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REVIEW

Percutaneous cryoneurolysis for acute pain management: current status and future prospects

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ABSTRACT

Introduction: Conventional nerve blocks utilize local anesthetic drugs to provide pain relief for hours or days following surgery or trauma. However, postoperative and trauma pain can last weeks or months. Ultrasound-guided percutaneous cryoneurolysis is an anesthetic modality that offers substantially longer pain relief compared to local anesthetic-based nerve blocks.

Areas covered: In this review, we discuss the history, mechanism of action, and use of ultrasound-guided percutaneous cryoneurolysis by anesthesiologists in the setting of acute pain management.

Expert opinion: Ultrasound-guided percutaneous cryoneurolysis offers the potential to provide weeks or months of pain relief following surgery or trauma. Compared to continuous local anesthetic-based peripheral nerve blocks, currently the gold standard for providing long duration postoperative analgesia, cryoneurolysis has benefits that include: 1) longer duration measured in weeks or months rather than days; 2) no external reservoir of local anesthetic to be carried by the patient; 3) no risk of infection; and 4) no risk of catheter dislodgement. However, cryoneurolysis can induce a prolonged motor block in addition to the sensory block, decreasing the appropriate indications to those in which potential sensory and motor deficits are acceptable. Additionally, cryoneurolysis of multiple nerves can have a substantial time requirement relative to conventional nerve blocks.

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Acute pain; cryoanalgesia; cryoneurolysis; postoperative pain; regional anesthesia; ultrasound

1. Introduction

The United States is currently in in the midst of an opioid epidemic, and many chronic opioid users receive their introduction to opioids in the form of treatment for acute pain [1]. Anesthesiologists, therefore, have a role in mitigating the chronic use of opioids [2], with multimodal opioid-sparing techniques, in particular regional anesthesia, having the potential to dramatically decrease opioid use following major surgery [3]. Historically, catheter-based continuous peripheral nerve blocks have offered the longest duration of analgesia in the regional anesthesiologist's armamentarium. This technique involves placement of a perineural catheter adjacent to a target nerve with local anesthetic drug delivered *via* the catheter [4]. However, while continuous peripheral nerve blocks greatly extend analgesia beyond the hours that can be provided by a single-injection of local anesthetic, the duration of the therapy is still limited to days – or, rarely, weeks – with infection risk increasing while the catheter remains *in situ* [5,6]. Thus, there is a societal need for an extended duration regional analgesic modality with a duration of the weeks to months patients may experience pain following major surgery or trauma.

Cryoanalgesia, broadly defined as the use of cold temperature to treat pain, is an analgesic modality that dates to ancient Egypt [7]. For much of its history, cryoanalgesia relied on ice, usually in the form of snow [8]. Modern cryoanalgesic devices utilize a closed system in which a pressurized gas, usually nitrous oxide, flows down a tube contained within the cryoneurolysis probe/cannula to a low-pressure closed end before being vented back along the length of the probe and out through the machine. As the gas enters the low-pressure chamber at the tip of the probe, the pressure drops and a corresponding volume expansion results in a precipitous decline in temperature. This phenomenon, first described by James Prescott Joule and William Thomson in 1852, is known as the Joule-Thomson effect [9]. Importantly, neither the gas nor any other substance is injected into the patient. As the temperature of the probe drops, an 'ice ball' encompassing tissue forms around its tip (Figure 1), resulting in a reversible axonal injury and analgesia in the distribution of the treated nerve [10]. This reversible axonal injury and associated analgesia is termed **cryoneurolysis**[9]. Cryoneurolysis has been employed for acute and chronic pain as both an open surgical procedure and, more recently, a percutaneous ultrasound guided procedure. This review focuses primarily on ultrasound-guided percutaneous cryoneurolysis for acute pain (Table 1).

2. Mechanism of action of cryoneurolysis

When nerve tissue is frozen, varying degrees of injury can be produced in a temperature dependent manner:

(A) When a nerve is frozen but the temperature does not drop below −20°C, **neuropraxia** occurs resulting in injury to the nerve not severe enough to cause

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Article highlights

- **Cryoanalgesia**, use of cold temperature to treat pain, is a concept that dates to ancient times.
- **Cryoneurolysis** occurs when nerves are subjected to temperatures between −20 and −100°C resulting in reversable axonal death distal to the treatment site, but leaving an intact endo-, peri-, and epineurium. As axons regenerate at a rate of 1-2 mm per day, the duration of analgesia is related to the distance between the cryoneurolysis site and the location of the pain.
- Historically, cryoneurolysis was performed as an open procedure through a surgical incision, but advancement in ultrasound guidance and percutaneous probes/cannulas has allowed anesthesiologists to apply cryoneurolysis to target nerves **percutaneously**.
- Cryoneurolysis produces a prolonged **sensory and motor block**, hence optimal target nerves are those with limited or no motor function. Major nerves may be targeted for amputation patients (e.g. femoral and sciatic nerves for lower extremity amputations).

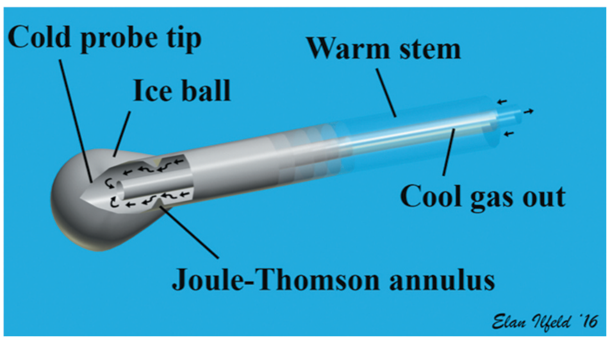

Figure 1. Schematic of a modern cryoneurolysis probe. Gas (nitrous oxide or carbon dioxide) flows from the machine to the tip of the probe. At the tip of the probe, the gas passes through a small annulus into a low-pressure chamber. This pressure drop results in a precipitous decline in temperature due to the Joule-Thomson effect, and an ice ball of frozen tissue forms around the tip of the probe.

degeneration of the axons. This generally induces a block lasting minutes to weeks [11].

(B) At temperatures between −20 and −100°C, axonal injury occurs and nerves undergo Wallerian degeneration. This phenomenon, eponymously named after Augustus Volney Waller, a British neurophysiologist, describes the process of axonal death distal to a site of injury occurring due to the fact that the nuclei and genetic information are contained in the proximal end of the cell. Importantly, at temperatures warmer than −100°C, the connective tissue surrounding the axon, consisting of *endoneurium, perineurium*, and *epineurium*, is not injured and remains intact. Axons can then regenerate at a rate of 1–2 mm per day along the surviving skeleton to reinnervate the tissue at the terminal nerve endings [12]. Thus, **cryoneurolysis** is successfully achieved at temperatures between −20 and −100°C [13,14]. Carbon dioxide and nitrous oxide, which respectively freeze to −55°C and −70°C via the Joule Thomson effect are the two most commonly used gases for cryoneurolysis. As the treated nerves regenerate at 1–2 mm per day, the duration of the induced block is variable, but proportional to the distance between the cryoneurolysis site and the terminal nerve branches responsible for the pain signals.

(C) When nerves are frozen to temperatures below −100° C, the connective tissues sheath around the nerve suffers irreversible injury (**neurotmesis**) and axons will not regenerate to reinnervate the tissue [11].

The duration of action of cryoneurolysis – dependent on the 1–2 mm per day regeneration rate of the treated axons – while greatly appealing from a pain control perspective, is simultaneously a limiting factor in its application. Weeks or months of muscle weakness is often unacceptable due to both negatively affecting participation in in physical rehabilitation and interference with activities of daily living. Indeed, it is the goal of utilizing regional anesthetics to *improve* participation in physical rehabilitation and *hasten* return to activities of daily living. Therefore, large nerves commonly blocked by regional anesthesiologists (e.g. femoral, sciatic, brachial plexus) are usually poor candidates for cryoneurolysis. Cryoneurolysis is optimally applied to nerves that have little or no motor function, or in situations where the innervated muscle is no longer functional or present (e.g. amputation). Nevertheless, for the limited applications that will be described, cryoneurolysis has the potential to provide pain relief that far surpasses the duration of other available regional anesthetics [4,5].

3. Intraoperative cryoneurolysis for acute pain

The first reports of cryoneurolysis for acute pain are found in the surgical literature, having been performed as an open – as opposed to percutaneous – procedure for postoperative pain following thoracotomy and inguinal herniorrhaphy.

Post-thoracotomy pain – Cryoneurolysis was first reported for acute pain as an analgesic modality to prevent post-thoracotomy pain in the 1970's [15]. This technique requires surgical exposure of the intercostal nerves to apply the cryoneurolysis device directly to the nerve. Randomized clinical trials over the subsequent decades comparing surgical intercostal cryoneurolysis to various conventional analgesic regimens for thoracotomy, mini-thoracotomy, and pectus excavatum repair have demonstrated mixed results. Several studies demonstrated benefits in pain scores, opioid consumption, tests of pulmonary function, and hospital length of stay [16–27]; while others failed to find significant benefit of open surgical intercostal cryoneurolysis compared to conventional oral, intravenous, and regional analgesics [28–33].

Post-inguinal herniorrhaphy pain – Surgical cryotherapy to the ilioinguinal, iliohypogastric, and genitofemoral nerves has yielded similar results in randomized trials. An early investigation demonstrated benefit of cryoneurolysis of the ilioinguinal nerve compared to paravertebral local anesthetic block or oral analgesics alone [34], while a subsequent trial failed to find benefit of cryotherapy compared to a sham procedure [35]. A third randomized trial of open cryoneurolysis of the ilioinguinal and genitofemoral nerves successfully treated postoperative neuralgia following inguinal herniorrhaphy [36].

The mixed results observed in these studies may be related to the widely variable techniques that were described. Amongst these studies there is great variability in the number and duration

Table 1. Reports of ultrasound-guided percutaneous cryoneurolysis applications for acute pain management following surgery or trauma within the peer-reviewed literature.

	Peripheral Nerve(s) Targeted	Source of Pain	Type of Report	Primary Findings
Upper Extremity				
Ilfeld [75]	Suprascapular nerve	Rotator cuff repair	Case Series (n = 2)	Decreased pain scores compared to historical controls, return to normal function in < 3 weeks
Gabriel [88]	Median, radial, and ulnar nerves	Partial hand amputation	Case report (n = 1)	Minimal pain reported in the hand following amputation despite history of chronic pain
Trunk				
Gabriel [67]	11^{th} Intercostal nerve	Percutaneous nephrolithotomy	Case report (n = 1)	15 days of relief from severe pain following percutaneous nephrostomy with stent placement
Gabriel [65]	2^{nd} – 5^{th} Intercostal nerves	Mastectomy	Case Series (n = 3)	Decreased pain scores and opioid consumption compared to historical controls
Finneran [61]	Intercostal nerves	Rib fractures	Case Series (n = 5)	All patients experienced decreased pain and improved incentive spirometry use for multiple weeks
Gabriel [67]	11^{th} Intercostal nerve	Iliac crest bone graft harvesting	Case report (n = 1)	Multiple weeks of relief from severe pain following iliac crest bone graft harvesting
Lower Extremity				
Dasa [78]	Anterior femoral cutaneous and infrapatellar branch of saphenous nerves	Knee arthroplasty	Retrospective cohort (n = 50)	Decreased opioid consumption, less pain interference with activities of daily living, and shorter hospitalization compared to historical controls
Radnovich [79]	Infrapatellar branch of the saphenous nerve	Knee osteoarthritis	Randomized trial (n = 180)	Improvement from baseline pain scores at 30, 60, and 90 days
Finneran [68]	Lateral femoral cutaneous nerve	Skin graft harvesting	Case Series (n = 2)	Minimal pain in the graft donor site for 7–9 days following surgery
Gabriel [67]	Tibial and superficial peroneal nerves	Burn to dorsal and plantar 1^{st} – 3^{rd} toes	Case report (n = 1)	14 days of pain relief allowing for burn management as outpatient
Gabriel [88]	Femoral and sciatic nerves	Lower extremity amputation	Case Series (n = 2)	Months of pain relieve with minimal phantom pain more than 6 months following surgery

of cryoneurolysis cycles, the extent of manipulation of the nerve (manipulation being an additional source of nerve injury), and surgical pain outside the expected distribution of the block. However, one aspect all these studies have in common is being performed as an open surgical procedure performed by a surgeon.

4. Percutaneous cryoneurolysis for acute pain

The development of percutaneous probes allowed for cryoneurolysis to be accomplished without an open surgical incision, and brought cryoneurolysis into the realm of regional anesthesiology. All percutaneous techniques differ from open surgical cryoneurolysis in an important manner: as the nerve is not surgically exposed and directly visible to the operator, there is the additional requirement of nerve localization. Various techniques to guide probe insertion have been described, including: anatomic landmark based techniques [37], nerve stimulation [38], and needle guidance using biplane radiographic [39,40], fluoroscopic [41,42], computed tomography [43–47], magnetic resonance [48–50], and ultrasound imaging [51,52]. Ultrasound guidance is particularly useful among these techniques as it allows the operator to position the cryoneurolysis probe directly adjacent to the nerve and permits real-time visualization of the ice ball

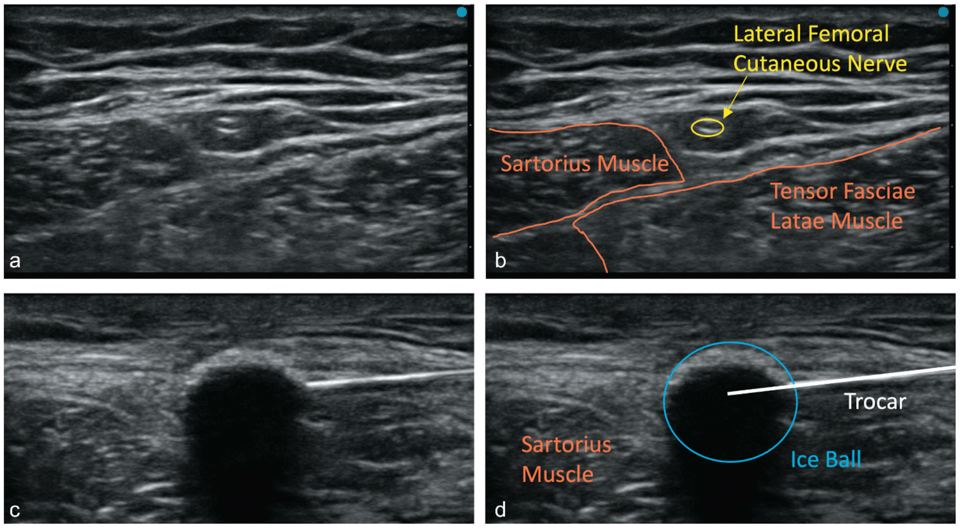

Figure 2. Ultrasound-guided cryoneurolysis of the lateral femoral cutaneous nerve. Use of ultrasound allows the trocar shaped cryoneurolysis probe to be positioned adjacent to the target nerve and real-time visualization of the ice ball enveloping the target nerve.

enveloping the targeted nerve without exposing patients to radiation (Figure 2) [53,54].

Ultrasound-guided percutaneous cryoneurolysis is particularly appealing to anesthesiologists as the technique is relatively similar to conventional local anesthetic based nerve blocks commonly performed by anesthesiologists in terms of needle/probe positioning and nerve localization. The ubiquity of ultrasound machines, availability of mobile console and handheld cryoneurolysis devices, and pervasive ultrasound skills amongst anesthesiologists may prove to be a confluence of factors allowing widespread adoption of this analgesic modality [55]. Recent case reports and series have suggested many acutely painful conditions that may benefit from ultrasound-guided percutaneous cryoneurolysis, although randomized trials are needed.

(A) *Rib fractures* – Rib fractures are associated with severe pain that may persist for weeks or months [56]. This pain is associated with decreased ability to deeply inspire, cough, and use incentive spirometry devices, all of which are factors predisposing these patients to pneumonia and increasing mortality [57]. Local anesthetic-based intercostal nerve blocks decrease pain and improve peak expiratory flow rates and arterial oxygen saturation on room air [58]. Unfortunately, likely due to the highly vascular nature of the intercostal space, these blocks have an even shorter duration than most single-injection nerve blocks, providing as little as 6 hours of analgesia [59]. While continuous thoracic epidural analgesia offers similar benefits, the duration is limited to the length of the patient's hospitalization and epidural catheterization limits systemic anticoagulation and is associated with infection risks [60]. Case reports suggest that ultrasound-guided percutaneous intercostal cryoneurolysis may confer similar benefits to local anesthetic nerve blocks for rib fracture patients, but with substantially longer duration [61]. Ongoing randomized clinical trials (ClinicalTrials.gov NCT04198662) should soon add to our understanding of the benefits of percutaneous intercostal cryoneurolysis in the setting of rib fractures.

(B) *Post-mastectomy pain* – Pain after mastectomy is frequently severe, but can be greatly decreased with single injection and continuous regional anesthetics [62,63]. Continuous paravertebral nerve blocks not only improve pain and quality of life during the infusion, but may also decrease the incidence of pain-related physical and emotional dysfunction more than 1-year following surgery [63,64]. In a case series of three women who received 2nd-5th percutaneous intercostal nerve cryoneurolysis in addition to continuous paravertebral nerve blocks prior to undergoing unilateral or bilateral mastectomy, patients reported lower pain scores, fewer sleep disturbances secondary to pain, and less opioid consumption compared to historical controls receiving continuous paravertebral blocks alone [65]. At least one randomized clinical trial is currently evaluating the benefits of percutaneous intercostal cryoneurolysis for post-mastectomy analgesia (ClinicalTrials.gov NCT03578237).

(C) *Burn management* – Split-thickness skin autografting is commonly utilized in the management of 2nd and 3rd degree burns. The autograft harvest site, or 'donor' site, is usually the thigh. Pain management in burn patients is often particularly difficult for clinicians, especially since these patients have pain from both the burn and the donor site. Unfortunately, opioid analgesia is generally the first line modality for treating pain in burn patients and is associated with induced hyperalgesia in this population [66]. Regional anesthesia offers an excellent analgesic alternative for both care of the burn site–dressing changes and debridements–as well as donor site harvesting. Ultrasound-guided percutaneous cryoneurolysis of various nerves has been utilized to provide extended duration analgesia for management of scalding injuries from boiling water in the dorsal and plantar aspects of the first through third toes as well as the lateral thigh [67,68]. Regional anesthetics performed prior to donor site harvesting allow for the distribution of a nerve block to be traced with ice and marked to ensure the surgeon harvests from within the blocked area of skin. Nerve blocks of the lateral femoral cutaneous nerve are especially appealing for this technique as this nerve has no motor function and, therefore, yields a *sensory only* block [69]. Percutaneous cryoneurolysis of the lateral femoral cutaneous nerve has been utilized to provide weeks of analgesia following autograft harvesting from the lateral thigh [68].

(D) *Total knee arthroplasty* – Total knee arthroplasty is one of the most common surgical procedures performed in the United States, and is expected to become even more prevalent in the coming decades [70]. Pain following this surgery lasts weeks or months, and opioid naïve patients undergoing knee arthroplasty frequently still require opioid analgesics 6-months following surgery [71]. As local anesthetic-based nerve blocks provide excellent analgesia and improved functioning following knee arthroplasty [72], cryoneurolysis would seem to be an excellent opioid sparing alternative following knee arthroplasty [73]. Pain following knee arthroplasty is mediated primarily by the femoral nerve. Unfortunately, conventional blocks for total knee arthroplasty, which rely on blocking the femoral nerve either proximally deep to the inguinal ligament or distally within the adductor canal, increase the risk of falls secondary to weakness of the quadriceps and inhibition of proprioception [74]. More distal, isolated sensory branches of the femoral nerve, including the anterior femoral cutaneous nerve and infrapatellar branch of the saphenous nerve, may be more opportune targets for percutaneous cryoneurolysis [75–77]. Currently there are no randomized clinical trials evaluating percutaneous cryoneurolysis for knee joint arthroplasty, however, a retrospective cohort study found a lower percentage of patients remaining hospitalized for greater than 1 day (67% vs 6%; $p < 0.001$), a 45% decrease in opioid consumption during the first 12 postoperative weeks ($p < 0.001$), and less pain interference with daily living activities at both 6 ($P < 0.001$) and 12 weeks ($P < 0.001$) comparing patients who did to those who did not receive preoperative cryoneurolysis prior to total knee arthroplasty [78]. Additionally, a randomized trial comparing percutaneous cryoneurolysis of the infrapatellar branch of the saphenous nerve to a sham procedure for symptomatic treatment of knee osteoarthritis demonstrated improvement from baseline pain scores at 30 ($P = 0.0004$), 60 ($P = 0.0176$), and 90 ($P = 0.0061$) days compared to sham [79].

(E) *Shoulder arthroplasty and arthroscopy* – With rich innervation and a high degree of mobility, surgeries on the shoulder result in significant pain for an extended duration. The primary nerve innervating the glenohumeral joint is the suprascapular nerve, which has successfully been targeted to provide analgesia following rotator cuff repair by cryoneurolysis in the suprascapular notch [75]. In addition to its sensory component to the shoulder joint, this nerve innervates muscles of the rotator cuff – namely the supraspinatus and infraspinatus – responsible for abduction and external rotation of the shoulder, respectively. Given the suprascapular nerve's combined motor and sensory function, there is concern that paralysis of these muscles for weeks or months may interfere with physical rehabilitation. Although, weakness of these muscles would potentially be counterbalanced by decreased pain and consequent improved passive range of motion. Additionally, some clinicians have expressed concern for long-term or permanent motor deficits in muscles innervated by nerves that have undergone cryoneurolysis. However, multiple preclinical studies have identified no long-term changes in the nerves themselves or the muscles they innervate following tibial and common peroneal nerve cryoneurolysis and recovery [80–82]. Further randomized trials will be needed to evaluate both 1) the effect of cryoneurolysis of the suprascapular nerve on pain and opioid consumption following painful shoulder surgeries and 2) whether this improvement in pain ultimately improves rehabilitation in the setting of the induced rotator cuff muscle weakness.

(F) *Limb amputations and Phantom limb pain* – Hundreds of thousands of patients undergo limb amputation annually in the United States for vascular disease, trauma, and cancer [83]. Of these patients, a substantial number will develop chronic, debilitating phantom pain in the amputated extremity [84,85]. Dense analgesia provided in the perioperative period, especially in the form of epidural anesthesia, decreases the incidence and severity of phantom pain [86]. However, epidural analgesia requires patients to remain hospitalized, is associated with infection risk with prolonged administration, and limits anticoagulation in these patients who are at high risk of thrombotic complications [87]. Cryoneurolysis may provide dense analgesia similar to epidural infusion of local anesthetic in amputation patients, but with dramatically longer duration of analgesia, no requirement for prolonged hospitalization, minimal infectious risk, and no restriction of systemic anticoagulation. Ultrasound-guided percutaneous cryoneurolysis of the femoral and sciatic nerves for lower extremity amputations and the terminal branches of the brachial plexus for upper extremity amputations has been described in case reports [88]. Of note, if there is any chance the surgeon may decide intraoperatively against amputation, cryoneurolysis should be performed *after* the surgery. In such situations, the patient should receive preoperative local anesthetic-based nerve blocks with cryoneurolysis performed in the recovery area or the following day. Thus, it is important for the anesthesiology team to communicate closely with the surgeon prior to performing the cryoneurolysis procedure.

5. Administration of percutaneous cryoneurolysis

Myriad protocols for percutaneous cryoneurolysis have been described over the past several decades; however, surprisingly little research has been done comparing various cryoneurolysis protocols in terms of the duration of freezing, number of cycles, pre-freeze administration of local anesthetic to the nerve, and optimal number of sites and proper location to administer the treatment to a given nerve. As the procedure is percutaneous and requires little or no sedation and minimal postprocedural monitoring, percutaneous cryoneurolysis can be performed in an ambulatory care setting. The probe entry site should be sterilely prepped and drapes may be placed for added sterility, although this is not generally necessary. The probe insertion site and the anticipated trajectory of the probe are anesthetized with local anesthetic. Injecting 2–3 mL of local anesthetic around the nerve prior to cryoneurolysis has several advantages: 1) allows for a diagnostic local anesthetic block prior to the therapeutic cryoneurolysis block to ensure that the correct nerve distribution will be covered by the cryoneurolysis, 2) decreases or eliminates pain in the distribution of the target nerve when performing the freezing procedure, and 3) ensures that the patient does not find the numbness too bothersome prior to committing to weeks or months of an insensate area. Regardless of the type of probe tip (cryoneurolysis probes have either trocar-shaped or blunt, rounded, tips), an introducer is generally required to facilitate piercing skin and fascial planes. An intravenous catheter of the same or slightly larger gauge works well; however, the introducer should be slightly withdrawn prior to beginning the freeze to prevent it from insulating the probe tip (Figure 3).

The duration and intensity of the cryoneurolysis block are related to the distance between the lesion and the terminal axons innervating the block distribution and the degree of axon disruption, respectively [89]. Most cryoneurolysis protocols that have been described use 1–3 freeze/thaw cycles per

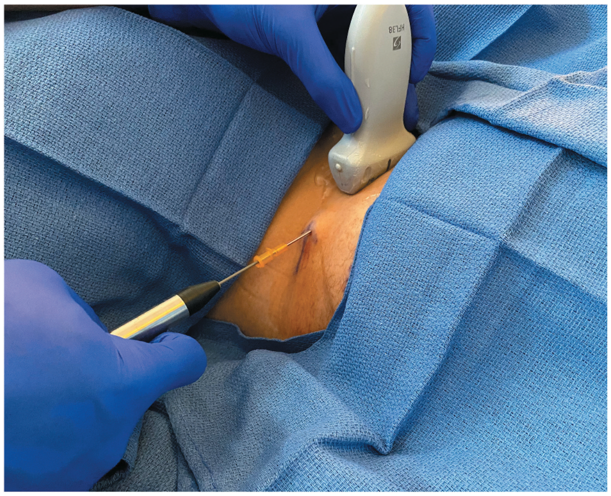

Figure 3. After sterilely prepping and anesthetizing the entry site, a 14-Gauge cryoneurolysis probe is inserted through a 14-Gauge intravenous catheter. The probe is directed toward the target nerve using in-plane ultrasound guidance.

nerve, each consisting of a freezing time of 30–120 seconds followed by a 30–60 second thaw. However, neither the optimal number of freezing cycles nor duration of therapy have been extensively evaluated.

A novel technique for cryoneurolysis has been described using a rat model in which a biocompatible ice slurry consisting of normal saline and glycerol is injected around the target nerve [90]. In this model, the injection successfully induced a months-long block in the treated nerves. This technique would offer many benefits over current percutaneous techniques for cryoneurolysis, most notably 1) dramatically reduced time required for the procedure, which itself is a major impediment to adoption of the technique; and 2) being much more similar to conventional ultrasound-guided local anesthetic-based nerve blocks, facilitating learning by anesthesiologists already skilled in this technique. However, studies of feasibility, safety, and efficacy in humans will be required.

Figure 4. Console based cryoneurolysis machine with a trocar shaped probe. The operator holds the probe in hand and activates the machine via a switch or foot pedal. The probe and the foot pedal are connected to the cryoneurolysis console via tubing. Console based machines offer the benefits of greater mobility and dexterity of the probe as the gas reservoir is not held in the operator's hand and lower cost per use. However, these devices are less portable and require a larger initial investment as well as storage space compared to handheld devices.

6. Equipment for percutaneous cryoneurolysis

Cryoneurolysis machines fall into two categories: 1) console-based and 2) handheld; and most currently-available devices are in the former category.

(A) *Console-based cryoneurolysis machines* generally consist of a console containing the gas regulators and nitrous oxide or carbon dioxide cylinder (usually on wheels for ease of transport), a cryoneurolysis probe connected to the console via tubing, and a foot pedal or switch for activating the machine (Figure 4). The operator holds the probe in one hand and activates the machine via the foot pedal. Console based machines offer multiple benefits: 1) greater mobility and dexterity of the probe in the operator's hand since the gas reservoir and activation switch are external to the probe, 2) reusable probes that are sterilized between patients resulting in a lower cost per use, and 3) ability to use the probe an any angle. However, these devices are less portable and require a much larger initial investment (usually in excess of 20,000 USD) as well as storage space compared to handheld devices.

(A) There is currently only one *handheld* cryoneurolysis device available within the United States. This device uses nitrous oxide cartridges and probes of various shapes and size that are inserted into the probe (Figure 5). It has the advantages of easy portability, lower initial investment price for the unit (approximately 5,000 USD), and a unique trident-shaped probe with an integrated heater to protect the skin when treating very superficial nerves. As the cartridges and probes are not reusable, the cost per treatment is considerably higher, and the device generates significantly more waste. Additionally, due to the mechanics of the gas flow in

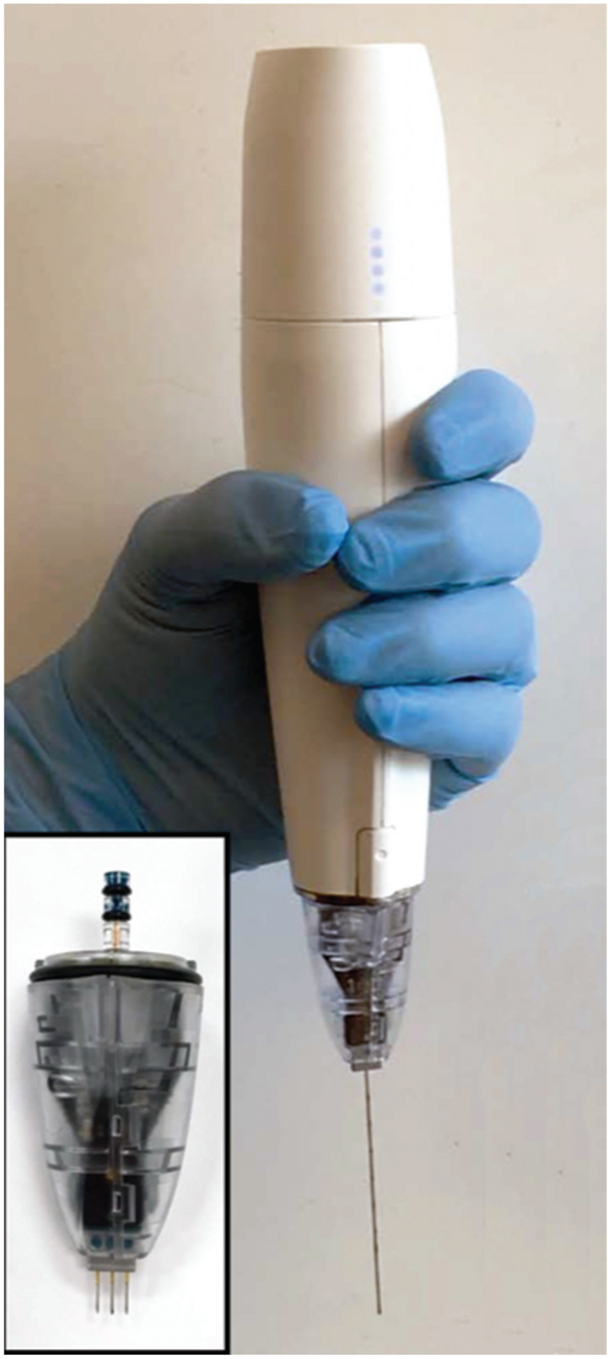

Figure 5. Handheld cryoneurolysis machine. The entire self-contained device is held in the operator's hand, which increases portability at the expense of dexterity. This device has a unique trident-shaped probe with an integrated heating element to protect the skin when treating very superficial nerves.

the device, the device must be held either upright or at an angle no greater than 45° perpendicular to the floor.

7. Cryoneurolysis for *acute* vs. *chronic* pain

This article focuses primarily on cryoneurolysis for *acute* pain; however, cryoneurolysis has also been successfully employed for *chronic* pain [9]. Numerous factors contribute to the difficulty in treating chronic pain, including myriad changes within the central nervous system nociceptive pathways [91]. This central sensitization may decrease the effectiveness of interventions focusing on *decreasing* the afferent signaling. Thus, interventions that *modulate* or produce *non-nociceptive* afferent signaling may, theoretically, be more beneficial than cryoneurolysis in patients suffering longstanding, chronic pain (e.g. peripheral nerve stimulation for chronic phantom limb pain) [92–94].

8. Potential complications of percutaneous cryoneurolysis

As with any procedure that punctures the skin, cryoneurolysis has nonspecific risks of causing bleeding/bruising, infection, pain at the insertion site, and injury to the target nerve–beyond what is intended–or surrounding structures. Risks specific to cryoneurolysis include neuropathic pain during the freezing procedure and skin discoloration when treating very superficial nerves.

(A) Bleeding – Bleeding from the probe insertion site is generally minor and treated by holding pressure, and some bruising should be expected. However, major bleeding as a result of vascular injury is very unlikely due to the large volume of blood flow acting as a source of heat and preventing cold injury the vessel wall. Indeed, application of extreme cold (−200°C) to vessel walls for periods of up to 10 minutes has not been shown to cause vessel rupture or thrombosis [95].

(B) Infection – When proper sterile technique is observed, infection risk should be minimal. One case report has documented a deep infection, which required treatment with intravenous antibiotics, following cryoneurolysis of the infrapatellar branch of the saphenous nerve for chronic osteoarthritis-related knee pain [96]. However, a recent review of percutaneous cryoneurolysis procedures in chronic pain patients did not document any infectious complications in 702 discrete treatments [54]. Thus, infectious complications would seem to be possible, but exceedingly rare, following cryoneurolysis.

(C) Nerve Injury – The goal of cryoneurolysis is axonal injury, leading to Wallerian degeneration, while leaving the surrounding connective tissues intact. It is possible that excessive manipulation of the target nerve could lead to more severe injury to the nerve resulting from the 'double-crush' phenomenon [97]. However, review of over 700 cryoneurolysis applications did not identify any cases of new neuropathic pain or permanent loss of nerve conduction [54]. Given the theoretical potential for more severe injury to the nerve than intended, physicians utilizing cryoneurolysis should understand the classification of nerve lesions. Sydney Sunderland classified nerve injuries as **neurapraxia, axonotmesis**, and **neurotmesis** in 1951[98]. He developed what is now referred to as the Sunderland grading system for nerve injuries, which further describes the degree of injury to a nerve [98].

a. ***Neurapraxia*** (Sunderland Grade I) – Localized myelin sheath damage with axons remaining intact. This type of injury may result from freezing temperatures between 0° and −20°C or intraoperative compression and typically resolves in *minutes to days*.

b. ***Axonotmesis*** **–** Complete interruption of axon continuity resulting in Wallerian degeneration, but with full or partial preservation of the supporting tissues of the nerve.

   (i) Sunderland Grade II – **This lesion is the goal of cryoneurolysis**. Axon continuity is lost, but the endoneurium, perineurium, and epineurium remain intact. Nerve regeneration occurs at a rate of *1–2 mm per day*.

   (ii) Sunderland Grade III – Axon continuity is lost and injury to *endoneurium* occurs.

   (iii) Sunderland Grade IV – Loss of continuity of *axons, endoneurium, and perineurium* with epineurium remaining intact. This injury type may result in *neuroma* formation requiring surgical intervention.

c. ***Neurotmesis*** (Sunderland Grade V) – Caused by *complete transection* of the nerve or exposure to temperatures below −100°C. Neurotmesis is characterized by loss of continuity of *axons, endoneurium, perineurium, and epineurium*. No recovery is possible without *early surgical intervention*.

(D) Pain – Local anesthetic is generally infiltrated at the insertion point and along the path of the cryoneurolysis probe; thus, there is generally only mild discomfort associated with probe insertion [9]. Additionally, the freezing procedure may result in a burning, neuropathic pain in the distribution of the target nerve [9]. Neuropathic pain during the cryoneurolysis procedure can be attenuated by either first injecting a small volume of local anesthetic around the nerve or using systemic opioid analgesics [9,61,68]. When this pain occurs, it is usually self-limiting and terminates within the first 30 seconds of the treatment [9].

(E) Skin Discoloration – Injury to the skin resulting in hypopigmentation when treating superficial nerves can be avoided by using a trident probe with an integrated heater (Figure 5) or by injecting a tumescent layer of local anesthetic or saline between the target nerve and the dermis to increase the depth of the nerve and thereby protect the skin from freezing temperatures [68].

9. Conclusion

In the setting of the opioid epidemic from which the Unites States is suffering, physicians managing acute pain need a diverse tool set of opioid sparing analgesic options. Conventional local anesthetic based nerve blocks provide excellent analgesia for hours to days; however, many acutely painful conditions outlast even continuous peripheral nerve blocks. Cryoneurolysis is a decades old technique with ancient origins that offers the potential for extended duration analgesia. The advent of ultrasound guidance has breathed new life into this technique and allowed anesthesiologists, already skilled in ultrasound-guided percutaneous procedures, to utilize cryoneurolysis for acute pain. Further, interventional radiologists and chronic pain physicians are also utilizing percutaneous cryoneurolysis, guided by ultrasound, computed tomography, and fluoroscopy to treat both acute and chronic pain [9,99,100]. Currently, the evidence supporting the use of ultrasound-guided percutaneous cryoneurolysis for acute traumatic and surgical pain comes primarily from case reports and series. Randomized clinical trials comparing percutaneous cryoneurolysis are indicated, and several are underway.

10. Expert opinion

Ultrasound-guided percutaneous cryoneurolysis offers the potential to provide weeks or months of analgesia, which is better matched to the time frame of pain resulting from many surgeries and some forms of trauma. Currently, the gold standard for providing long duration postoperative analgesia is continuous peripheral nerve blocks; however, this therapy is limited to days or, rarely, weeks. Compared with conventional nerve blocks, benefits of cryoneurolysis include: 1) longer duration measured in weeks or months rather than days; 2) no risk of catheter dislodgement; and 3) decreased risk of infection. As many anesthesiologists are skilled in navigating a block needle adjacent to a target nerve utilizing ultrasound guidance, performing percutaneous cryoneurolysis is usually familiar. Cryoneurolysis may even prove technically easier compared to conventional peripheral nerve blocks as the target nerve need only be in close enough proximity to the nerve to encompass it within the ice ball. In contrast, a block needle may be in close proximity to the target nerve but not successfully administer local anesthetic to the nerve if not in the correct fascial plane. Just as with conventional, local anesthetic based nerve blocks, cryoneurolysis produces both a sensory and motor block. Thus, optimal target nerves are those with limited or no motor function as a prolonged motor block of a major peripheral nerve would likely hinder rehabilitation and risk patient self-injury (e.g. femoral nerve motor block leading to quadriceps weakness and associated falls) [74]. However, major nerves may be targeted for amputation patients (e.g. femoral and sciatic nerves for lower extremity amputations).

The most significant drawback of cryoneurolysis compared to conventional regional anesthetics is the time required for administration. While the time required to treat a single nerve may not be significant – on the order of 5–10 minutes depending on the protocol utilized – treatment of multiple nerves (e.g. cryoneurolysis of multiple intercostal nerves for rib fracture or postmastectomy analgesia) can limit applicability. However, this time cost must be weighed against the benefits of significantly prolonged analgesia and decreased infection risk. This would likely represent the greatest barrier to percutaneous cryoneurolysis becoming a widely adopted analgesic modality in clinical practice within the acute perioperative time period.

Conventional peripheral nerve blocks are generally administered either in the preoperative area or the operating room prior to or just following the induction of anesthesia. Given the rapid pace of the perioperative environment, the added time for cryoneurolysis would likely require patients to arrive 1–2 hours earlier than the normal time or a presurgical visit exclusively for the cryoneurolysis procedure in the days preceding the surgery. In either case, the anesthesiologist responsible for the intraoperative care would likely be unable to perform the cryoneurolysis procedure. However, new techniques using biocompatible ice slurry as a perineural injection for cryoneurolysis may drastically decrease the time required. If this modality proves safe and effective in humans, it may allow cryoneurolysis to be accomplished in an amount of time similar to that required for a single-injection peripheral nerve block. This would allow patients to have cryoneurolysis performed quickly at bedside in the preoperative area, or even in the operating room as most single-injection peripheral nerve blocks are administered currently. The future appears bright for a renaissance of this timeworn and underutilized technique.

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