

AANA Journal Course

Cryoneurolysis for the Treatment of Sensory Nerve Pain

Alison Smiley, CRNA

Jason McGuire, PhD, CRNA

Acute and chronic pain account for high costs both societally and economically, estimated in the United States to be \$635 billion. Untreated or undertreated acute pain is associated with substantial morbidity and may become chronic pain. Surgical patients are at an increased risk of long-term opioid use or addiction. Overdose from drugs of abuse, including opioids, is the leading cause of death due to injury in the United States. Traditional pain management strategies for acute and chronic pain have focused on opioid medications, which are often associated

with severe side effects. Cryoneurolysis is a minimally invasive, nonsurgical, nonpharmacologic pain management technique that uses cold temperatures to ablate the sensory nerves that cause pain. Because of its safe and reversible nature, cryoneurolysis should be considered as part of a multimodal pain management plan in patients experiencing pain originating from sensory nerves.

Keywords: Acute pain, chronic pain, cryoanalgesia, cryoneurolysis, nonpharmacologic pain management.

Objectives:

At the completion of this course, the reader should be able to:

1. Describe how cryoneurolysis can be used to treat acute and chronic pain as part of a multimodal pain control strategy.
2. Identify the surgical and nonsurgical indications for which cryoneurolysis may be considered as a method for acute and chronic pain control.
3. Describe the physiologic mechanisms involved in reversible nerve axon destruction.
4. Discuss the scientific evidence in support of cryoneurolysis therapy and the potential complications associated with its application.
5. Identify how cryoneurolysis is used to decrease the need for opioid therapy while decreasing complications and improving patient satisfaction.

Introduction

Drug overdose is the leading cause of death due to injury in the United States, with 6 in 10 drug-related deaths involving opioids.¹ Patients undergoing surgery are at an increased risk of long-term opioid use, which may lead to dependency or addiction.² This epidemic has prompted the formation of a multidisciplinary task force

to address opioid prescribing practices and emphasize the importance of multimodal pain management strategies.³ According to the American Pain Society (APS), multimodal pain management techniques include both pharmacological and nonpharmacologic analgesic modalities.⁴ The use of multimodal pain management has been endorsed by the American Association of Nurse Anesthetists (AANA), as well as the APS, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists as part of their clinical practice guidelines.^{4,5} One potential nonpharmacologic addition to a multimodal pain management plan is the use of cold temperatures to ablate the sensory nerves that cause pain, known as cryoneurolysis. This minimally invasive therapy may provide superior pain relief, compared with standard treatment modalities, in patients experiencing pain caused by sensory nerves.

This *Journal* course will summarize the physiologic mechanisms involved in the application of cryoneurolysis through a presentation of the scientific evidence in support of this therapy. Associated complications will be explored. The learner will be able to identify common surgical and nonsurgical conditions of acute and chronic pain in which cryoneurolysis has shown success. Finally, a discussion will address the practical application of this novel treat-

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ment compared with other nonpharmacologic methods in an effort to decrease the need for prescription opioids.

Literature Search Methods

An electronic database search was conducted in May 2017 using the Cumulative Index to Nursing & Allied Health Literature (CINAHL), PubMed, Cochrane Database, and Google Scholar. The following search terms were used: *cryoablation*, *cryoablation pain*, *cryoneurolysis*, *cryoanalgesia*, and *percutaneous cryoablation*. Search inclusion criteria comprised peer-reviewed journal articles between the years 2000 and 2017, articles on human adult subjects, articles examining cryoneurolysis of sensory nerves, and articles comparing cryoneurolysis with traditional pain management techniques. Exclusion criteria included malignancy, nonhuman subjects, and cryoneurolysis of the motor nerves. The Matrix Method⁶ was employed to structure and organize the literature review.

Nine articles were selected for final review (Table). For the purposes of this *Journal* course, the term *cryoneurolysis* is used to describe any technique that uses direct application of cold temperatures to cause reversible damage to sensory nerves.

Physiologic Mechanisms of Cryoneurolysis

Cryoneurolysis is a minimally invasive procedure that uses the direct application of freezing temperatures to peripheral sensory nerves, resulting in nerve axon destruction. Based on the concept of wallerian degeneration, cryoneurolysis allows for reversible nerve axon damage.⁷ First described by Augustus Waller, wallerian degeneration refers to the neuronal changes that occur distal to nerve axon destruction.⁸ When temperatures of -20 to -100°C are applied directly to a nerve using a cryoprobe, axon destruction occurs.⁹ Commercially available cryoprobes employ the use of a fine-gauge hollow cannula with a closed tip through which a gas cryogen is pressurized (Figure 1).⁹ When the pressurized gas reaches the tip of the cryoprobe, rapid expansion occurs, producing a decline in temperature (Joule-Thomson effect) and formation of an ice ball (Figure 1).⁹ The cryogenic gas is vented out the handle of the cryoprobe, preventing the gas from entering the body.¹⁰ If temperatures do not fall below -100°C , the epineurium and perineurium are preserved (Figure 2), allowing for future nerve regeneration.¹¹ Surrounding tissues are protected from injury through several unique design features of the modern cryoprobe, including insulation on the proximal portion of the cannula and precise ice ball formation allowing for application only to the desired nerve tissue. Cryoprobe design also includes an integrated temperature monitor to ensure that temperatures do not fall below -100°C .⁹ Likewise, many cryoprobes pair with nerve stimulation technology to allow for motor nerve stimulation and localization, increasing the safety profile of the cryoneurolysis procedure.⁹

Histological studies suggest that the rate of nerve recovery is directly proportional to the duration of cryoprobe application.¹² Cryoneurolysis is not known to cause neuroma formation, which is a painful area of aberrant nerve tissue growth following nerve injury. Neuromas have been associated with other nerve ablation techniques, such as radiofrequency ablation (RFA).⁹

History

Cold therapy is a well-researched method of analgesia used for decades. The first cryoprobe dates to the early 1960s when neurosurgeon Dr Irving Cooper used cryoneurolysis to treat movement disorders such as Parkinson disease.¹³ The application of cold temperatures to sensory nerves has been explored in detail since that time with a wide range of applications, including postthoracotomy pain, trigeminal neuralgia, and analgesia for orthopedic surgery. Cryoneurolysis has evolved since the days of Cooper; modern cryoprobes offer much more precise application (Figure 3).

Total Knee Arthroplasty and Osteoarthritis

The use of cryoneurolysis has been explored as part of a multimodal pain management plan for patients undergoing total knee arthroplasty (TKA). A retrospective chart review of 100 patients undergoing TKA compared a treatment group that received cryoneurolysis and a standard multimodal pain regimen with a control group that received a standard multimodal pain regimen only.¹⁴ Cryoneurolysis of the infrapatellar branch of the saphenous nerve (IPBSN) and anterior femoral cutaneous nerve (AFCN) was performed in the treatment group 5 days before scheduled TKA.¹⁴ The standard multimodal pain control regimen consisted of prescribed pregabalin, acetaminophen, and celecoxib; adductor canal block; spinal anesthesia; and postoperative opioids as needed.¹⁴ Hospital length of stay (LOS) of 2 days or longer was significantly higher in the control group, 67.3% compared with 6.1% ($P < .0001$) in the treatment group, with a greater portion of the treatment group with LOS of 0 or 1 day.¹⁴ Cumulative prescribed morphine equivalence was significantly decreased in the treatment group, with $2,069.12 \pm 132.09$ mg compared with control groups $3,764.42 \pm 287.95$ mg during the 12-week postoperative period ($P < .0001$).¹⁴ Patient-reported pain intensity scores were significantly decreased in the treatment group compared with the control group ($P < .0001$).¹⁴ These findings suggest that preoperative cryoneurolysis of the IPBSN and AFCN in patients before TKA is associated with decreased hospital LOS, less pain, and reduced need for postoperative opioids.

The use of cryoneurolysis has been studied among patients experiencing pain from osteoarthritis (OA). In a prospective double-blind, randomized controlled study by Radnovich et al,¹⁰ cryoneurolysis was exam-

Source	Sample and evidence level	Cryoneurolysis target	Nerve isolation method	Diagnostic nerve block	Follow-up	Findings
Moorjani et al, ¹² 2001	N = 200; RCT of patients undergoing thoracotomy	ICN	Direct visualization at thoracotomy incision site	Not applicable	3, 5, 7, 10, 15, and 30 d	Treatment group had significantly lower use of opioids ($P < .01$) and lower VAS pain scores vs control group Control group required opioid analgesia for a longer time vs cryoneurolysis group Cryoneurolysis group had improved FEV ₁ and FVC values vs treatment group
Radnovich et al, ¹⁰ 2017	N = 161; RCT of patients with grade 2 or 3 OA ^a and radiographic evidence of OA	ISN	Treatment line identified using anatomical landmarks	≥ 50% reduction in VAS pain score after diagnostic nerve block to IPBSN	30, 60, 90, and 120 d	Treatment group had significantly improved WOMAC pain scores at 30 d after treatment ($P = .004$) and up to 90 d after treatment ($P = .0061$) vs sham group Functional scores significantly improved at 30 and 90 d in treatment group vs sham group ($P = .0012$ vs $P = .0172$) LOS: control group: 33/49 had LOS ≥ 2 d; treatment group: 3/49 had LOS ≥ 2 d ($P < .0001$) Cumulative morphine equivalent narcotic use in 12 wk postoperatively: 3,764.42 ± 287.95 mg in control group vs 2,069.12 ± 132.09 mg in treatment group ($P < .0001$) Patient-reported pain scores significantly decreased in treatment group vs control group ($P < .0001$)
Dasa et al, ¹⁴ 2016	N = 100; retrospective chart review of patients undergoing TKA	AFCN and ISN 5 d before TKA	Treatment line identified using anatomical landmarks	Not discussed	6 and 12 wk	VAS pain scores were significantly improved in patients at all follow-up points ($P < .001$); at 1-y follow-up, 62% of patients had ≥ 50% or complete pain reduction; preprocedure mean VAS score was 7.8 ± 1.4 vs 3.28 ± 2.37 at 1 y after procedure ($P < .001$) No reported complications Cryoneurolysis safe and effective and not inferior to radiofrequency nerve ablation Average VAS score was 7.7 before the procedure vs 3.0 at 6 mo and 4.2 at 12 mo after the procedure
Barlocher et al, ²⁰ 2003	N = 50; prospective study of patients with lower back pain secondary to lumbar facet syndrome	Lumbar medial branch	Fluoroscopy guidance	≥ 50% reduction in pain from diagnostic nerve block as criterion to proceed with cryoneurolysis	6 wk; 6 and 12 mo	Statistically significant increase in pain vs pretreatment at all posttreatment times; average preprocedure VAS 8.3 ± 1.9 vs 2.3 ± 1.5 at 1 mo after cryoneurolysis treatment 11 patients required repeated cryoneurolysis procedure, with no reported complications
Birkenmaier et al, ¹⁸ 2007	N = 46; prospective study of patients with lower back pain unresponsive to conservative treatment for ≥ 3 mo	Lumbar medial branch	Fluoroscopy guidance	Positive result to diagnostic nerve block with ≥ 50% reduction in pain for ≥ 3 h	6 wk; 3, 6, and 12 mo	
Yoon et al, ¹¹ 2016	N = 22; prospective study of patients with refractory peripheral neuropathy	Affected nerve	Ultrasound guidance	Positive result to diagnostic nerve block	1 wk; 1, 3, 6, 9, and 12 mo	

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Moesker et al, ²⁴ 2014	N = 5; prospective study of patients with limb amputation experiencing phantom limb pain	Affected nerve	Not discussed	Positive result to diagnostic nerve block	Up to 5 y	3 of 5 patients received 90%-100% pain relief vs pretreatment pain levels; all patients received at least some degree of pain relief
Koethe et al, ²² 2014	N = 1; case report of patient with refractory postthoracotomy pain	ICN	Ultrasound and CT guidance	Not discussed	8 wk	8 wk of pain relief after treatment No reported complications

Table. Evidence Examining Use of Cryoneurolysis for Treatment of Peripheral Sensory Nerve Pain

Abbreviations: AFCN, anterior femoral cutaneous nerve; CT, computed tomography; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICN, intercostal nerves; IPBSN, infrapatellar branch of the saphenous nerve; ISN, internal saphenous nerve; LOS, length of stay; OA, osteoarthritis; RCT, randomized controlled trial; TKA, total knee arthroplasty; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

ined for treatment of pain associated with knee OA. A diagnostic nerve block of the IPBSN that resulted in at least 50% reduction in pain during symptom aggravation was considered inclusion criteria.¹⁰ The treatment group received cryoneurolysis of the IPBSN, whereas the sham group underwent an identical procedure using an inactive cryoprobe.¹⁰ Compared with the sham group, the treatment group showed significantly improved Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores at 30 days after treatment ($P = .0004$) and for up to 90 days after treatment ($P = .0061$).¹⁰ Functional scores remained significantly improved at 30 and 90 days in the treatment group compared with the sham group ($P = .0012$ and $P = .0172$, respectively).¹⁰ Total WOMAC scores remained significantly improved at 90 days after cryoneurolysis in the treatment group compared with the sham group ($P = .0108$).¹⁰ In patients who responded positively to treatment, defined as 30% improvement or better from pretreatment symptoms, continued pain relief remained for up to 150 days after treatment.¹⁰ The results of this study suggest that care providers can anticipate a decrease in pain scores among their patients who receive cryoneurolysis of the IPBSN in the treatment of knee OA.

The use of anatomical landmarks, electrical nerve stimulation, and ultrasonography have all been safely used to identify neural structures during the performance of peripheral nerve blockade. Hu et al¹⁵ explored the use of anatomical landmarks to target cryoneurolysis therapy in patients with knee pain. Transcutaneous electrical nerve stimulation and ultrasound imaging were used to establish visual and palpable anatomical landmarks in which to perform cryoneurolysis, referred to as a treatment box.¹⁵ The location of the sensory nerves in patients was further validated through subsequent comparison with cadaver models. The treatment box was shown to contain most of the sensory nerve branches of the inferior and superior aspects of the patella. Sensory innervation to the patella is variable among individuals and cryoneurolysis using these targeted anatomical landmarks may decrease the time required to perform cryoneurolysis procedures because imaging techniques are not required.

Cryoneurolysis may be a valuable addition to a multimodal pain protocol, used both preoperatively and postoperatively for TKA to reduce the use of opioid pain medications and to decrease hospital LOS.¹⁶ A practice guideline for pain control strategies for TKA recommends consideration of cryoneurolysis as part of a multimodal pain management technique.¹⁷

Lumbar Facet Joint

Low back pain is a common complaint with complex origins. One possible cause of low back pain is zygapophyseal joint pain, also termed lumbar facet joint pain. Cryoneurolysis has been shown to reduce complaints of

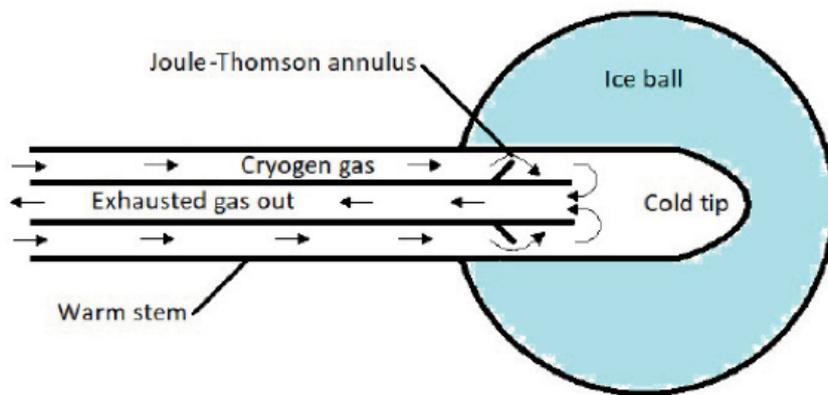


Figure 1. Joule-Thomson Effect and Ice Ball Formation From Cryoprobe

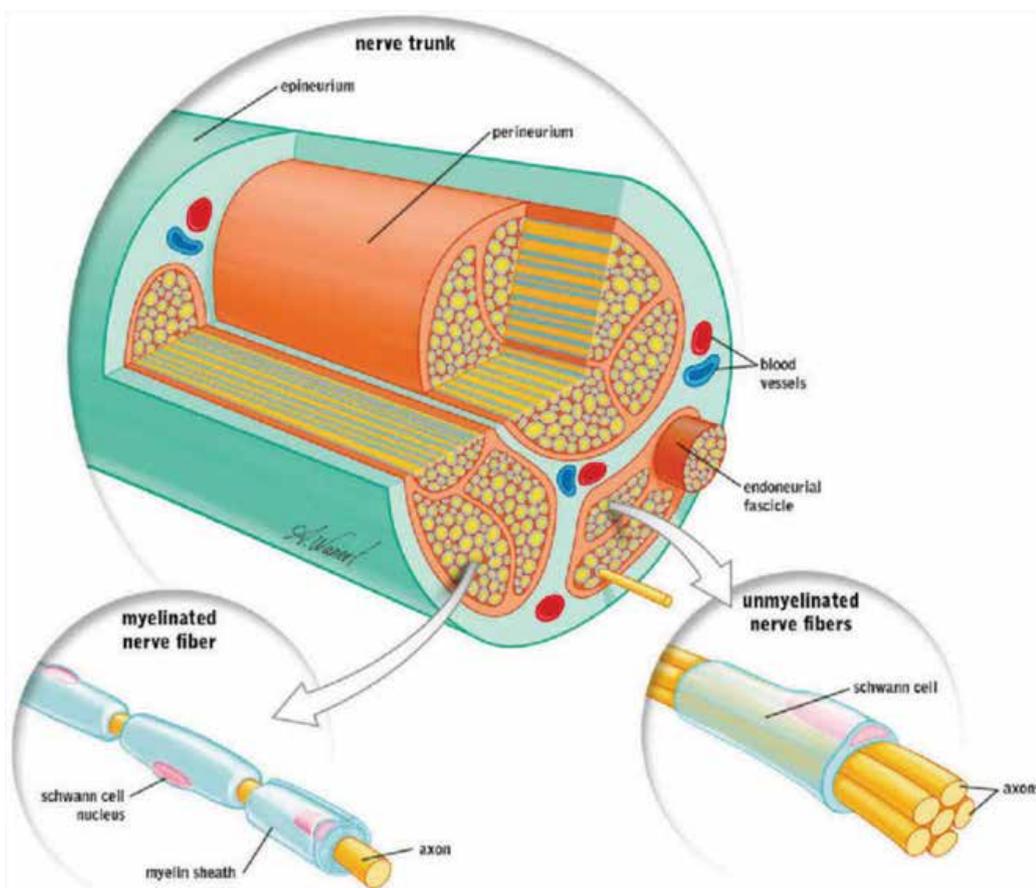


Figure 2. Nerve Fiber Cross-section
(Reprinted with permission from Myoscience)

lower back pain by targeting the involved zygapophysal joint.^{18,19} The utility of cryoneurolysis for lumbar facet joint pain was examined in a prospective study of 46 patients in whom conservative treatment previously failed.¹⁸ Following a positive diagnostic medial branch nerve block, cryoneurolysis was performed. Success of treatment was defined as postprocedure pain level less

than or equal to 50% of measured pretreatment levels.¹⁸ Average pain scores were significantly decreased from a mean pretreatment level, on a visual analog scale (VAS), of 7.7 to 3.0 and 4.2 at 6 and 12 months, respectively ($P < .0001$).¹⁸ This suggests that cryoneurolysis is a safe and effective treatment of pain of the lumbar facet joints.

Cryoneurolysis has been examined as an alternative



Figure 3. Handheld Cryoprobe (Iovera, Myoscience)
(Reprinted with permission from Myoscience)

to surgical intervention for the management of lumbar facet joint pain. Fifty patients with lumbar facet joint pain were given diagnostic nerve blocks to the medial branch of the lumbar zygapophyseal joint.²⁰ After positive results to diagnostic nerve blockade, cryoneurolysis of the lumbar medial branch was performed.²⁰ Lumbar facet joint pain is traditionally diagnosed through physical examination, which may be unreliable, emphasizing the importance of diagnostic nerve block when isolating the causative nerve. Sixty-two percent of patients experienced greater than 50% or complete pain relief at 1-year postprocedure follow-up.²⁰ The VAS pain scores were improved in all 50 patients during postprocedure visits ($P < .001$), with a preprocedure mean VAS score of 7.8 ± 1.4 compared with 3.28 ± 2.37 at 1-year after the procedure.²⁰ Of the patients who had not previously undergone spinal surgery, there was an 85% success rate compared with 47% in those who had undergone previous spinal surgery ($P < .01$).²⁰ No complications were reported, concluding that cryoneurolysis should be considered a safe and effective means of treating lumbar facet joint pain.

Thoracotomy

Thoracotomy is associated with severe postoperative pain, resulting in severe pulmonary complications, including inadequate respirations, impaired cough and clearance of secretions, and pneumonia. Postthoracotomy pain is multifactorial in nature and may be due to incisional damage to musculature and intercostal nerves (ICNs) as well as pleural manipulation secondary to chest tube placement. Traditionally, treatment of postthoracotomy pain included thoracic epidural and pharmacologic analgesia.²¹ Moorjani et al¹² conducted a randomized clinical trial examining 200 patients undergoing thoracotomy. The treatment group received cryoneurolysis, and the control group received conventional analgesia. There was no

discernable difference when the investigators considered anesthetic technique and postoperative nursing care.¹² Cryoneurolysis was performed to the ICNs at the level of the incision and 1 nerve cephalad and 2 nerves caudal to the incision, before thorax closure.¹² Postoperative pain and respiratory function were assessed in both the treatment group and control group. The treatment group had a statistically significant improvement in pain scores and decreased opiate requirements ($P < .05$), as well as improved respiratory function; however, the latter improvement was not statistically significant.¹²

Percutaneous cryoneurolysis of the ICNs poses risks, including hemothorax and pneumothorax resulting from improper placement of the cryoprobe. Visualization techniques such as ultrasonography and computed tomography (CT) guidance provides superior visualization of the cryoprobe ice ball during ICN cryoneurolysis and may reduce the frequency of complications.²² Damage to the ICNs is a frequent cause of postthoracotomy pain. A report explored percutaneous ICN cryoneurolysis for intractable postthoracotomy pain syndrome using cone-beam CT guidance for probe placement.²² Eight weeks of pain relief after the procedure was reported without complication.²² Cryoneurolysis of the ICNs should be considered as a viable option to relieve postthoracotomy pain, thereby lessening the requirement for opioid pharmacologic therapy.

Other Indications

Neuropathic pain is associated with multiple disease states, including diabetes, HIV infections, and renal disease, and it may lead to substantial loss of function and decreased quality of life. Yoon et al¹¹ conducted a prospective study of 22 patients undergoing cryoneurolysis for treatment of peripheral neuropathy refractory to first- and second-line treatment modalities. The study examined a diverse range of nerves treated with cryoneu-

rolysis that included plantar neuromas and ilioinguinal, posterior tibial, saphenous, gluteal, sural, geniculate, and digital nerves.¹¹ All study participants had a positive response to diagnostic nerve blockade before cryoneurolysis treatment.¹¹ Average VAS pain scores before treatment were 8.3 ± 1.9 ; posttreatment average pain scores were 2.3 ± 2.5 ($P = .0001$) at 1 month and 5.1 ± 3.7 ($P = .03$) at 12 months.¹¹ Of the 22 study participants, 11 required repeated cryoneurolysis at an average interval of 9.3 months after original treatment; no reported complications occurred from repeated cryoneurolysis.¹¹

In one of the most comprehensive reviews of the varied uses of cryoneurolysis, Trescot²³ describes multiple clinical indications for cryoneurolysis in interventional pain management. Cryoneurolysis was discussed for a wide range of diagnoses, including craniofacial pain secondary to trigeminal neuralgia, chest wall pain after thoracotomy, abdominal and pelvic pain, low back and lower extremity pain, and upper extremity pain.²³ Trescot²³ provides an in-depth discussion of the neural origins of pain as well as a detailed description of the cryoneurolysis procedures for each indication. The author recommends cryoneurolysis be considered as an effective, reversible option for sensory nerve pain secondary to a low side effect profile.²³ Diagnostic nerve blockade and careful localization of the involved nerve before any cryoneurolysis interventions may improve success of the therapy while decreasing potential risks.

Cryoneurolysis has been used to reduce phantom limb pain, which results from aberrant neuronal signaling following amputation of a limb. Symptoms can include perceived sensation or pain in the missing limb. The etiology of phantom nerve pain is complex and may have both central and peripheral causes. Cryoneurolysis was performed on transected nerves in 5 patients who had previously undergone limb amputation and were experiencing phantom limb pain.²⁴ The involved nerve was identified through patient reports of pain in the affected portion of the amputated limb.²⁴ A nerve stimulator was used to reproduce phantom pain. If a diagnostic nerve block provided relief, the results were considered positive and a cryoneurolysis procedure was performed.²⁴ Postcryoneurolysis VAS pain scores were reduced in all patients, with 1 patient reporting a pretreatment VAS pain score of 10, which was reduced to 0 after cryoneurolysis treatment.²⁴ The use of analgesics, including morphine, gabapentin, and amitriptyline, was reduced in all study participants.²⁴ All patients treated received at least some degree of pain relief, with 3 of the 5 patients experiencing 90% to 100% relief of phantom limb pain symptoms lasting from 2.5 to 5 years after treatment.²⁴

Discussion

The rate of complications from cryoneurolysis is minimal and includes localized bruising,¹⁶ bleeding at the probe

insertion site,²⁵ numbness to the treatment area,¹² and one occurrence of vasovagal reaction thought to be patient specific and unrelated to the procedure.²⁶ Other potential side effects include infection, skin necrosis/ischemia, and damage to surrounding tissues, although none were reported in the literature.²⁵

A canine study examined the potential risk that freezing temperatures pose to blood vessels.²⁷ Direct application of liquid nitrogen at temperatures of -180°C to -196°C was applied to major blood vessels for up to 10 minutes, with no evidence of blood vessel rupture, blood coagulation, or thrombosis.²⁷ The temperature extremes and procedure duration used in the study were much greater than clinically utilized cryoprobes, indicating that modern cryoneurolysis probes do not pose severe risk to surrounding blood vessels. There were no reports of permanent nerve damage from cryoneurolysis procedures.^{10,23} Cryoneurolysis is a safe procedure, and when careful localization of the target nerves is employed, damage to surrounding tissue is rare.

In any examination of the efficacy of cryoneurolysis, it is necessary to discuss alternative nerve ablating techniques currently being used to treat pain from sensory nerves. Radiofrequency ablation (RFA) is an alternative nerve ablation technique that uses the heat produced from a medium-frequency alternating current, generating nerve necrosis through coagulation when applied.²⁸ Unlike cryoneurolysis, RFA may not provide a uniform nerve lesion, resulting in inadequate ablation.²⁸ One study examining RFA efficacy in the treatment of chronic knee pain found that some patients experienced transient excruciating pain during RFA lesioning.²⁸ This is not a concern during cryoneurolysis procedures. Intense pain during RFA treatment may require the use of preprocedure analgesia, sedation, or anesthesia for the patient to tolerate the procedure.²⁸ The heat generated during RFA may result in damage to surrounding tissues and structures, decreasing the safety of this therapy.⁹ Unlike cryoneurolysis, RFA has been associated with neuroma formation.²⁸ Birkenmaier et al¹⁸ suggest that cryoneurolysis is not inferior to RFA procedures for treatment of lumbar facet joint pain. Further studies are needed to compare the duration of pain relief from cryoneurolysis with that provided by RFA.

When considering use of cryoneurolysis, the provider must appreciate the potential for variability in individual patient neural anatomy. Anatomical variance necessitates establishing the exact origin of the pain. The literature highlights the importance of diagnostic nerve blocks and the use of imaging technology such as ultrasonography or CT when one is isolating the sensory nerve before a cryoneurolysis procedure.²³ Several studies recommend the use of small volumes of local anesthetic (1-2 mL) when a diagnostic nerve block is performed before cryoneurolysis, to reduce local anesthetic spread and lessen the risk of

false-positive results.^{18,20} Meticulous nerve isolation may prevent untoward effects, such as damage to surrounding tissues with the cryoprobe. Improper technique may be a factor in patients who did not receive adequate pain relief following cryoneurolysis procedures. Placement of the cryoprobe in relation to the nerve is a factor contributing to treatment success, with one study finding that longitudinal placement of the cryoprobe was associated with improved nerve ablation and greater analgesia after the procedure.²⁰ This finding highlights the importance of proper training and intimate knowledge of neural anatomy when one performs cryoneurolysis procedures.

To achieve degeneration of the nerve axon and myelin sheath, while preserving the epineurium and perineurium (wallerian degeneration), the provider must maintain cryoneurolysis temperatures between -20°C and -100°C .⁹ Temperatures below this range result in irreversible nerve damage and the risk of neuroma formation.⁹ The use of nitrous oxide or carbon dioxide gas as cryogens may increase the safety profile of cryoprobe devices.⁹ The boiling points of nitrous oxide (-88°C) and carbon dioxide (-79°C) make these gases ideal for use as cryogens because they cannot reach temperatures colder than -100°C , allowing for reversible nerve regeneration following cryoneurolysis treatment.⁹ The length of time and number of freeze cycles needed to provide adequate nerve lesioning is variable among studies and may depend on the size of the nerve to be ablated. Freeze cycles may range between 30 seconds and several minutes, and multiple lesions may be required along the length of the nerve.²⁵ Further studies are needed to establish optimal cryoprobe temperature and length of freeze cycles.

Cryoneurolysis nerve blocks are similar in procedure to other nerve block and nerve ablation techniques, including peripheral nerve block and RFA. Providers should have extensive training in the use of imaging technologies, including ultrasound and CT guidance to improve the success of cryoneurolysis nerve block procedures. Nurse anesthetists interested in developing the skill set required to perform cryoneurolysis pain management procedures should seek training in ultrasound and CT imaging techniques and become experts in the anatomy of peripheral sensory nerves. The recent advent of pain management fellowship programs for CRNAs can provide training in nerve block techniques, which may be translated to cryoneurolysis procedures.²⁹ As of 2016, the Centers for Medicare and Medicaid Services introduced several *Current Procedural Terminology (CPT)* codes related to cryoneurolysis procedures for upper and lower extremity peripheral nerves performed using image guidance.³⁰ The ability of CRNAs to bill for these procedures will vary depending on the state in which they practice.

One possible explanation for the variability of results within and among the published studies may be inconsistencies between provider techniques. Differences in

cryoprobe devices used or the variable freeze cycles or temperatures used for cryoneurolysis may also contribute to variability in treatment success. Limitations of the literature reviewed in this *Journal* course include the use of a retrospective study,¹⁴ small sample sizes,^{11,24} and lack of randomization of some studies.^{11,14,18,20} Included case reports may not be generalizable to larger populations.^{22,24} Confounding factors include the use of subjective data such as patient-reported symptoms and functional status. Some studies used only one surgical or nursing team to provide care for all study subjects, potentially introducing bias.^{12,14} The necessity for subject cooperation may result in an inability to control for use of additional pain medication or modalities not approved in the study protocols. A large-scale study is needed to examine the use of cryoneurolysis in the perioperative period to improve the generalizability of study findings to larger populations.

Conclusion

The estimated annual cost of chronic pain in the United States is \$635 billion.³¹ Chronic pain is known to have a substantial deleterious impact on economic productivity, including missed days of work, resulting in an estimated \$191 to \$226 billion in lost wages.³¹ Untreated or undertreated acute pain may lead to complications, including prolonged hospitalization, unnecessary suffering, and chronic pain.³² A practice statement by the AANA recommends that nerve ablation techniques, including cryoneurolysis, should be considered as part of a multimodal pain management technique.⁵ Traditional pain management strategies for chronic and acute pain have focused on opioid pain medications, which are associated with side effects, including respiratory depression, ileus, and dependency or addiction. The societal and economic costs of pain management are too large to ignore, driving the need for further development of multimodal pain management strategies. Because of its safe and reversible nature, cryoneurolysis should be considered as a viable addition to multimodal pain management plans in patients who experience pain originating from sensory nerves.

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AUTHORS

Alison Smiley, CRNA, was a master of science in nursing (MSN) nurse anesthesia student at Florida Gulf Coast University in Fort Myers, Florida, at the time she submitted this manuscript. This manuscript was the culmination of the capstone project for the MSN Nurse Anesthesia Program.

Jason McGuire, PhD, CRNA, is an associate professor and the Southwest Florida Endowed Chair of Nursing at Florida Gulf Coast University. He is an expert nurse anesthesia clinician and an experienced researcher and author in the field of emergence delirium and obstructive sleep apnea. He is a passionate educator of nursing, anesthesia, research, and evidence-based practice.

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