual recovery of full normal function observed by 8 weeks following treatment. Short-term histological results showed that axonal degeneration had occurred within 7 days of treatment, while the epineurial and perineurial structures remained intact. Progressive axonal regeneration was followed with recovery to normal structures observed 24 weeks after final treatment. Repeat treatments also exhibited reproducible patterns of weakening and complete recovery with each successive treatment. Long-term follow-up also demonstrated consistent nerve regeneration with no cumulative change in either morphology or functionality. Similarly, histological results found full recovery of the normal

surrounding tissue structures (muscle, fat, and vessels) in all animals (Figure 4).

4. Safety of cryoneurolysis

Cryoneurolysis using nitrous oxide or carbon dioxide is an inherently safe technique because the treatment temperature cannot grow colder than the boiling point of either gas (nitrous oxide: −88°C; carbon dioxide: −79°C), thereby ensuring that the resulting nerve injury is reversible and that there is no effect on the connective structures. In addition, many of the surrounding structures such as the connective tissues of the nerves and blood vessels, as well as the bone, have been found to resist freeze injury [32]. The result is that the extracellular matrix and scaffold structure of the nerves and vessels remain intact, allowing the affected axon/myelin sheath or vascular cells to regenerate and repair the injury site. In comparison, heat lesions have been found to not only destroy cells but also disrupt the structural matrix, resulting in a narrower therapeutic window [33–35]. A recent study [36] demonstrated that following a traumatic peripheral nerve injury, the regenerated myelin sheath was thinner and exhibited a decreased intermodal length. This was attributed to insufficient stimulation of redifferentiated Schwann cells and/or by inhibitory signals. It is not clear that this would be the case for regeneration following cryoneurolysis as the rate of regeneration and functionality following treatment has been demonstrated to be repeatable [31]. This difference may be due to the fact that the chemical cascades which follow
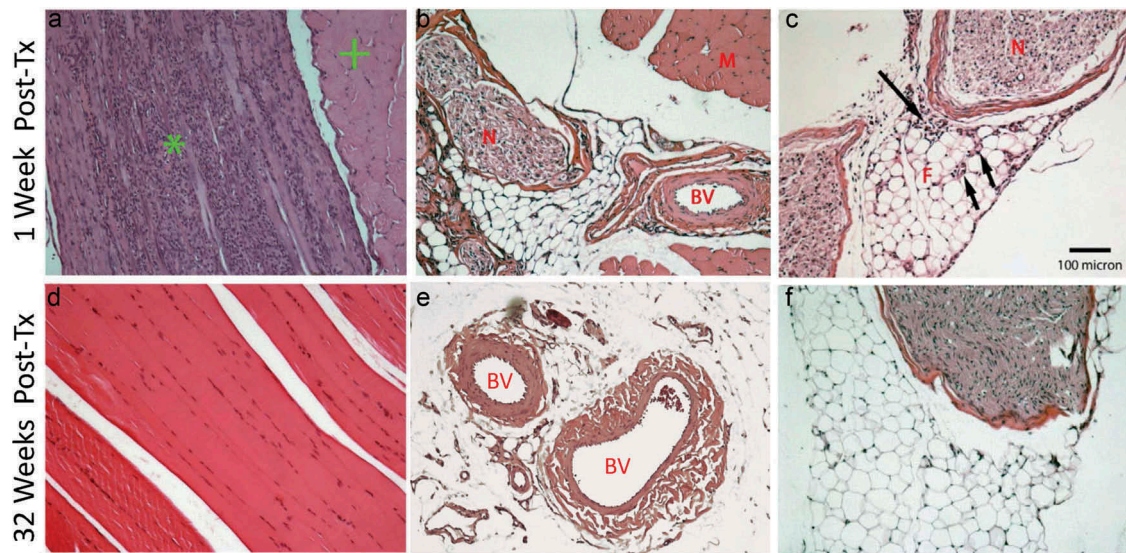
Figure 4. Recovery of surrounding tissues after cryoneurolysis (image courtesy of Myoscience).

cryoneurolysis likely differ from those following a traumatic insult, since there is limited inflammatory response to cryoneurolysis.

Evidence of the inherent safety of cryoneurolysis may be found in its history spanning half a century: in more than 50 years of use, there have been no published cases of permanent nerve damage, and only a single case of neuritis following treatment [37]. These findings are consistent with a study cited by Zhou and colleagues [38] in which none of 6000 patients treated with cryoneurolysis for acute or chronic lower back pain reported a subsequent neuroma or neuritis.

Histological results from animal studies involving the application of cold to nerves and blood vessels support these data. For example, one study involving the treatment of rats with a single or three repeated cryoneurolysis treatments demonstrated that at 8–32 weeks posttreatment, the blood vessels, fat tissue, and surrounding muscles appeared normal [31]. In this same study, it was found that the small arterioles in proximity to the treatment site showed rare fibrinoid degeneration, but their lumens remained patent. Khairy [35] examined the effects of treating atrial and ventricular structures in a canine model with various cooling rates to −55° and −75°C, revealing that the underlying tissue and extracellular matrix architecture were preserved and there was no evidence of endocardial thrombus formation. These results hold even at colder temperatures: two studies which examined the effect of liquid nitrogen (−196°C) on canine carotid and femoral arteries (*in vivo*) [39] as well as the porcine vena cava [40] demonstrated necrosis of the affected cells, but the collagen and elastic structure remained largely intact. Though the mildest treatment used in these studies was colder and larger than what would theoretically be produced in a cryoneurolysis treatment, the vessels were able to provide blood flow and regenerate with normal function and histological features, suggesting the wide therapeutic index and impressive margin of safety when using cryoneurolysis.

4.1. Side effects and contraindications

The potential side effects of cryoneurolysis include bleeding, bruising, redness, and infection at the site of treatment. Unsurprisingly, an insensate area may develop in the region of treated nerve. When treating chronic pain, a diagnostic block performed in advance will allow the patient to experience the result prior to cryoneurolysis. General contraindications to cryoneurolysis include patients with cryoglobulinemia, cold urticarial, and Reynaud's syndrome.

Skin and hair in the general proximity of treatment may be affected if the target nerve is relatively superficial. To protect the skin and hair, some newer devices designed for treatment of superficial nerves include an integrated skin warmer that protects the dermis and hair follicles from subdermal or follicular necrosis. However, in the instances when a cryoneurolysis device is used without thermal skin protection, hyper- or hypo-pigmentation may occur and alopecia may develop at the site of treatment, particularly at the eyebrow when treating the supraorbital nerve [37].

5. State of the technology

A cryoprobe consists of a hollow cannula that contains a smaller inner cannula. A pressurized cryogen gas at approximately 800 psi travels down the outer cannula and is released into the distal cannula tip. The rapid expansion of the gas at the cannula tip extracts surrounding heat, a process known as the Joule–Thompson effect (Figure 5). As a result of the temperature drop, an ice ball forms at the tip of the probe (Figures 6(a,b)). The gas is then vented through the inner cannula. In this way, the closed-end cannulas ensure that no gas is injected into the body. Most cryoprobes have an integrated thermistor to assess tip temperature and an insulated design permitting electrical current application to aid in motor nerve localization when combined with a nerve stimulator and to limit the ice ball formation to the tip of the probe. Most cryoprobes include a
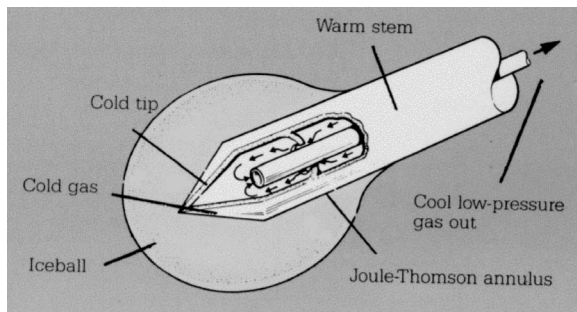
Figure 5. Joule-Thompson effect (image courtesy of Epimed).

Table 2. Table of available cryoprobes for cryoneurolysis.

Cryoprobe diameter	Needle gauge	Ice ball size (mm)
Portable device [41]		
0.7 mm	22G	9.4 × 5.4 oval
0.4 mm	27G	5.7 × 7.8 oval
Console-tethered device [37]		
2.0 mm	14G	5.5 ball
1.4 mm	17G	3.5 ball

intraoperative intercostal cryoneurolysis. The size and probe lengths vary, depending on the medical need (Table 2). Cryoprobes may be either reusable or disposable.

5.1. Console-tethered devices

For console-tethered devices, the cryoprobe is connected to the console and cryogen tank by a long flexible tube (Figure 7). Because of the high gas pressure of the console-based devices, the cryoprobe held at any angle will still function appropriately, and the large tank of cryogen gas allows more freeze cycles. Resulting ice balls range in size from 3.5 to 5.5 mm in diameter [37] or 6 mm in diameter [41]. The reusable probe and tubing can be steam or gas sterilized (Epimed International, Farmers Branch, TX, USA), and, in Europe, there are disposable systems (Metrum Cryoflex, Warsaw, Poland). These console systems also usually include a sensory and motor stimulation component that allows for more precise sensory nerve localization in the awake patient, as well as confirmation of intended or unintended motor stimulation. The probes for these systems are usually large (12-16 gauge), though smaller systems (20-25 gauge) are being developed. In general, the bigger the probe, the bigger the ice ball, and the more nerve that is then incorporated into the ice ball, which should increase the probability of a successful lesion. However, this larger probe may be more challenging to place, and the larger ice ball also increases the risk of skin damage when addressing superficial nerves.
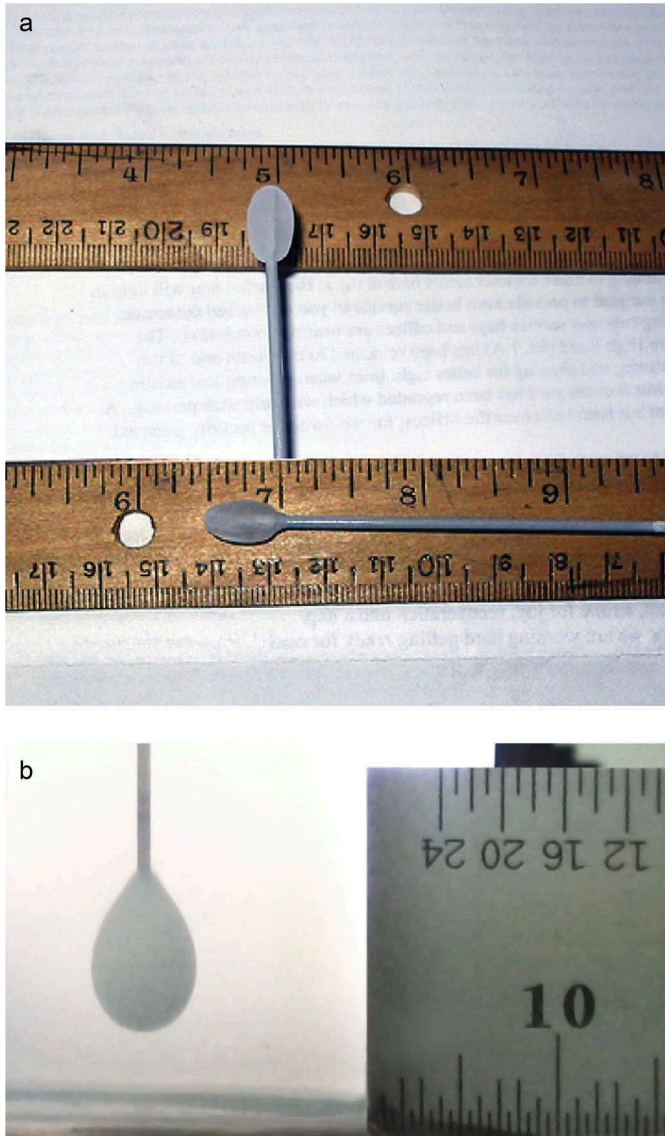

Figure 6. (a) Ice ball formation for a console-tethered device (image courtesy of Epimed) with a ruler showing centimeters and inches on the bottom and top, respectively, of each ruler; (b) Ice ball formation for a handheld unit (image courtesy of Myoscience) with a ruler showing millimeters and inches on the bottom and top, respectively, of the ruler.

Figure 7. Example of a console-tethered cryoneurolysis system (image courtesy of Andrea Trescot, MD).

proximal portion of the probe that is insulated as well as a distal portion that is uninsulated, though one probe (Atricure-USA, Raleigh, NC, USA) is flexible and uninsulated, used for

An additional console system is now available for intraoperative intercostal cryoneurolysis to treat postoperative pain after thoracic surgeries; this system utilizes a flexible uninsulated probe that freezes along its entire length, which is positioned along the length of the nerve before wound closure (Atricure-USA, Raleigh, NC, USA). Because the probe is flexible, it can be molded to match the contours of the rib. This system is only used intraoperatively to provide postoperative analgesia after open chest procedures.

5.2. Handheld devices

Currently, there is only one handheld cryoneurolysis device: the iovera° system (Myoscience, Fremont, CA, USA). The iovera° system cryoprobe diameters range in size from 0.4 to 0.7 mm and are controlled by a battery-powered, portable handpiece (Figure 8). During treatment, compressed nitrous oxide flows from a consumable cartridge through the insulated handpiece, which is used to cool the sterile, disposable, single-patient-use Smart Tips (Figure 8). The currently available iovera° system Smart Tips includes a 3-needle 6.9-mm tip (27 G) and a single-needle 55-mm tip (22 G), with ice ball sizes of 5.7mm × 7.8 mm and 9.4 mm × 5.4 mm, respectively [42]. Since the 6.9-mm tip is used to treat superficial peripheral nerves, it has been designed with an integrated skin warmer that protects the dermis and hair follicles from subdermal vascular occlusion and subsequent dermal necrosis, which can occur with larger, console-tethered probes that do not have skin warmers.

The handheld device can be used in a variety of settings, but does require that the patient be positioned so that the handpiece remains vertical in order to maintain the pressure of the cryogen. Though the Smart Tips are sterile, the handpiece and the nitrous oxide canisters are not. For this reason, a sterile sleeve or bio-occlusive dressing must be used as a barrier in a sterile environment. There is no sensory or motor stimulation function, and, because the probe must be held at least mostly upright, ultrasound or fluoroscopic positioning may be difficult. However, due to the portable nature of the handpiece and the small footprint of the charging dock, the device may better fit in an office setting as well as in a hospital or ambulatory surgery center where multiple departments may share the same handpiece.

6. Clinical applications

6.1. Perioperative treatment for post-surgical pain

Postoperative pain is an issue in up to 60–90% of surgical cases during the first 24 postoperative hours [43]. In some cases, pain is often difficult to control for multiple days or weeks. For example, patients undergoing a total knee arthroplasty (TKA) typically experience significant postoperative pain for 1–2 months [44–46]. However, the most common analgesic – opioids – are associated with undesirable side effects such as nausea, vomiting, pruritis, respiratory depression, sedation, and ileus [44,46,47]. Furthermore, the threat of prescribed opioid drug abuse is persistent and growing, with the annual economic cost of nonmedical use of prescription opioids in the U.S. estimated at over $53 billion in 2011 [48]. As recently as 2014, the U.S. Department of Health and Human Services stated that Federal agencies should promote nonopioid pharmacological therapies as part of an overall pain management plan [49]. In addition, a variety of organizations, such as the American Society of Anesthesiologists, also recommend employing an individualized, multimodal treatment plan to manage pain to minimize opioid requirements [50,51].

Cryoneurolysis may be an excellent addition to a multimodal analgesic regimen, providing potent, localized analgesia with a duration that is typically on the order of weeks to months. Preoperative cryoneurolysis may allow for a reduction
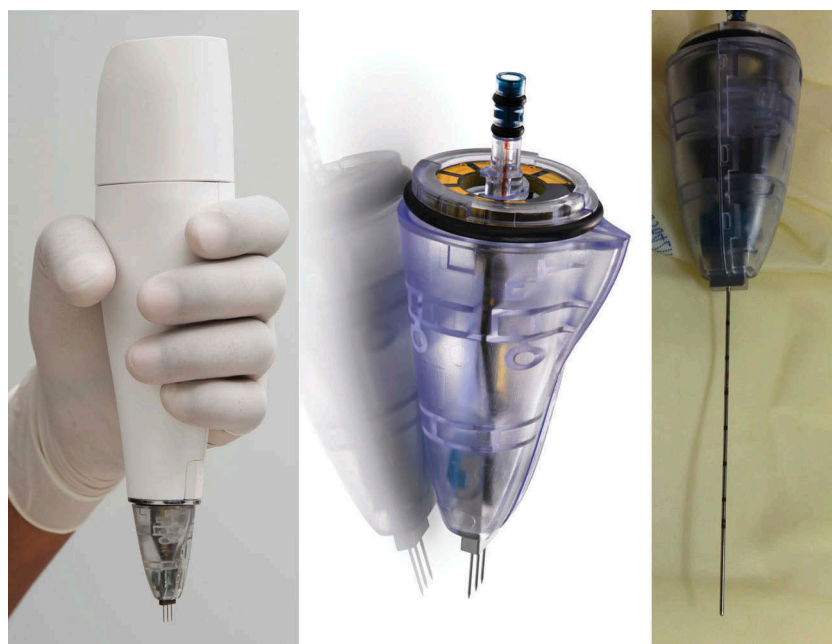

Figure 8. The hand held iovera° system and two single-patient-use Smart Tips (image courtesy of Myoscience).

in opioid and non-steroidal anti-inflammatory drug require-ments both prior to and following surgery.

As an example, the infrapatellar branch of the saphenous nerve (IPBSN) is solely a sensory nerve that innervates the anterior and inferior parts of the knee capsule as well as the skin over the antero-medial knee [52–56]. Several studies (including two randomized, double-blinded, placebo-con-trolled trials) have examined the efficacy of a selective nerve block of the IPBSN for treatment of postoperative knee pain [57–61]. Trescot described the use of cryoneurolysis of the IPBSN for knee pain in 2003. In 2006, Lundblad [62] estab-lished a technique which utilized ultrasound to identify the IPBSN and inject levobupivacaine (Chirocaine, Abbott Scandinavia AB, Solna, Sweden) perineurally. The success rate was 90% and the duration of the block usually exceeded 16 h, which makes it potentially useful for postoperative analgesia for surgical procedures of the knee.

Although a definitive study involving cryoneurolysis has yet to be published, there is currently evidence from local anes-thetic-induced anesthesia suggesting that cryoneurolysis would provide postoperative analgesia. A randomized, dou-ble-masked, placebo-controlled clinical trial (n = 64) of patients undergoing anterior cruciate ligament repair involved an IPBSN block with levobupivacaine (Chirocaine, Abbott Scandinavia AB, Solna, Sweden) 10–20 min prior to the proce-dure [57]. At 16–24 h postoperatively, the percent of patients with a pain score higher than 3 (out of 10) was lower in the block group than the sham group (P = 0.0117). A similar randomized, double-masked, placebo-controlled clinical trial (n = 68) involving patients undergoing simple knee arthro-scopy reported statistically significant reductions in early post-operative numerical rating scale (NRS) pain scores (immediately and 1 h postoperatively) for those patients who received the IPBSN block with local anesthetic prior to the procedure (P = 0.03) [58]. These patients also reported less nausea and significantly improved Lysholm knee scores (a measure of activity level) at 12 weeks posttreatment (P = 0.03 and P = 0.04).

A proof-of-concept study suggested that cryoneurolysis could also be used to effectively block the IPBSN for at least 30 days [63]. In this study, the IPBSN was located using anato-mical landmarks [54]. Subsequently, a method for locating the anterior femoral cutaneous nerve (AFCN), which innervates the anterior superior part of the knee capsule and may offer additional postoperative relief, was defined and validated in a cadaveric model [64].

A recent retrospective chart review of 100 patients who underwent a TKA examined a cryoneurolysis-treated group versus a historical control group [61]. Half of the patients received a cryoneurolysis treatment (iovera° system, Myoscience, Fremont, CA, USA) to the IPBSN and AFCN 5 days prior to TKA. The other half of patients received the same standard preoperative and postoperative care, but did not receive cryoneurolysis (not randomized). The average mor-phine equivalent of opioids consumed over the 12-week per-iod following surgery was lower for the cryoneurolysis-treated group (2069 mg) compared to the control group (3764 mg; P < 0.0001). The average length of hospital stay was also lower in the cryoneurolysis-treated group (0.8 days) compared to the

control group (1.7 days; P < 0.0001). Though the two groups showed similar pain and functionality scores, the cryoneuro-lysis patients requested half as much opioid to achieve similar analgesia. Further, the cryoneurolysis-treated group had a shorter length of hospital stay and showed a significantly greater reduction in symptoms than the control group at 6 weeks (P = 0.0037) and 12 weeks (P = 0.0011) as measured by the Knee Injury and Osteoarthritis Outcome symptoms subscore.

A randomized, double-masked, sham-controlled trial is cur-rently ongoing to reexamine these findings with a prospective, experimental study design (http://www.clinicaltrials.gov; NCT02284113). This investigation will also measure patient satisfaction and rehabilitation end points such as range-of-motion and ambulation ability. The results presented here suggest that cryoneurolysis may be promising as part of a multimodal pain regimen for TKA and may be an effective and safe method for reducing postoperative opioid use and length of hospital stay.

Other randomized, controlled trials have shown that cryo-denervation significantly reduces persistent postsurgical pain and/or opiate requirements following thoracotomy [65] and tonsillectomy [66].

6.2. Postoperative cryoneurolysis

Persistent nerve entrapment and nerve pain are not uncom-mon after TKA, partly because of trauma to the nerves by the tourniquet [67] and partly by trauma to the knee nerves from the surgery itself [52], and, this can result in poor TKA outcomes.

A case report of cryoneurolysis for the treatment of refrac-tory knee pain after TKA was recently presented [68]. At 3 months post-TKA, a 75-year-old female patient reported marked stiffness of the knee and intractable pain. She also expressed that she had difficulty performing daily tasks and sleeping because of the knee pain. After 33 sessions of indivi-dualized postoperative physical therapy, the patient was dis-charged for failure to make progress and, despite the fact that her radiographs revealed a well-aligned and well-fixed cemen-ted TKA, she was scheduled to undergo knee manipulation under general anesthesia. After discussion with the surgeon, an office-based cryoneurolysis treatment with the iovera° sys-tem (Myoscience, Fremont, CA, USA) was performed on the IPBSN using anatomical landmarks and ultrasound for nerve localization. The visual analogue score (VAS) for pain decreased from 10/10 at baseline to 0/10 at 15 min postpro-cedure. Following her cryoneurolysis treatment, she allowed aggressive manipulation of her knee, with increases in both extension and flexion. A collective decision was made to cancel her upcoming surgery and to restart physical therapy. At the follow-up 10 weeks later, the patient was also able to participate in an aggressive home exercise program with increased range of motion and function, and reported signifi-cant satisfaction with the results of her surgery.

In a second case report [69], a 59-year-old obese male presented with severe constant bilateral thigh pain of 3 months duration following a bilateral TKA. He was diag-nosed with meralgia paresthetica due to lateral femoral

cutaneous nerve entrapment but failed physical therapy and multiple analgesic regimens. Cryoneurolysis, using the iovera° system (Myoscience, Fremont, CA, USA), was performed on both nerves under ultrasound guidance. The patient reported pain relief immediately, and reported a VAS pain score of 2/10 at his 3-month follow-up.

Other uses of postoperative cryoneurolysis include as treatment for postherniorrhaphy pain [70], and postthoracotomy pain [71], .Cryoneurolysis may be an effective treatment for these pains and should be considered prior to more invasive solutions. Other indications may develop as the interest in perioperative cryoneurolysis grows.

6.3. Treatment of chronic pain

Cryoneurolysis of sensory peripheral nerves has been used for many decades to treat chronic pain [37,72–75]. Many of these patients find rehabilitation to be ineffective because pain limits their ability to accomplish certain activities. However, a cryoneurolysis treatment may allow patients to proceed with a painless rehabilitation program, thereby leading to an increased ability to complete physical therapy. Since cryoneurolysis allows for complete nerve regeneration, the patient would then regain of function following treatment. Uncontrolled studies suggest cryoneurolysis relieves pain in patients with disorders as diverse as postherpetic neuralgia [76], occipital neuralgia [77], and neuromas [78,79], as well as intractable facial [27,75,80–82], temporomandibular joint [83], lumbar zygapophysial joints [84], intercostal neuralgia [85,86], plantar fasciitis [87], phantom limb pain [88], as well as perineal and pelvic pain [89]. Pain relief duration ranges from 2 months to a few years [75,80]. Ultrasound guidance has improved the localization and thus efficacy of the cryoneurolysis [90].

6.4. Treatment of lumbar facet joint pain

Three recent prospective clinical trials described the use of cryoneurolysis for the treatment of lumbar facet joint pain. In one study of 46 patients who underwent cryoneurolysis [91] (Lloyd Neurostat 2000, Spembly Medical Systems, Hampshire, UK), results showed that the mean pain VAS score decreased significantly from 7.7 at baseline to 3.2 at 6 weeks and 3.3, 3.0, and 4.2 at 3, 6, and 12 months, respectively ($P < 0.0001$). The sole complication was a vagus-induced syncope.

Another study [92] demonstrated that of the 50 patients who underwent cryoneurolysis (Lloyd Neurostat, Spembly Medical, Hampshire, UK), 62% experienced greater than a 50% reduction in pain (deemed a responder) after 1 year and 76% experienced a reduction in VAS pain score of 3 or more after 1 year. The results also showed that 85% of patients who had not undergone spinal surgery were responders compared to just 47% of those who had undergone previous spinal surgery. In addition, 64% of those who were unable to work prior to cryoneurolysis returned to work after the procedure. The improvement in mean VAS scores in all 50 patients (responders and nonresponders) was significant at all

postoperative visits and there were no complications associated with treatment.

A study which followed from this [93] utilized computerized tomography to locate the medial nerve branch prior to cryoneurolysis treatment (Spembly Medical, Hampshire, UK) in 76 patients. Results were consistent with those of the previous study in that 56% of the patients were responders (>50% reduction in pain VAS) after 1 year, with responders reporting a median duration of pain relief lasting 14 months. Similarly, it was found that the duration of relief was significantly longer for patients with no prior surgical treatment of the relevant spinal segment than for those who had previously undergone surgery ($P < 0.03$). In addition, pain medication was reduced in 61% of patients and 29% of those who had stopped working were able to return to work after treatment. A subset of the population underwent a second ($n = 18$), third ($n = 7$), and fourth ($n = 1$) treatment with a duration of pain relief similar to that after the first treatment ($P < 0.05$). None of the patients in the entire population reported any side effects.

6.5. Treatment of chronic knee pain secondary to osteoarthritis

A small proof-of-concept study ($n = 10$) was carried out to examine the effect of cryoneurolysis of the IPBSN for the treatment of chronic knee pain due to osteoarthritis using anatomical landmarks [63,64]. After treatment with the iovera° system (Myoscience, Fremont, CA, USA), the average pain scores (NRS) decreased from a baseline of 6 to 1, 2, and 2 after 0, 7, and 30 days, respectively. At 7 and 30 days posttreatment, 90% of patients reported that they would have the treatment again. These results are consistent with an unpublished clinical trial (http://www.clinicaltrials.gov; NCT01704157; Myoscience, data on file) in which 33 adults with knee osteoarthritis received cryoneurolysis to the infrapatellar branch of the saphenous nerve. At 7 days posttreatment, 91% of subjects had reduced pain, and 30 days following treatment, the NRS reduction averaged 4 points on the 0–10 pain NRS ($P < 0.0001$). The average Western Ontario and McMaster Universities Arthritis Index improvement of ≥2 points per question occurred in 77% of subjects, with an overall decrease of 86 points, representing a 70% improvement from baseline ($P < 0.0001$). A randomized, double-masked, sham-controlled trial is ongoing to provide definitive data (http://www.clinicaltrials.gov; NCT02260921).

6.6. Treatment of spasticity

Spasticity is a motor disorder that occurs frequently in individuals with stroke, traumatic brain injury, spinal cord injury, cerebral palsy, and multiple sclerosis [94]. Clinical manifestations of spasticity include muscle spasms, involuntary jerking motions, exaggerated reflexes, and stiff or tight muscles and joints [94]. Marked spasticity and the associated abnormal postures can cause pain and loss of strength, dexterity, and range of motion; interfere with performance of daily activities and sleep; disturb gait and balance; and impair quality of life [94,95].

Current treatment options for spasticity include oral medications, intrathecal baclofen, and local injection of phenol, alcohol, or botulinum toxin. Although all of these treatments can be effective, each has limitations. Oral medications cause systemic side effects and are ill-suited to target regional or focal spasticity [96]. Intrathecal delivery of baclofen reduces the incidence of systemic side effects, but is invasive and costly [96]. Injection of phenol or alcohol is often painful and can cause tissue necrosis and sensory dysesthesias [96]. Use of botulinum toxin may be of limited use in treating large muscles, can lead to the development of clinical resistance, and includes the risk of diffusing beyond the target muscle, causing unwanted muscular weakness [97,98].

6.6.1. Treatment of motor nerves

Two recent preclinical reports described the feasibility of using freezing temperatures to treat motor nerves for treating movement disorders [30,31]. The first study [30] demonstrated that cryoneurolysis treatment of the rat tibial nerve resulted in temporary (8 weeks) reduction of physiological function of the hind limb. Histological observations of the nerve revealed demyelination and axonal degeneration by 2 weeks posttreatment followed by complete axonal regeneration and remyelination by 16 weeks posttreatment. There were no permanent or long-term changes to function and structure of the nerves. Results of the second study [31] determined that even after multiple treatments, the animals experienced complete regeneration of the nerves and of all of the tissues in and around the treated area without fibrotic activity or scar tissue.

6.6.2. Treatment of upper limb spasticity

Neurolysis with alcohol or phenol has been used for spasticity for many years, but the risk of unintended spread of medication has limited its use. Case reports of the use of cryoneurolysis for spasticity have been in the literature since 1998 [99], and the precise neurolytic capability of cryoneurolysis may be very useful. A small proof-of-concept study examined the use of cryoneurolysis in the treatment of upper limb spasticity [100]. Nineteen patients at two different sites received a cryoneurolysis treatment of the musculocutaneous nerve (iovera° system, Myoscience, Fremont, CA, USA); the nerve was localized with either ultrasound and/or nerve stimulation. At 1 week and 4 weeks posttreatment, 74% and 79% of patients, respectively, showed at least a 1-point reduction on the Modified Ashworth Scale (MAS). Among the responders at the 4-week follow-up, 20% had 1-point reduction, 27% a 2-point reduction, 47% a 3-point reduction, and 7% had a 4-point reduction of the MAS. The patients showed statistically significant improvements on the MAS, Tardieu Scale V1 and V2, and spasticity NRS at all posttreatment time points. The most common side effects were bruising, swelling, and local pain at the site of treatment. Though this first examination of cryoneurolysis for treatment of upper limb spasticity demonstrated statistically significant clinical improvements, further study is warranted.

7. Expert commentary and five-year view

Cryoneurolysis is a well-proven technique, with more than 50 years of evidence. However, the technique had fallen out of favor because of a lack of training programs. The combination of new cryoneurolysis technology, the recognition that peripheral nerve pathology can lead to persistent pain problems, the development of ultrasound localization of peripheral nerves, and the recognition that aggressive preoperative pain management can prevent long-term pain conditions have all lead to a resurgence of interest in cryoneurolysis. This technique is reversible, long-lasting, and readily available in the office or operating room to provide pain relief.

As the movement to reduce opioid use grows, the treatment of chronic or postoperative pain with cryoneurolysis will become more attractive as it has been proven effective with a safety profile that is superior to systemic pharmacological solutions or other neurolysis therapies. Cryoneurolysis may also present treatment options for movement disorders, such as spasticity. Further, cryoneurolysis may appear as a more economically attractive treatment, particularly for the treatment of postoperative pain, as it has the potential to reduce opioid-related side effects, acute care facility costs, nosocomial infections, and has the potential to promote an earlier return to work.

8. Conclusions

Cryoneurolysis is a well-established technology that has been in use for more than 50 years, and has been demonstrated to be a safe and effective option for the treatment of peripheral sensory nerves. New technological advances, such as the handheld iovera° system, have enabled a treatment that is more flexible and less invasive, and perhaps better suited to treat superficial nerves. This has led to a renewed interest in cryoneurolysis as a means for the treatment of acute and chronic pain as well as, potentially, movement disorders. The clinical evidence presented here highlights the impact that cryoneurolysis could have on the treatment of peripheral nerves as part of a changing health-care landscape.

Declaration of interest

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