DOI: 10.1111/papr.13182

REVIEW

The applications of cryoneurolysis for acute and chronic pain management

Emily Biel DNP, CRNA[1] | Edwin N. Aroke PhD, CRNA, FAAN[2] | John Maye PhD, CRNA[3] | Sarah Jingying Zhang PhD, CRNA[3,4,5]

[1]Nurse Anesthesiology Program, University of South Florida, Tampa, Florida, USA

[2]University of Alabama at Birmingham School of Nursing, Birmingham, Alabama, USA

[3]School of Nursing, University of South Florida, Tampa, Florida, USA

[4]University of California San Francisco, San Francisco, California, USA

[5]Samuel Merritt University, Oakland, California, USA

Correspondence
Sarah Jingying Zhang, University of South Florida Nurse Anesthesiology Program, 12901 Bruce B. Downs. Blvd, MDC22, Tampa, FL, 33612, USA.
Email: sarahjingyingz@usf.edu

Abstract

Background: Cryoneurolysis is a term used to describe the application of extreme cold to targeted nerve tissue. The primary goal of the application of a thermal neurolytic technique is to disrupt the conduction of pain signals from the periphery to the central nervous system and eliminate or diminish the experience of pain. Recent advancements in ultrasound technology coupled with the development and approval of handheld devices specifically designed to deliver cryoneurolysis has expanded the use of this modality in the perioperative setting.

Application: Surgical procedures including total knee arthroplasties, shoulder arthroplasties, thoracotomies, and mastectomies have all demonstrated long-term pain relief benefits when cryoneurolysis has been administered days to weeks prior to the planned procedure. In addition, the newly designed handheld device allows for office-based clinical use and has been utilized for various chronic pain conditions including neuropathic and phantom limb pain.

Conclusion: The evidence clearly demonstrates that cryoneurolysis has a low risk profile and when administered appropriately, provides prolonged analgesia without promoting motor blockade. This narrative review article describes the unique mechanism of action of cryoneurolysis for prolonged pain relief and provides emerging evidence to support its applications in both acute and chronic pain management.

KEYWORDS
acute and chronic pain management, cryoanalgesia, cryoneurolysis, regional anesthesia, ultrasound

INTRODUCTION

Cryotherapy is a general term that has been used to describe the local or general use of low temperatures for medical treatment. It depends on the application of extreme cold to destroy targeted tissue, which can include targeted nerve tissue. While the terms cryoanalgesia, cryoablation, and cryoneuroablation are frequently used interchangeably to describe cryotherapy, they have subtle differences. When low temperatures are applied directly to nerves, it is referred to as cryoneurolysis, and this process is often utilized for pain relief (cryoanalgesia). On the other hand, cryoablation refers to the process of destroying tissue (eg, tumors) with extreme cold. Thus, an interventional technique that temporarily destroys nerves can also be referred to as cryoneuroablation. For this review article, cryoneurolysis will be the term utilized most often to describe this treatment strategy. Recent improvements in this analgesic technique allow its utilization in various clinical settings, including perioperative and office-based clinical applications.

Historically, the early perioperative use of cryoprobes required a surgical incision to reversibly ablate the target nerve and provide analgesia in procedures such as tonsillectomies,[1] thoracotomies,[2] and herniorrhaphy.[3,4] Recent advancements in cryoablation has enabled percutaneous administration, which has substantially increased the scope and applications of cryoneurolysis.[5] Furthermore, the advancement in cryoneurolysis equipment combined with the use of ultrasound imaging has broadened the scope of cryoneurolysis application to chronic painful conditions such as intractable neuropathic and neoplastic pain.[6] The real-time imaging of ultrasound guidance enables the precise application to specific peripheral nerves, raising the possibility of cryoneurolysis in providing longer-lasting site-specific pain management. High-resolution ultra-sound guidance provides the opportunity of targeting deeper structures within the nervous system.

Although traditional site-specific regional anesthesia with local anesthetic provides excellent pain relief, the analgesic effects of peripheral nerve block can be short-lived. In addition, in-situ catheters that prolong analgesia also decrease motor, sensory and proprioception, while increasing the risk of infection, falls, and overall burden on the patient and family members with catheter/pump care.[7] Emerging evidence suggests that cryoanalgesia may be superior to regional anesthesia in terms of duration of analgesia and side effects profile (Table 1).[7] A case series reported the utilization of ultrasound-guided percutaneous cryoneurolysis to treat pain successfully in surgical patients following procedures such as shoulder rotator cuff repair, total knee arthroplasty, lower limb amputation, iliac crest bone harvesting, postnephrostomy incisional pain, and lower extremity burns.[8,9] All cases of the patients who underwent orthopedic shoulder or knee surgery reported prolonged analgesia with significantly reduced pain scores (VAS <2) and opioid consumption compared to the historically used continuous brachial and femoral peripheral nerve blocks.[10,11]

Cryoanalgesia provides nonopioid pain relief with a lower risk of infection and no potential for local anesthetic toxicity and catheter dislodgement/leakage commonly seen with other pain management techniques.[7] As the United States battles the ongoing opioid epidemic, nonpharmacological approaches provide an attractive alternative. Also, the wide margin of safety margin with cryoanalgesia surpassing traditional local anesthetic-based peripheral nerve blocks enhances their clinical utility.[6] Hence, it is a great alternative to treat acute and chronic pain in perioperative and office-based settings.

Despite its increasingly recognized role in pain management, the use of cryoneurolysis is limited in clinical practice. This narrative review article aims to increase the reader's knowledge about cryoneurolysis and its application in the perioperative and office-based setting. Specifically, the mechanism of cryoanalgesia, common protocol of cryoneurolysis, and contraindications are discussed. Lastly, pain management options with cryoanalgesia are explored.

HISTORY OF CRYOANALGESIA

For medicinal use, the local application of low temperatures has been documented for centuries. Precisely, the use of low temperature as a form of analgesia dates back to the ancient Greeks and Egyptians.[12] Hippocrates is credited with the first written accounts of using ice and snow applied to wounds for pain relief and inflammation in 460 BC.[12] In the 1800's, Arnott described the use of severe cold at −20°C to relieve neuropathic and cancer pain.[13] In 1866, Ether spray was introduced by Richardson as a topical anesthetic, followed by ethyl chloride spray in 1891.[12] Given that these sprays caused a frosted state (freezing) with loss of sensation or feeling (numb), the term "to freeze" became synonymous with "to numb."

While the act of using cold to suppress pain has been around since the early Greeks and Egyptians, cryoneurolysis was not used specifically for tissue destruction until the 19th century.[14] Advancements in cryotechnology have allowed the use of much colder temperatures (as cold as −196°C) to ablate nerves reversibly.[5] Even though the French military applied ice and snow to wounds for regional analgesia, the first commercially developed

TABLE 1 Comparison of regional anesthesia and cryoanalgesia

	Pros	Cons
Regional Anesthesia (continuous peripheral nerve blocks, epidurals/spinals)	Effective short-term analgesia Well-studied Improved efficacy/safety with ultrasound Generally easy to perform Well-tolerated Minimal side effects Quick onset of action	**Short duration of analgesia lasting up to 1 week** Continuous PNBs and epidurals require catheter/pump care More complications associated with indwelling catheter (ie, infection, catheter migration, ineffectiveness)
Cryoanalgesia	Prolonged analgesia lasting weeks to months with significant reduction of opioid consumption. Minimal side effects Easy to perform Well-tolerated Quick onset of action Handheld cryoneurolysis devices, portable, and cost-effective	Unpredictable duration of analgesia Requires repeat treatments (~every 3 months or when pain returns) Can lead to muscle weakness, which may be undesirable for certain procedures Limited use in current practice

cryoanalgesia device was not designed until the early 1960s.[15] In 1961, Cooper et al. developed a hollow tube containing liquid nitrogen that achieved a temperature of −190°C and led to modern-day cryoanalgesia.[12] In 1976, Lloyd et al. proposed neuroablation at a cold temperature and coined the term “cryoanalgesia” for its use in pain management.[16] He demonstrated that cryoanalgesia was superior in that it prevented the neuralgia and neuritis that often accompanies neuroablation with phenol, alcohol, or surgical lesions.[17]

The modern techniques of cryoneurolysis administration has evolved over time from a blind approach using surface landmarks and nerve stimulation to the use of advanced imaging guidance including computed tomography [CT], magnetic resonance imaging [MRI], and/or ultrasound. Using a percutaneous approach, the integration of advanced imaging guidance further unlocked a myriad of potential applications for cryotechnology. Specifically, ultrasound guidance has enabled nerves to be localized and cryoablated in tissues that were once deemed unsafe, including the peroneal, suprascapular, superior cuneal, femoral, sciatic, ilioinguinal, genitofemoral, and saphenous nerves.[18]

As cryotechnology advances, handheld devices with cryoprobes made it possible easily to visualize nerve anatomy with ultrasound guidance.[19] Cryoprobes have differently sized needle tips that can be used to produce varying ice ball sizes on targeted superficial peripheral nerves (Figure 1A). These devices are portable and contain a small charging dock. They can be used in conjunction with ultrasound, allowing for convenient use in an office setting as well as in hospitals or ambulatory surgery centers where multiple departments may share the same handpiece[5] (Figure 1B). The accessibility of ultrasound devices, ultrasound imaging proficiency among anesthesia providers, and FDA-approved handheld cryoneurolysis devices have allowed cryoanalgesia to become a practical intervention for acute and chronic pain management.

MECHANISM OF ACTION

Cryoneurolysis is the direct application of cold temperatures, (approximately −70°C) to ablate the targeted nerve, resulting in reversible neuronal injury to the peripheral sensory nerve. The effect of cryoablation and the degree of tissue injury depends on the temperature of the cryoprobe. While mild temperature (+10°C to −20°C) causes little or no neuronal injury, reversible destruction of the axon, called Wallerian degeneration, occurs in temperatures between −20°C to −100°C.[20] It is important to note that this degeneration includes the axon and myelin sheath but not the endoneurium, which is unaffected by the focused cold therapy. Wallerian degeneration occurs distally from the site of ablation, and the induced block lasts until axon regeneration.[21] Generally, axonal regeneration occurs at a rate of approximately 1–2 mm per day, and once the axon has regenerated it reconnects with the sensory receptor, and conduction can start again.[5] Regrowth of axons into the perineurium eventually restores sensation and the block functionally resolves.[21] Thus, pain sensation may return over time (after weeks to months) and requires repeat administration of cryoneurolysis.[22] In fact, repeating cryoneurolysis in the same anatomic location for subsequent surgical procedures does not result in negative sequelae.[6]

Modern cryoprobes utilize gas instead of ice or snow to generate extremely low temperatures. The cryoprobes consist of a hollow tube ranging from 1.4 mm to 2 mm[12] (Figure 1). Inside the hollow tube is a smaller inner tube that injects pressurized gas (usually carbon dioxide or nitrous oxide) at 600 to 800 psi. The pressurized gas travels down the inner tube and is released through a very fine aperture into the larger outer tube at a much lower pressure (10–15 psi), allowing the gas to expand rapidly into the distal tip.[12] As the gas moves from high to low pressure through the narrow aperture, the rapid expansion causes a dramatic decrease in temperature, forming an ice ball at the tip of the probe (the Joule-Thomson

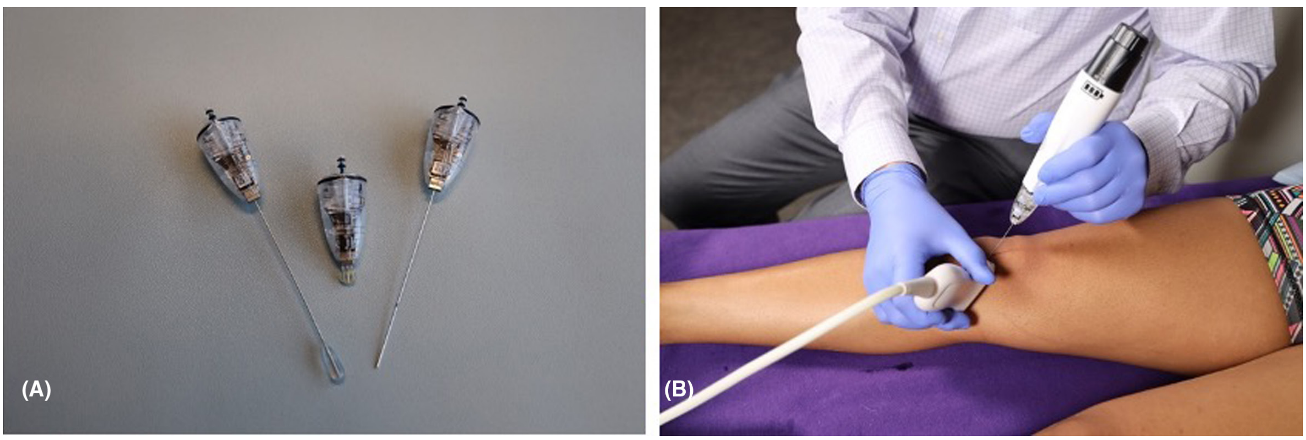

FIGURE 1 (A) Needle tips from handheld cryoneurolysis devices. (B) FDA-approved handheld cryoneurolysis devices used in combination with ultrasound-guidance. Courtesy of I over.

effect).[6] The subsequent ice crystals formed in this process induce vascular damage to the vasa nervorum, producing severe endoneural edema, which results in long-term pain relief.[12] The gas is then evacuated back to the machine through a large diameter tube located in the center of the shaft (Figure 2). This ensures that no gas enters the patient's tissues.[12]

The extent and duration of analgesia are the result of the degree of cold obtained and the duration of exposure.[23] Also, the degree of coldness and tissue injury depends on the gas utilized because the temperatures produced by the probe cannot be lower than the boiling point of the gases (nitrous oxide: −88°C; carbon dioxide: −79°C). Thus, irreversible nerve damage is less likely to occur with these gases because it typically occurs with temperatures around −100°C.[6] Furthermore, most nerve cryoprobes have a built-in nerve stimulator for localization of the nerve and a thermistor to detect the temperature at the tip.[12] Together, these features provide a wide margin of safety for these devices. When performing cryoneurolysis, a series of two to three-minute freezes with 30 s of defrosting between each cycle is recommended.[12] Adequate thawing of more than 20 s but less than 40 s allows subsequent freezes to increase the size of the freeze zone, optimizing the result.[12] Note: Cryoprobes for tumor ablation do not generally include nerve stimulators and use liquid nitrogen without the Thomas-Joule effect.

APPLICATION IN ACUTE PAIN MANAGEMENT

The application of cryoneurolysis in acute pain management is continually expanding to an array of surgical procedures. The increased scope of cryoneurolysis can largely be attributed to the advent of ultrasound-guidance, which enables precise location to reach the specific nerves. While the earliest accounts of using cryoanalgesia began with cryoablation of the intercostal nerves in thoracotomy surgery, it has recently been explored for postoperative pain in mastectomy surgery, shoulder arthroplasty, and total knee arthroplasty. Table 2 summarizes the application of cryoanalgesia in acute pain management with the search terms either cryoanalgesia, cryoneurolysis or cryoablation and pain. These procedures may cause moderate to severe postoperative pain, and if not adequately controlled, can lead to chronic pain. Thus, these procedures are amenable to the long-lasting benefits of cryoneurolysis. Recent data have supported the use of cryoneurolysis in these procedures and demonstrated its safety, efficacy, and long-lasting pain control.[23–28]

Thoracotomy

Thoracotomy is one of the most painful operations where inadequate control of pain is associated with increased postoperative morbidity.[24] Additionally, chronic postsurgical pain has been reported to occur in 22–67% of thoracotomy patients.[24] Thoracic epidural analgesia is traditionally the gold standard for controlling post-thoracotomy pain. Unfortunately, epidural anesthesia is not suitable for all patients, as it carries potential risks and limitations including epidural perforation, hematoma, infection, hypotension/bradycardia, and urinary retention. In addition, epidural placement can be technically more challenging to perform, and even the most

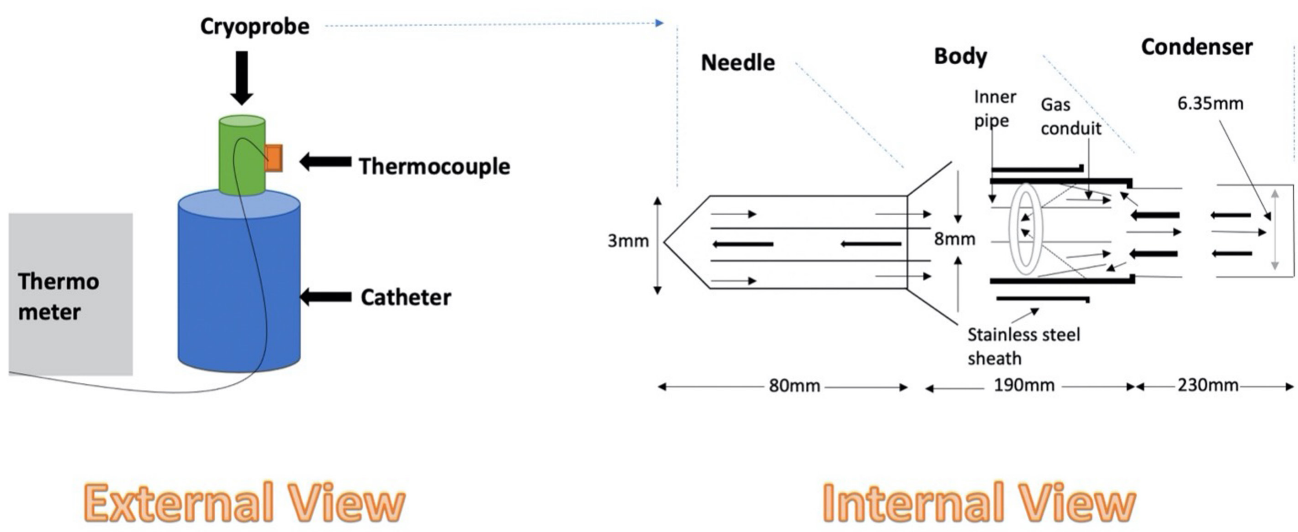

FIGURE 2 Schematic diagram of cryoprobe via external and internal view. The cryoprobe consists of the needle, body and condenser. Inside the needle, a thermocoupled meter is attached to the cryoprobe inside the catheter tip to monitor the temperature during cryoablation. Inside the body and condenser, pressurized gas travels down the inner tube and is released through a very fine aperture into the larger outer tube at a much lower pressure, allowing the gas to expand rapidly into the distal tip. The rapid expansion of gas moving from high to low pressure through the narrow aperture causes a dramatic decrease in temperature (the joule-Thomson effect).

TABLE 2 Summary of clinical studies on using cryoneurolysis in treating acute postoperative pain

Author/year	Subject	Clinical application	Results	Limitations
Nelson et al. (1974)	38	Thoracotomy	Cryoneurolysis statistically decreased postoperative narcotic usage without neuritis or neuromas within 24 months of follow-up	Limited sample size, nonrandomization of study groups
Yang et al. (2004)	90 (45 cryo + epidural)	Thoracotomy	Patients in cryoneurolysis + epidural group experienced less pain and required less rescue morphine by postoperative days 6 and 7	Failure to isolate effects of cryoneurolysis itself as it was also used with an epidural in the study group
Ju et al. (2017)	107	Thoracotomy	No significant difference in patient satisfaction scores or on NRS at rest or in motion between the two groups during the 3 postoperative days	Large loss of follow-up, which may have confounded the results
Clemence et al. (2020)	117 (25 cryo)	Thoracotomy	Cryoneurolysis group had reduced average narcotic usage by 28 MME in 10 days after extubation, but there were no differences in pain scores	Retrospective design, risk of surgeon bias since cryoneurolysis was selected on surgeon preference
Gabriel et al. (2020)	3	Mastectomy	All patients reported a pain score of 0 for all postoperative days without requiring any supplemental opioid analgesics	Small sample size. Case report study, thus results cannot be generalized
Radnovich et al. (2017)	180	Total knee arthroplasty	Patients who received active treatment had statistically significant greater change from baseline in the WOMAC pain subscale score at days 30, 60, and 90	Potential patient bias as patients began to accurately guess their treatment group based on their response to treatment over time, which may have biased results in favor of active treatment
Das et al. (2016)	100	Total knee arthroplasty	Significantly lower proportion of patients in the treatment group had a length of stay of ≥2 days compared with the control group and required 45% less opioids during first 12 weeks after surgery	Retrospective, nonrandomized study, lack of blinding of patients and investigators, which may have led to biased results, limited generalizability of findings.
Mihalko et al. (2020)	124	Total knee arthroplasty	The cryoneurolysis group had improved functional scores/numerical improvements in pain scores with significant improvements in current pain	Lack of sham-control group. Conducted at a single site. Thus, results may not be generalizable
Ilfeld et al. (2017)	2	Shoulder arthroplasty	Both patients experienced a pain score of <2 on 0–10 NRS, required less opioids compared to historic controls, and regained motor function within 2–3 weeks postoperative	Case report with small number of participants. Results cannot be generalized

experienced providers may fail the epidural placement, leading to unsatisfactory analgesia.[24] Hence, there is a need for alternative effective pain management in this population.

Cryoneurolysis has been used and demonstrated comparable efficacy in treating acute postoperative thoracotomy pain compared to epidural analgesia. Due to easy identification of the intercostal nerves through the thoracotomy incision, cryoablation of the nerves intraoperatively is one of the most extensively studied among all of the postoperative indications for cryoneurolysis. Several studies have demonstrated that cryoneurolysis of the intercostal nerve provides significant and long-lasting postoperative pain, particularly with relief of incisional pain.[25,26,29] For instance, Nelson et al. first described intraoperative intercostal cryoneurolysis of 76 individuals in 1974. Those treated with cryoneurolysis demonstrated significantly reduced postoperative opioid use (cryo 661.0 mg vs. no cryo 855.2 mg of meperidine, $p<0.05$). Patients who received cryoneurolysis did not develop neuritis or neuromas within 24 months of follow-up.[25] These findings were supported by a randomized controlled trial (RCT) with 90 participants undergoing thoracotomy.[29] Forty-five patients received epidural alone for the first 7 days postoperatively, and 45 patients received combined epidural analgesia with intraoperative cryoneurolysis. Postoperatively, those in the cryoneurolysis with an epidural group experienced significantly less postoperative pain on day 7 and required less morphine on day 6 and day 7 compared to the epidural only group.[24] However, cryoneurolysis combined with epidural failed to decrease the incidence of long-term pain and numbness when assessed 6 months after surgery.[29] Similarly, Ju et al.[24] compared thoracic epidural analgesia with intercostal nerve cryoneurolysis for post-thoracotomy acute pain in 107 adult patients in an RCT. They did not find significant differences between groups on the numeral rating scales (NRS) at rest or on motion during the first three postoperative days.[24] Even though patient satisfaction was similar between these two groups, there was a slightly higher incidence of pruritus in the epidural morphine group.[24] A retrospective cohort study of 117 patients undergoing open thoracic or thoracoabdominal aortic aneurysm repair did not find significant differences in pain score between the cryoneurolysis group and the control group whose pain was managed pharmacologically.[26] However, there was a significantly reduced narcotic usage by 28 MME in 10 days after extubation in the cryoneurolysis group.[26]

Taken together, these results suggest that cryoneurolysis of the intercostal nerve may be as effective as thoracic epidural analgesia in preventing acute postoperative thoracotomy pain. In addition, cryoneurolysis eliminates the need for catheter care, and continuous monitoring.[12] Compared with conventional pain modalities, cryoneurolysis is an excellent alternative to reduce narcotic use postoperatively. Thus, the use of cryoneurolysis may be an alternative to adequately control postoperative pain with minimal opioid consumption in the perioperative period, especially when thoracic epidural analgesia is contraindicated or cannot be placed.

Mastectomy

Pain following mastectomy is often challenging to treat with local anesthetic-based regional anesthetic techniques and often results in persistent postmastectomy pain, lasting multiple weeks.[30] Cryoneurolysis has recently been demonstrated to be a novel yet effective analgesic modality with promising results for managing postmastectomy pain. Ultrasound-guided percutaneous intercostal nerve cryoneurolysis has been performed to treat unilateral and bilateral postoperative mastectomy pain.[30] In three case reports, ultrasound-guided percutaneous cryoneurolysis was performed on four proximal ipsilateral intercostal nerves of T2-5, with 3 cycles of 2 min of freezing followed by a 1-min thawing period. All patients reported a mean pain score on the numeral rating scale of 0 for each postoperative day before discharge to home. No patients required supplemental opioid analgesics during the entire postoperative period.[30] Thus, analgesia from cryoneurolysis more closely matches the duration of mastectomy pain than other currently described techniques. This is noteworthy, as pain from mastectomy surgery has been shown to outlast single-injection nerve blocks and even continuous perineural local anesthetic infusions, such as thoracic paravertebral block (PVB) and erector spinae plane blocks (ESP).[19] Currently, there is no study directly comparing the efficacy between PVB/ESP blocks and percutaneous intercostal nerve cryoneurolysis. While these case reports show promising results, randomized controlled trials should be performed to properly quantify the potential risks and benefits of using cryoneurolysis in postmastectomy patients.

Total knee arthroplasty

While cryoneurolysis is commonly employed for patients undergoing thoracotomy and mastectomy, orthopedic procedures such as total knee arthroplasty (TKA) are increasingly reaping the benefits of cryoneurolysis for postoperative pain management. Cryoneurolysis of the superficial genicular nerves (infrapatellar branch of the saphenous nerve [IPBSN] and anterior femoral cutaneous nerve [AFCN]) has been used for postoperative pain management in patients undergoing TKA.[28] These nerves innervate the anterior aspect of the knee where pain often occurs in response to the surgical incision and soft tissue damage during TKA.[27] Cryoneurolysis of the genicular nerves has demonstrated effective and prolonged postoperative pain in patients undergoing TKA.[27] This conclusion is supported by the multicenter, randomized, double-blind, sham-controlled trial study of cryoneurolysis, including 180 patients (n = 121 active treatment, n = 59 sham treatment). The study reported that patients who received active treatment with cryoneurolysis of the infrapatellar branch of the saphenous nerve (IPBSN) had a significant improvement in functional performance and pain score at Days 30, 60, and 90 compared to the sham group.[28]

Consistent with this finding, a retrospective study of 100 patients undergoing TKA demonstrated that preoperative cryoneurolysis of the superficial genicular nerves (SGN) resulted in overall better clinical performance than standard multimodal pain regimens. Those in the cryoneurolysis group had a shorter postoperative length of stay (6% vs. 67%, stayed ≥2 days, $p < 0.0001$). In addition, the cryoneurolysis group consumed 45% less MME opioids during the 12 weeks following surgery. They also reported less pain intensity and interference in daily activities as measured by Patient-reported Outcomes Measurement Information System (PROMIS) ($p < 0.0001$) 6 weeks after the surgery.[19] Moreover, Mihalko et al performed an unblinded RCT to compare the efficacy of cryoneurolysis treatment before TKA against standard care at reducing postoperative opioid use.[27] Patients either received cryoneurolysis (n = 62) of the SGN 3–7 days before TKA or current preoperative standard of care (SOC, n = 62). The current SOC treatment consisted of spinal anesthesia and a single-injection adductor canal block along with local infiltration analgesia (periarticular and posterior capsule; 1% lidocaine) during surgery. Compared to the SOC group, the cryoneurolysis group had improved functional scores and numerical improvements in pain scores with significant improvements in observed current pain from baseline to the 72-h and 2-week follow-up assessments. Of note, the significant improvement in pain scores observed at 72 h and 2-week postsurgery may be attributed to the longer duration of cryoneurolysis. Furthermore, the study reported that cryoneurolysis significantly reduced opioid consumption in total daily MME from discharge to the 6-week study follow-up assessment (4.2 vs. 5.9 mg; $p = 0.0186$).[27]

Taken together, these studies suggest that cryoneurolysis leads to decreased postoperative pain scores, opioid consumption, and hospital lengths of stay in patients undergoing TKA. Besides its success in improving pain scores, cryoneurolysis improved functional performance such as pain interference in daily activities, reduced stiffness, and improved physical function, all of which can contribute to better quality of life. Thus, cryoanalgesia may be a better alternative as part of multimodal analgesia for patients undergoing TKA.

Shoulder arthroplasty

Suboptimal pain management after shoulder arthroplasty remains a major concern despite the increased utilization of brachial plexus blockade.[31] Interventions such as continuous interscalene blocks that can be performed for moderately painful orthopedic shoulder surgery have a high failure rate of up to 25% and significant inherent risks (eg, pneumothorax, phrenic nerve injury, and diaphragm paralysis).[10] Hence, patients who have respiratory compromise may require an alternative for postoperative pain management. Cryoneurolysis of the suprascapular nerve has been effectively and safely performed for postoperative analgesia. The suprascapular nerve arises from the upper trunk of the brachial plexus and innervates the supraspinatus, infraspinatus, and the shoulder joint.[8,12]

Ilfeld et al. (2017) reported preoperative ultrasound-guided percutaneous cryoneurolysis for postoperative analgesia in two patients undergoing shoulder surgery.[8] Using a portable ultrasound, they ablated the suprascapular nerve superior to the suprascapular notch. Both patients experienced adequate postoperative analgesia with pain scores consistently <2 (NRS of 0–10) and required significantly less opioid relative to historic controls.[8] The main limiting factor regarding cryoneurolysis for postoperative pain in shoulder arthroplasty is the potential to cause complete sensory and motor block, with an unpredictable duration of action. This is because the suprascapular nerve innervates approximately 65% of the shoulder joint.[8] Weakening or paralyzing the supraspinatus and infraspinatus muscles could theoretically compromise rehabilitation of the shoulder joint if motor function is impaired for multiple months.[20] However, cryoneurolysis to the nerve has not been shown to affect rehabilitation in the early postoperative period because patients have regained full motor function by the time aggressive physical therapy begins. The patients had full motor functions in approximately 2–3 weeks following the original procedure in these case reports.[8] Given the limited evidence supporting the use of cryoneurolysis for pain management after shoulder surgery, there is a need for well-designed, large-scale studies.

APPLICATIONS IN OFFICE-BASED CRYONEUROLYSIS PROCEDURES

Chronic pain poses a major challenge worldwide, leading to significant clinical, social, and economic impacts. The use of cryoneurolysis in chronic pain management continues to gain favor as its efficacy and low side effect profile are demonstrated in the literature (Table 3). In particular, cryoneurolysis can be used as office-based procedure to treat various chronic pain pathologies, including knee pain attributed to osteoarthritis, temporomandibular joint (TMJ) disorders, neuropathic pain syndromes, and even phantom limb pain.[28,32–37] The advancement of ultrasound imaging made the office-based cryoneurolysis possible to provide pain treatment that otherwise would need to be performed with fluoroscopy in the outpatient hospital setting. Recent studies suggest that cryoneurolysis can provide an effective, safe, and nonpharmacological therapeutic option to treat an array of chronic pain conditions, but that further research is still required. The potential benefits of cryoneurolysis for patients suffering from chronic painful conditions include increased functional capacity and quality of life and the decreased need for potent pharmacological agents such as opioids and NSAIDs. This method of chronic pain management should continue to be explored to manage difficult to treat pain pathologies, if appropriate.

Chronic knee pain

Chronic knee pain, the primary symptom of knee joint osteoarthritis (OA), continues to grow as a leading cause of disability in the US and results in decreased mobility, quality of life, and function.[32] Cryoneurolysis as a novel treatment modality has the ability to ablate the sensory nerves, for example, genicular nerve or periarticular branches of the saphenous nerve with cold temperature to provide analgesia of the knee with minimal side effects. After the sensory blockade has resolved, it can safely be repeated in the same location. A recent multicenter, double-blind RCT examined the effectiveness of cryoneurolysis in the treatment of knee pain as a result of OA via cryoneurolysis of the infrapatellar branch of the saphenous nerve (IPBSN).[28] As aforementioned, this is a sensory nerve that innervates the anterior and inferior

TABLE 3 Summary of clinical studies using cryoneurolysis in treating chronic pain conditions

Author/year/type	Subject	Clinical application	Results	Limitations
Radnovich et al. (2017)	180	Total Knee Arthroplasty	Compared to the sham group, patients who received active treatment had statistically significant greater change from baseline in the WOMAC pain subscale score at days 30, 60, and 90	Potential patient bias as patients began to accurately guess their treatment group based on their response to treatment over time, which could bias results in favor of active treatment
Sidebottom et al. (2011)	17	Temporomandibular Joint	Significant improvement in visual analogue pain scores (VAS) from 6.8 to 2.0. The mean number of pain-free months after treatment was 7	Retrospective review, small sample size
Yoon et al. (2016)	22	Refractory Peripheral Neuropathy	Mean pain levels were 8.3 before intervention and 2.3 at 1 month, 3.2 at 3 months, 4.7 at 6 months, and 5.1 at 12 months after, which was statistically significant	Prospective study. Small sample size with a majority of patients being male (59%), thus results cannot be generalizable
Dalili et al. (2021)	3	Neuropathy-mediated anterior thigh pain	Median pain intensity decreased from 8 preprocedure to 1 postprocedure. The cryoanalgesia effected lasted for 12 months in all three patients	Small sample size
Rhame et al. (2011)	1	Sural Neuroma	Each treatment consisted of excellent relief for 3 months following each serial treatment, over a 3 year period	Case report, results cannot be generalized
Moesker et al. (2014)	5	Phantom Limb Pain	Three of the five patients had a 90–100% decrease in pain	Retrospective design; results not generalizable, only male patients in study, small sample size

portion of the knee as well as the skin over the anteromedial knee and is a prime target for nerve blockade to reduce knee pain. Participants were randomly selected to receive either cryoneurolysis or sham procedures and followed for up to 180 days. The sham group underwent the same procedure with no cold treatment. Compared to the sham group, patients who received cryoneurolysis had a significantly greater change from baseline in the Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain subscale score at Days 30, 60, and 90. Interestingly, there was no significant difference in WOMAC pain at Day 120. Thus, it was concluded that cryoneurolysis of the IPBSN resulted in significantly decreased knee pain compared to the sham group for up to 150 days and appeared safe and well-tolerated. A similar study by Nygaard et al.[22] is currently underway and pending publication. While there is a paucity of research currently available regarding the role of cryoneurolysis in managing chronic OA knee pain, this article shows promising results. Cooled radiofrequency ablation (RFA) is another modality of therapy that has shown favorable outcomes in treating knee pain.[38–40] Similar to cryoneurolysis, RFA relieves knee pain by targeting genicular nerve and/or periarticular branches of the saphenous nerve. Although there is no study comparing the efficacy of these two modalities, current data supports the use of RFA for treating knee pain.[38–40] Similar to portable cryoneurolysis, RFA can be used in a clinic setting of a pain office.

Temporomandibular disorders

Temporomandibular disorders (TMD) can be subdivided into muscular or articular derangements characterized by functional, intraarticular clinical problems and pain. Pain is the most dominant symptom of TMD and is frequently localized pain to jaws, temporomandibular joint, and mastication muscles.[41] Historically, treatment included a surgical intervention for refractory cases, but increasingly, there is a movement towards nonsurgical, conservative management.[41,42] One nonsurgical modality that has been considered is cryoneurolysis of a branch of the trigeminal nerve to relieve painful TMD. The rationale for this technique is to control the pain fibers to the lateral capsule and the terminal portion of the auriculotemporal nerve.[41] This auriculotemporal nerve derives from the third division of the trigeminal nerve. Sidebottom et al. published a retrospective analysis on 17 patients who failed conservative management of their TMJ pain and were not surgical candidates. All patients received cryoneurolysis in the auriculotemporal nerve and TMJ capsule region with and positive effects. They reported an improvement in the pain VAS from 6.8 to 2, and a mean of seven pain-free months.[33] Hence, cryoneurolysis may be a useful adjunct to the management of intractable pain in the TMD. Given the paucity of evidence evaluating the role of cryoneurolysis for chronic TMD pain, further research is needed in this area.

Neuropathic pain

The role of cryoneurolysis in neuropathic pain management has received slightly more attention in areas involving research and application, particularly concerning refractory neuropathic pain. In 2016, Yoon et al enrolled 22-patients for cryoneurolysis of refractory peripheral neuropathy and showed significant mean reductions in VAS scores for pain over a 12-month period: 8.3 at baseline, 2.3 at 1 month, 3.2 at 3 months, 4.7 at 6 months, and 5.1 at 12-months.[34] Another study reported the effects of cryoneurolysis on three patients with recalcitrant neuropathic anterior femoral cutaneous nerve pain. Median pain intensity scores were decreased from 8 before cryoneurolysis to 1 after cryoneurolysis. Remarkably, the pain score of 1 persisted throughout the 12-month follow-up period.[36] Lastly, a case study involving a refractory sural neuroma, with ensuing pain and hyperalgesia, was evaluated for treatment with cryoneurolysis after six-years of medical and surgical management consisting of physical therapy, gabapentin, amitriptyline, desipramine, hydrocodone-acetaminophen and surgical excision of the neuroma, which had little effect. The cryoneurolysis had profound analgesia, to the extent that the patient claimed to have forgotten that he had pain in his leg. At the time of publications, the patient had received monthly cryoneurolysis for 3 years with great analgesia and no complications or adverse events.[35]

Phantom limb pain

Phantom limb pain (PLP) is considered a special kind of neuropathic pain that has also been treated with cryoneurolysis. In PLP, the patient typically reports pain in the body region no longer present. Risk factors include female gender, upper extremity amputation, presence of preamputation pain, and residual pain in the stump.[43–45] While the exact mechanism of PLP is poorly understood, cryoneurolysis has been used to manage PLP. Using this approach, Moesker *et al*. reported a successful reduction of PLP in six patients. Undoubtedly, identifying the peripheral nerve carrying the sensation is essential for successful ablation. However, the PLP can be reproduced and exacerbated with the correct placement of the nerve stimulator. Once identified, injection of local anesthesia at the site may temporarily diminish the pain. If the peripheral nerve injection provided temporary relief, the final treatment with cryoneurolysis can prolong the duration of analgesia. Of the five patients who received cryoneurolysis of the PLP-causing nerve, three reported >90% improvement in pain as measured by the VAS score for pain at 2.5 years and 5 years; one patient had a 40% reduction and another a 20% reduction. The two patients with the least amount of effect from cryoneurolysis were lost to follow-up at 5 months due to death from natural causes.[37] Although both central and peripheral components are likely involved in PLP, treatment of a peripheral nerve locus may be considered to provide long-term relief of PLP. Thus, cryoneurolysis should continue to be explored for patients with PLP and those undergoing limb amputation.

Risks & contraindications

Despite cryoneurolysis being a safe procedure, there are risks and contraindications that all providers must consider. Potential side effects of cryoneurolysis include bleeding, bruising, and very rarely, infection.[6] Skin and hair in the general proximity of treatment may be affected, especially if the target nerve is superficial. Hyperpigmentation, depigmentation, and alopecia may occur at the site of injury, particularly near the eyebrow when treating the supraorbital nerve.[12] There is mild to moderate discomfort at the site with the initial application that typically resolves within 30 s. Providers should educate patients about the expected numbness that accompanies the procedure and that it will not simply lead to pain relief.[12] Others have suggested that patients be allowed to "preview" the numbing effect, as some patients have found the numbness to be bothersome.[12] As with any procedure, informed consent and realistic expectations can improve outcomes.

Generally, contraindications to cryoneurolysis are similar to contraindications for peripheral nerve blocks, including patient refusal, infection (local and systemic), anticoagulation, bleeding disorders, localized infection, and patients with cryoglobulinemia, cold urticarial, and Raynaud's syndrome.[6] Cryoneurolysis is contraindicated when extremity muscle weakness is unacceptable, such as ablating the femoral nerve for analgesia following knee surgery, as a weak quadriceps muscle prevents postoperative ambulation.[6] Figure 3 depicts a schematic for determining the viability of cryoneurolysis depending on nerve anatomy. Currently, there are no published reports of neuroma formation or permanent nerve injury.[6] However, three clinical trials performed cryoneurolysis of the intercostal nerves for thoracotomy and reported increased risk of postoperative neuropathic pain, whereas many others found no such association.[2]

DISCUSSION

Cryoneurolysis devices are FDA-approved handheld instruments used in combination with ultrasound guidance to treat acute and chronic types of neuropathic pain related to osteoarthritis, postherpetic neuralgia, plantar fasciitis, intercostal pain, and posterior anteriolateral femoral cutaneous pain.[8,36,46–49] Although repeat procedures may be needed as the axon regenerates,

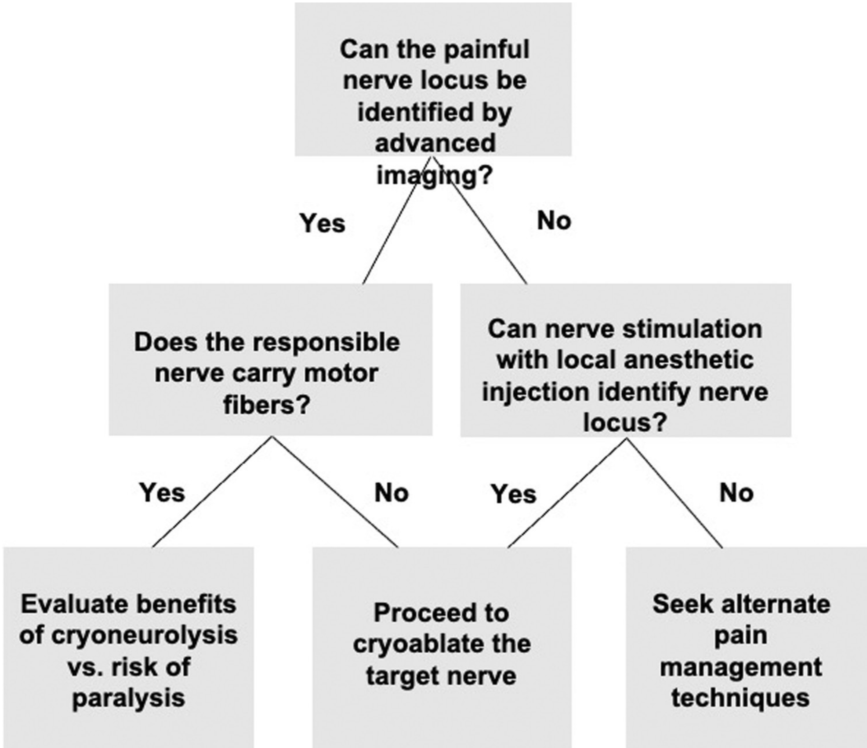

FIGURE 3 Flow diagram depicting the process for determining the viability of cryoneurolysis.

the returned pain intensity following cryoneurolysis may be less severe because of pain modulation, through the descending inhibitory pathway. This is due to modulation of the descending inhibitory pathway.[5,50] Many persistent or chronic pain conditions are associated with prolonged functional changes in the hyperexcitability of the dorsal horn in the central nervous system.[51,52] Such activity-dependent neuroplasticity leads to spinal central sensitization.[51] It has been suggested that the ascending-descending loop activated central sensitization in response to prolonged stimulation can be interrupted by Wallerian degeneration, allowing for reversal of central sensitization.[50] In addition, there is enhanced net descending inhibition after inflammation at sites of nerve lesion following cryoneurolysis.[5] This is supported by the nerve injury model in an animal model that lesions of the nerve produce an attenuation of hyperalgesia and hypersensitivity to noxious stimuli.[5,50]

In summary, this narrative review demonstrates that cryoneurolysis is very much a safe and effective treatment for many acute and chronic pain conditions. It provides great pain relief with less risk compared to other forms of neurolysis. Furthermore, cryoneurolysis may be a viable option to treat other intractable neuropathic pain where the nerve is superficial and can be identified under ultrasound. As ultrasound use becomes a more standardized tool in clinical practice, anesthetists will be able to routinely perform cryoneurolysis both perioperatively and in the outpatient management of chronic pain. Pain management techniques are continually improving to provide enhanced benefit and safety for all patients. Cryoneurolysis has demonstrated great potential, but further research should be performed to better quantify the benefits of cryoneurolysis for an array of acute and chronic painful conditions.

FUNDING INFORMATION

Edwin N. Aroke is supported by an R01 grant from the NIH/NIAMS (R01AR079178). Sarah Zhang is supported by OREF grant (A136242).

CONFLICTS OF INTEREST

The authors declared no financial relationships with any commercial entity related to the content of this article. The authors did not discuss off-label use within the articles.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Edwin N. Aroke https://orcid.org/0000-0002-8355-0870
Sarah Jingying Zhang https://orcid.org/0000-0003-4638-0611

REFERENCES

1. Robinson SR, Purdie GL. Reducing post-tonsillectomy pain with cryoanalgesia: a randomized controlled trial. Laryngoscope. 2000;110(7):1128–31. https://doi.org/10.1097/00005537-200007000-00011
2. Khanbhai M, Yap KH, Mohamed S, Dunning J. Is cryoanalgesia effective for post-thoracotomy pain? Interact Cardiovasc Thorac Surg. 2014;18(2):202–9.
3. Wood GJ, Lloyd JW, Bullingham RE, Britton BJ, Finch DR. Postoperative analgesia for day-case herniorrhaphy patients. A comparison of cryoanalgesia, paravertebral blockade and oral analgesia. Anaesthesia. 1981;36(6):603–10. https://doi.org/10.1111/j.1365-2044.1981.tb10324.x
4. Callesen T, Bech K, Thorup J, Andersen J, Nielsen R, Roikjaer O, et al. Cryoanalgesia: effect on postherniorrhaphy pain. Anesth Analg. 1998;87(4):896–9. https://doi.org/10.1097/00000539-199810000-00028
5. Ilfeld BM, Preciado J, Trescot AM. Novel cryoneurolysis device for the treatment of sensory and motor peripheral nerves. Expert Rev Med Devices. 2016;13(8):713–25. https://doi.org/10.1080/17434440.2016.1204229
6. Ilfeld B, Gabriel R, Trescot A. Ultrasound-guided percutaneous cryoneurolysis for treatment of acute pain: could cryoanalgesia replace continuous peripheral nerve blocks? Br J Anaesth. 2017;119:709–12.
7. Ilfeld BM. Continuous peripheral nerve blocks: an update of the published evidence and comparison with novel, alternative analgesic modalities. Anesth Analg. 2017;124(1):308–35. https://doi.org/10.1213/ANE.0000000000001581
8. Ilfeld BM, Gabriel RA, Trescot AM. Ultrasound-guided percutaneous cryoneurolysis providing postoperative analgesia lasting many weeks following a single administration: a replacement for continuous peripheral nerve blocks?: a case report. Korean J Anesthesiol. 2017;70(5):567–70.
9. Gabriel R, Finneran J, Asokan D, Trescot A, Sandhu N, Ilfeld B. Ultrasound-guided percutaneous cryoneurolysis for acute pain managment: a case series. A&A Case Reports. 2017;9(5):129-132.
10. Ilfeld BM, Morey TE, Wright TW, Chidgey LK, Enneking FK. Continuous interscalene brachial plexus block for postoperative pain control at home: a randomized, double-blinded, placebo-controlled study. Anesth Analg. 2003;96(4):1089–95.
11. Ilfeld BM, Mariano ER, Girard PJ, Loland VJ, Meyer SR, Donovan JF, et al. A multicenter, randomized, triple-masked, placebo-controlled trial of the effect of ambulatory continuous femoral nerve blocks on discharge-readiness following total knee arthroplasty in patients on general orthopaedic wards. Pain. 2010;150(3):477–84.
12. Trescot AM. Cryoanalgesia in interventional pain management. Pain Physician. 2003;6(3):345–60.
13. Arnott JM. On severe cold or congelation as a remedy of disease. Welcome Domain. Public Domain Mark, 1848.
14. Dasa V, Lensing G, Parsons M, Bliss R, Preciado J, Guirguis M, et al. An ancient treatment for present-day surgery: percutaneously freezing sensory nerves for treatment of postsurgical knee pain. Techniques in Regional Anesthesia and Pain Management. 2014;18(4):145–9.
15. Cooper IS, Lee AS. Cryostatic congelation: a system for producing a limited, controlled region of cooling or freezing of biologic tissues. J Nerv Ment Dis. 1961;133:259–63.
16. Lloyd J, Barnard J, Glynn C. Cryoanalgesia: a new approach to pain relief. Lancet. 1976;308(7992):932–4.
17. Nehme A, Warfield C. Cryoanalgesia: freezing of peripheral nerves. Hosp Pract (Off Ed). 1987;22(1A):71–7.
18. Bittman RW, Behbahani K, Gonzalez F, Prologo JD. Interventional cryoneurolysis: what is the same, what is different, what is new? New York: Thieme Medical Publishers; 2019. p. 374–80.
19. Dasa V, Lensing G, Parsons M, Harris J, Volaufova J, Bliss R. Percutaneous freezing of sensory nerves prior to total knee arthroplasty. Knee. 2016;23(3):523–8. https://doi.org/10.1016/j.knee.2016.01.011
20. Ilfeld BM, Finneran JJ IV. Cryoneurolysis and percutaneous peripheral nerve stimulation to treat acute pain: a narrative review. Anesthesiology. 2020;133(5):1127–49.
21. Finneran Iv JJ, Gabriel RA, Swisher MW, et al. Ultrasound-guided percutaneous intercostal nerve cryoneurolysis for analgesia following traumatic rib fracture – a case series. Korean J Anesthesiol. 2020;73(5):455–9. https://doi.org/10.4097/kja.19395
22. Nygaard NB, Koch-Jensen C, Vaegter HB, Wedderkopp N, Blichfeldt-Eckhardt M, Gram B. Cryoneurolysis for the management of chronic pain in patients with knee osteoarthritis; a double-blinded randomized controlled sham trial. BMC Musculoskelet Disord. 2021;22(1):228. https://doi.org/10.1186/s12891-021-04102-1
23. Evans P, Lloyd J, Jack T. Cryoanalgesia for intractable perineal pain1. J R Soc Med. 1981;74(11):804–9.
24. Ju H, Feng Y, Yang B-x, Wang J. Comparison of epidural analgesia and intercostal nerve cryoanalgesia for post-thoracotomy pain control. Eur J Pain. 2008;12(3):378–84.
25. Nelson K, Vincent R, Bourke R, et al. Intraoperative intercostal nerve freezing to prevent postthoracotomy pain. Ann Thorac Surg. 1974;18(3):280–5.
26. Clemence J Jr, Malik A, Farhat L, Wu X, Kim KM, Patel H, et al. Cryoablation of intercostal nerves decreased narcotic usage after thoracic or thoracoabdominal aortic aneurysm repair. Semin Thorac Cardiovasc Surg. 2020;32:404–12.
27. Mihalko WM, Kerkhof AL, Ford MC, Crockarell JR Jr, Harkess JW, Guyton JL. Cryoneurolysis before Total knee arthroplasty in patients with severe osteoarthritis for reduction of postoperative pain and opioid use in a single-center randomized controlled trial. J Arthroplast. 2021;36(5):1590–8.
28. Radnovich R, Scott D, Patel A, et al. Cryoneurolysis to treat the pain and symptoms of knee osteoarthritis: a multicenter, randomized, double-blind, sham-controlled trial. Osteoarthr Cartil. 2017;25(8):1247–56.
29. Yang M, Cho C, Kim YC. The effects of cryoanalgesia combined with thoracic epidural analgesia in patients undergoing thoracotomy. Anaesthesia. 2004;59(11):1073–7.
30. Gabriel RA, Finneran JJ, Swisher MW, Said ET, Sztain JF, Khatibi B, et al. Ultrasound-guided percutaneous intercostal cryoanalgesia for multiple weeks of analgesia following mastectomy: a case series. Korean J Anesthesiol. 2020;73(2):163–8.
31. Williams G, Kraeutler MJ, Zmistowski B, Fenlin JM. No difference in postoperative pain after arthroscopic versus open rotator cuff repair. Clin Orthop Relat Res. 2014;472(9):2759–65.
32. Nguyen US, Zhang Y, Zhu Y, Niu J, Zhang B, Felson DT. Increasing prevalence of knee pain and symptomatic knee osteoarthritis: survey and cohort data. Ann Intern Med. 2011;155(11):725–32. https://doi.org/10.7326/0003-4819-155-11-201112060-00004
33. Sidebottom A, Carey E, Madahar A. Cryoanalgesia in the management of intractable pain in the temporomandibular joint: a five-year retrospective review. Br J Oral Maxillofac Surg. 2011;49(8):653–6.
34. Yoon JHE, Grechushkin V, Chaudhry A, Bhattacharji P, Durkin B, Moore W. Cryoneurolysis in patients with refractory chronic peripheral neuropathic pain. J Vasc Interv Radiol. 2016;27(2):239–43.
35. Rhame EE, DeBonet AF, Simopoulos TT. Ultrasonographic guidance and characterization of cryoanalgesic lesions in treating a case of refractory sural neuroma. Case Rep Anesthesiol. 2011;2011:1–4.
36. Dalili D, Ahlawat S, Rashidi A, Belzberg AJ, Fritz J. Cryoanalgesia of the anterior femoral cutaneous nerve

(AFCN) for the treatment of neuropathy-mediated anterior thigh pain: anatomy and technical description. Skelet Radiol. 2021;50(6):1227–36.
37. Moesker AA, Karl HW, Trescot AM. Treatment of phantom limb pain by cryoneurolysis of the amputated nerve. Pain Pract. 2014;14(1):52–6.
38. Franco CD, Buvanendran A, Petersohn JD, Menzies RD, Menzies LP. Innervation of the anterior capsule of the human knee: implications for radiofrequency ablation. Reg Anesth Pain Med. 2015;40(4):363–8.
39. Davis T, Loudermilk E, DePalma M, Hunter C, Lindley D, Patel N, et al. Prospective, multicenter, randomized, crossover clinical trial comparing the safety and effectiveness of cooled radiofrequency ablation with corticosteroid injection in the management of knee pain from osteoarthritis. Reg Anesth Pain Med. 2018;43(1):84–91.
40. Choi W-J, Hwang S-J, Song J-G, Leem JG, Kang YU, Park PH, et al. Radiofrequency treatment relieves chronic knee osteoarthritis pain: a double-blind randomized controlled trial. Pain. 2011;152(3):481–7.
41. Sidebottom AJ. TMJ pain and cryoanalgesia. J Oral Biol Craniofacial Res. 2013;3(3):123–5.
42. Herb K, Cho S, Stiles MA. Temporomandibular joint pain and dysfunction. Curr Pain Headache Rep. 2006;10(6):408–14.
43. Richardson C, Glenn S, Nurmikko T, Horgan M. Incidence of phantom phenomena including phantom limb pain 6 months after major lower limb amputation in patients with peripheral vascular disease. Clin J Pain. 2006;22(4):353–8.
44. Flor H. Phantom-limb pain: characteristics, causes, and treatment. The Lancet Neurology. 2002;1(3):182–9.
45. Nikolajsen L, Christensen KF. Phantom limb pain. Nerves Nerve Injuries. 2015;2:23–34.
46. Bellini M, Barbieri M. Cooled radiofrequency system relieves chronic knee osteoarthritis pain: the first case-series. Anaesthesiol Intensive Therapy. 2015;47(1):30–3.
47. Filippiadis D, Bolotis D, Mazioti A, Tsitskari M, Charalampopoulos G, Vrachliotis T, et al. Percutaneous imaging-guided techniques for the treatment of benign neuropathic pain. Diagn Interv Imaging. 2021;102(1):11–8.
48. Law L, Rayi A, Derian A. Cryoanalgesia. Treasure Island (FL): Statpearls Publishing; 2018.
49. Ba Y-F, Li X-D, Zhang X, Ning ZH, Zhang H, Liu YN, et al. Comparison of the analgesic effects of cryoanalgesia vs. parecoxib for lung cancer patients after lobectomy. Surg Today. 2015;45(10):1250–4.
50. Ren K, Dubner R. Descending modulation in persistent pain: an update. Pain. 2002;100(1):1–6.
51. Tao Z-Y, Wang P-X, Wei S-Q, Traub RJ, Li J-F, Cao D-Y. The role of descending pain modulation in chronic primary pain: potential application of drugs targeting serotonergic system. Neural Plast. 2019;2019:1–16.
52. Kwon M, Altin M, Duenas H, Alev L. The role of descending inhibitory pathways on chronic pain modulation and clinical implications. Pain Pract. 2014;14(7):656–67.

How to cite this article: Biel E, Aroke EN, Maye J, Zhang SJ. The applications of cryoneurolysis for acute and chronic pain management. Pain Pract. 2023;23:204–215. https://doi.org/10.1111/papr.13182