ANESTHESIOLOGY

Cryoneurolysis and Percutaneous Peripheral Nerve Stimulation to Treat Acute Pain

A Narrative Review

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ABSTRACT

Two regional analgesic modalities currently cleared by the U.S. Food and Drug Administration hold promise to provide postoperative analgesia free of many of the limitations of both opioids and local anesthetic-based techniques. *Cryoneurolysis* uses exceptionally low temperature to reversibly ablate a peripheral nerve, resulting in temporary analgesia. Where applicable, it offers a unique option given its extended duration of action measured in weeks to months after a single application. *Percutaneous peripheral nerve stimulation* involves inserting an insulated lead through a needle to lie adjacent to a peripheral nerve. Analgesia is produced by introducing electrical current with an external pulse generator. It is a unique regional analgesic in that it does not induce sensory, motor, or proprioception deficits and is cleared for up to 60 days of use. However, both modalities have limited validation when applied to acute pain, and randomized, controlled trials are required to define both benefits and risks.

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POTENT site-specific analgesia may be provided with regional anesthetics and analgesics. Unfortunately, prevalent local anesthetic-based regional techniques such as single injection and continuous peripheral nerve blocks have their own set of limitations such as inducing motor, sensory, and proprioception deficits that possibly increase the risk of falling;[1] limited duration;[2] and, for ambulatory patients with perineural catheters, the burden of carrying an infusion pump and local anesthetic reservoir.[3–5] There is new evidence that suggests two analgesic alternatives currently cleared by the U.S. Food and Drug Administration—cryoneurolysis and ultrasound-guided percutaneous peripheral nerve stimulation—hold promise to provide postoperative analgesia free of many of the major limitations of both opioid analgesics and currently prevalent regional analgesic options (table 1).

Cryoanalgesia

"Cryoanalgesia"[6]—the use of cold temperature to treat pain—is hardly a new concept: it was described by the ancient Egyptians and Hippocrates.[7] Although a French military surgeon within Napoleon's army delivered intraoperative regional anesthesia by applying ice and snow to injured limbs before amputation,[8] it was not until 1961 that the first closed cryoprobe apparatus was described.[9] Modern cryoprobes, often termed "cannulas," are essentially a tube-within-a-tube that convey a gas at a high pressure (600 to 800 psi) down their length, through a small annulus (0.002 mm), and into a low-pressure closed end before being vented back up the length of the probe (fig. 1).[10] No gas ever comes into contact with body tissues. The pressure drop at the probe tip results in a corresponding volume expansion and decrease in temperature because of the Joule–Thomson effect.[11] An ice ball forms around the end of the probe, which induces neuronal injury within the affected area.[12]

Mechanism of Action

The degree of injury and ultimate effects are primarily determined by tissue temperature.[13] Neuropraxia occurs with temperatures between +10°C to −20°C, with little or no injury to anatomic structures and highly variable neural recovery requiring minutes to a few weeks.[14] However, between −20°C to −100°C, Wallerian degeneration (axon breakdown or "axonotmesis") occurs distal to the lesion, resulting in "cryoneurolysis",[15] reliably inhibiting afferent and efferent signal transmission for multiple weeks or months as the axon regenerates.[14] Importantly, at temperatures warmer than −100°C, the endoneurium, perineurium, and epineurium remain intact,[14] allowing reliable regrowth of the axon distally from the point of treatment.[11,16] In contrast, at temperatures colder than −100°C, the endoneurium may be irreversibly injured ("neurotmesis"), inhibiting reliable axon regrowth.[14] Therefore, for cryoneurolysis, the target temperature is between −20°C and −100°C. It is for this reason that nitrous oxide or carbon dioxide are most frequently used for cryoneurolysis[9]—as opposed to "cryoablation," in which permanent tissue destruction is desired (*e.g.*, tumor ablation)[17]: these two gasses become solid below their boiling point of −88° and −78°C, respectively, and

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Table 1. Relative Attributes of Five Regional Analgesic Modalities That May Be Used to Treat Acute Pain

	Local Anesthetic-based Peripheral Nerve Blocks	Liposome Bupivacaine in Peripheral Nerve Blocks	Continuous Peripheral Nerve Blocks	Percutaneous Cryoneurolysis	Percutaneous Peripheral Nerve Stimulation
Analgesia duration (typical)	< 1 day	1–3 days	Up to 7 days	Weeks to months	Up to 60 days
Administration time	+	+	++	++ to ++++*	+++
Titratable	No	No	Yes	No	Yes
Applicable anatomic locations	++++	+†	++++	++	+++
Sensory deficits	++++	+	++	++++	0
Motor deficits	++++	+	++	+++	0
Cost (per application)	+	++	++	+	++++
Follow-up time requirements	+	+	++++	+	+++

*Total duration required for cryoneurolysis is significantly dependent upon the number of treated nerves (*e.g.*, treating eight intercostal nerves for a bilateral mastectomy requires significantly longer than a single application for a rib fracture). †At the time of this writing, the single liposome bupivacaine formulation approved for clinical use by the U.S. Food and Drug Administration is approved exclusively for only two peripheral nerve blocks (transversus abdominis plane and interscalene for shoulder surgery).

therefore inherently limit the cooling process to within a safe—and therapeutic—range.[18]

The 1 to 2 mm/day rate of axon regrowth distally from the point of treatment provides both the primary benefit and limitation of cryoneurolysis when applied to acute pain: analgesia may be provided for weeks or months with a single treatment, although the actual duration is highly variable and based in large part on the distance from the point of cryoneurolysis to the terminal nerve branches innervating the affected tissue.[16,19–21] The consequence is that cryoneurolysis is optimally applied when prolonged analgesia is required; yet an extended and somewhat unpredictable duration of hypesthesia, muscle weakness (or paralysis), and possibly decreased proprioception are acceptable.[22] There are therefore limited applications involving acute pain (table 2); however, for circumstances in which these limitations are acceptable, a peripheral nerve block using cryoneurolysis appears to be a promising analgesic technique with a unique duration of action orders of magnitude beyond current local anesthetics.[22]

Intraoperative Application to Acute Pain

The initial report of postsurgical analgesia using cryoneurolysis involved intraoperative application to surgically exposed intercostal nerves during thoracotomy.[29] Subsequently, multiple randomized, controlled trials involving thoracotomy[58] demonstrated analgesic, opioid-sparing, and pulmonary function benefits, as well as a shortened length of hospitalization and fewer opioid-related adverse effects,[19,24,30–37,39,40,43,48,58] some with superiority over other regional analgesic techniques.[24,31,32,35,48] In contrast, six randomized trials failed to identify cryoneurolysis benefits.[39–44] Similarly, for inguinal herniorrhaphy one randomized, sham-controlled trial involving intraoperative cryoneurolysis was negative,[50] whereas another reported multiple benefits including lower pain scores, lower oral analgesic requirements, and earlier resumption of normal activity.[49] Of note, a third study applying cryoneurolysis to patients with chronic postherniorrhaphy pain revealed a 90% success rate in decreasing pain levels by 75 to 100%.[59] Differences in findings may be due to differing cryoneurolysis protocols with various freeze durations, number of cycles or treated nerves, extent of nerve manipulation, drain placement or surgical pain outside the distributions of treated nerves, inadequately powered sample sizes,[41] differing outcome measures, and numerous other factors.[58,60,61] Regardless, additional study is certainly warranted to clarify the potential benefits and risks, as well as the optimal application technique, when treating post-thoracotomy and herniorrhaphy pain.

Imaging

The development of percutaneously inserted cryoprobes greatly increased possible analgesic applications because surgical exposure of the target nerve was no longer required.[6] Anatomic landmarks (blind)[62] and/or nerve stimulation initially guided probe insertion,[6,63] but these techniques were eventually supplemented/replaced with biplane X-rays,[64,65] fluoroscopy,[66,67] computed tomography,[67–72] magnetic resonance imaging,[73–75] and ultrasound.[76,77] Imaging not only improves nerve targeting,[78] but—most importantly—enables real-time evaluation of the ice ball's envelopment of the target nerve.[79,80] Ultrasound-guided percutaneous cryoneurolysis can now be provided on an outpatient basis without sedation, resulting in a plethora of reports involving the treatment of chronic pain.[17,71,72,81–89] The technique is nearly identical to placing a single-injection peripheral nerve block, only instead of injecting local anesthetic through a hollow-bore needle to envelope the target nerve, the probe is inserted adjacent to the nerve and activated with an ice ball forming at the tip that envelopes the target.[11] Because thin, difficult-to-image fascial layers between the probe and epineurium—that would inhibit local anesthetic spread—are irrelevant with cryoneurolysis, it appears easier to administer than local anesthetic-based peripheral

Fig. 1. A modern cryoneurolysis probe ("cannula") produces extremely cold temperatures at its tip due to the Joule–Thomson effect resulting from gas flowing from a high- to low-pressure chamber (*top panel*). Examples of handheld (*left panel*; Iovera Focused Cold Therapy, Myoscience, USA, with *inset* of optional trident probe) and portable console (*right panel*; PainBlocker, Epimed International, USA) cryoneurolytic devices. Used with permission from Brian M. Ilfeld, M.D., M.S.

Table 2. Reported Cryoneurolysis Applications to Acute Pain Management Administered Either Percutaneously or *via* the Surgical Incision

	Case Reports and Series	Retrospective, Controlled Studies		Randomized, Controlled Trials	
		Positive	Negative	Positive	Negative
Head and neck					
Tonsillectomy				Robinson *et al.* (n = 59)[23]	
Trunk					
Mini-thoracotomy				Bucerius *et al.* (n = 57)[24]	
Thoracotomy	Johannesen *et al.* (n = 22)[25]	Glynn *et al.* (n = 58)[28]		Brichon *et al.* (n = 120)[30]	Gwak *et al.* (n = 50)[39]
	Maiwand *et al.* (n = 100)[26]	Nelson *et al.* (n = 76)[29]		Joucken *et al.* (n = 96)[31]	Ju *et al.* (n = 107)[40]
	Maiwand *et al.* (n = 600)[27]			Katz *et al.* (n = 24)[32]	Miguel *et al.* (n = 45)[41]
				Momenzadeh *et al.* (n = 60)[33]	Müller *et al.* (n = 63)[42]
				Moorjani *et al.* (n = 200)[19]	Mustola *et al.* (n = 42)[43]
				Pastor *et al.* (n = 100)[34]	Roxburgh *et al.* (n = 53)[44]
				Roberts *et al.* (n = 144)[35]	
				Rooney *et al.* (n = 75)[36]	
				Sepsas *et al.* (n = 50)[37]	
				Yang *et al.* (n = 90)[38]	
Pectus excavatum repair		Graves *et al.* (n = 25)[45]		Graves *et al.* (n = 20)[48]	
		Harbaugh *et al.* (n = 32)[46]			
		Keller *et al.* (n = 52)[47]			
Herniorrhaphy				Wood *et al.* (n = 30)[49]	Callesen *et al.* (n = 15)[50]
Percutaneous nephrolithotomy	Gabriel *et al.* (n = 1)[51]				
Rib fracture(s)	Finneran *et al.* (n = 5)[52]				
	Vossler and Zhao (n = 1)[53]				
Iliac crest grafting	Gabriel *et al.* (n = 1)[51]				
Mastectomy		Gabriel *et al.* (n = 6)[54*]			
Extremities					
Amputation	Gabriel *et al.* (n = 3)[51]				
Burns	Gabriel *et al.* (n = 1)[51]				
	Finneran *et al.* (n = 3)[55]				
Skin graft harvesting	Finneran *et al.* (n = 2)[55]				
Knee arthroplasty	Ilfeld *et al.* (n = 3)[56]	Dasa *et al.* (n = 100)[57]			
Rotator cuff repair	Ilfeld *et al.* (n = 2)[56]				

*This retrospective study reported a dramatic difference between the treatment (cryoneurolysis) and control groups, but due to a very small sample size (n = 6), statistics were not applied to the data.

nerve blocks.[22] Although application of percutaneous cryoneurolysis to acute pain has been lacking, recently published cases suggest a possible renaissance.[10]

Percutaneous Application to Acute Pain

Treatment of intercostal nerves provides analgesia of the trunk for procedures or injuries that produce moderate-to-severe pain of an extended duration measured in at least weeks, if not months. For example, providing potent, site-specific analgesia after percutaneous nephrolithotomy can permit hospital discharge.[51] Repeated debridement of burns frequently requires potent analgesia, and effective pain control was reported using percutaneous cryoneurolysis after a scalding injury from boiling water in the dorsal and plantar aspects of the first to third toes.[51] Severe pain from traumatic rib fractures often decreases patients' ability to breathe deeply and cough efficiently, greatly increasing their risk of pneumonia that is, in itself, a cause of mortality among the elderly.[90] Local anesthetic-based intercostal nerve blocks and epidural infusions provide potent analgesia, improve peak expiratory flow rates, and improve arterial oxygen saturation on room air but have duration of actions measured in hours or days and not the weeks or months required for fracture healing.[91] Case reports suggest that cryoneurolysis of solely the involved intercostal nerves may provide potent analgesia, thus avoiding the need for hospitalization, obviating opioid requirements, improving breathing/coughing, and therefore decreasing the risk of pulmonary comorbidity.[52,53] Three patients who received cryoneurolysis of the second to fifth intercostal nerves before uni- or bilateral mastectomy reported a near-painless postoperative course without any opioid requirements or sleep disturbances, a significant improvement over historic controls.[54]

Ultrasound-guided percutaneous cryoneurolysis may also be used in the extremities, such as to provide analgesia

after limb or digit amputation of either the upper or lower extremity.[92] If there is any risk of a canceled case, it is recommended to administer local anesthetic-based nerve blocks preoperatively and the cryoneurolysis only after the amputation. Similarly, cryoneurolysis may provide palliative analgesia during end-of-life care,[22] or pain control during weeks of postburn debridement and redressing of an extremity.[51,55] Relatedly, split-thickness skin grafts are frequently harvested from the lateral thigh, and cryoneurolysis of the lateral femoral cutaneous nerve has been used to provide multiple weeks of potent analgesia.[55]

Pain after knee arthroplasty is notoriously challenging to treat and frequently lasts multiple weeks or even months,[93] and consequently may be a suitable procedure for cryoneurolysis.[94] However, application to the femoral nerve at the inguinal ligament or even more distally within the adductor canal has a high probability of inducing quadriceps weakness.[95] Therefore, investigators have targeted exclusively sensory nerves surrounding the knee, including the anterior femoral cutaneous and infrapatellar branch of the saphenous nerve.[56,57,96] A retrospective cohort study reported that treatment of these nerves 1 week before total knee arthroplasty resulted in a lower proportion of patients remaining hospitalized for more than 1 day (67% *vs.* 6%; $P < 0.001$), 45% less opioid consumption during the first 12 postoperative weeks ($P < 0.001$), and less pain interference with daily living activities at both 6 and 12 weeks ($P < 0.001$ for both).[97] Unfortunately, no randomized trial involving the use of perioperative cryoneurolysis for knee arthroplasty has been reported in the peer-reviewed literature. However, one randomized, double-masked, sham-controlled study involving nonsurgical chronic osteoarthritis knee pain demonstrated significant improvement in functioning 30, 60, and 90 days after cryoneurolysis compared with a sham procedure.[98]

Similarly, total shoulder arthroplasty and other major shoulder procedures can result in a prolonged period of pain of multiple weeks. The suprascapular nerve innervates approximately 65% of the shoulder joint and has been targeted for cryoneurolysis to provide analgesia after rotator cuff repair.[56] The suprascapular nerve contains both sensory and motor fibers, and weakening or paralyzing the supraspinatus and infraspinatus muscles for potentially multiple months may compromise rehabilitation of the shoulder joint. Cryoneurolysis has been applied clinically to mixed sensory-motor nerves for decades without any reported clinically detectable muscle weakness after nerve regeneration.[11] However, various investigators have suggested the possibility of subclinical residual and persistent motor weakness caused by either incomplete regeneration or motor unit clustering.[99] There are preclinical data from laboratory animals suggesting decreased nerve conduction velocities 90 days after cryoneurolysis of intercostal nerves, but all physiologic and behavioral measures fully returned to normal by that time point (subsequent time points were not evaluated).[100] Importantly, treatment with 10% procaine HCl to intercostal nerves within the same animal study resulted in similar deficit and recovery patterns.[100] In contrast, three preclinical studies designed specifically to address this issue revealed no long-term changes to the structure or function of mixed nerves and their motor targets after tibial or common peroneal nerve cryoneurolysis and subsequent axonal regeneration and remyelination[99,101,102]—even with repeated applications.[101]

Administration Protocol

As noted previously, the clinical findings of randomized, controlled trials are somewhat mixed.[58] This is probably due at least in large part to the myriad of freezing protocols used by investigators. Considering cryoanalgesia has been cleared by the U.S. Food and Drug Administration for over a half century, there are surprisingly little clinical data regarding optimizing its administration. In most cases, ultrasound-guided percutaneous cryoneurolysis may be performed in unsedated patients by first applying cutaneous local anesthetic to the probe entry point, the anticipated probe trajectory, and—frequently—a couple of milliliters perineurally (without local anesthetic, stinging may be initially experienced that dissipates after 15 to 30 s).[11] The onset profile and maximum blockade intensity remain undefined, partially because local anesthetic is usually deposited immediately before the cryoneurolysis procedure and thus covers the latter's onset profile. The ultimate effectiveness and duration of action of the treatment are dependent upon a number of factors, but the two most influential are the amount of axon disruption (injury) and the distance of the cryolesion from the terminal nerve branches, respectively.[103] Thus, the longer the duration of action desired, the more proximal the cryolesion should be administered.

The amount of axon disruption is determined by a number of factors, the most important of which is the tissue temperature. However, if an adequate lesion is induced between −20°C and −100°C, the duration of analgesia is independent of both the duration of freezing and application of repeated freezing cycles.[103] Nevertheless, these two factors can enable the administration of an "adequate lesion," which involves all of the nerve axons for a minimum critical length because myelinated fibers can still conduct through small inactive segments of axons.[104] Because the minimum critical length has yet to be defined in humans (it is 4 mm in cats),[104] maximizing lesion length is prioritized. This is not difficult for a surgically exposed nerve because repeated serial applications may be applied adjacent and overlapping each other.[29] However, for percutaneous cryoneurolysis the ice ball diameter is increased with a longer duration of application as the cold overcomes warmer tissue until a terminal size is reached when the ice itself becomes an insulation layer between the cold probe and unaffected tissue at the ice ball's periphery. Once the ice ball reaches maximum diameter, little is gained by extending the freeze

duration further when using nitrous oxide or carbon dioxide.[105] For temperatures colder than approximately −50°C, a single application is adequate for the axons enveloped in the ice ball.[105] However, the volume of the ice ball may be increased by letting the tissue thaw and then repeating the freeze–thaw cycle.[106] With each successive freeze–thaw cycle, the ice ball diameter increases until a new maximum effect is realized, thereby maximizing the cryolesion length.[106]

The optimal freeze and thaw durations, as well as the number of freeze–thaw cycles, have yet to be determined.[11] However, common percutaneous techniques involve a freeze of 30 to 120 s followed by a thaw of 30 to 60 s, frequently repeated 1 or 2 times. Regardless of the number of cycles administered, it is imperative that after each freeze the probe remain fixed until ice ball resolution to avoid tearing of involved tissues.[11]

A completely novel cryoneurolysis administration technique involves the use of ice slurry infiltrated around a nerve, administered in a similar manner to a single-injection local anesthetic-based peripheral nerve block.[107] However, this technique has only recently been reported in a laboratory rat model, and efficacy and safety in humans remains unknown.

Equipment

Nearly all cryoneurolysis machines approved by the U.S. Food and Drug Administration are portable console devices most easily used and transported using a dedicated cart containing the gas supply in a standard e-cylinder (fig. 1). However, there is a recently developed handheld option that uses miniature nitrous oxide cartridges.[108] Unique features of this device are its portability (fits in a lab coat pocket), disposable probes and gas cartridges, battery rechargeability, and two unique trident probes with integrated heaters that protect the skin when treating superficial nerves.[108] Potential drawbacks include relatively flexible probes that can be challenging to use for deep targets, the requirement of holding the probe at a maximum angle of 45° relative to the floor that limits approaches during treatment, a maximum probe length of 9 cm, and a smaller diameter ice ball relative to console-based devices.[108] In contrast, the console devices utilize reusable probes that require sterilization between uses but are somewhat easier to maneuver because of their relative stiffness, are available longer than 9 cm, may be used at any angle relative to the floor, have probes that are easier to visualize with ultrasound (because of large gauge and rigidity), and frequently produce a larger ice ball.[11]

Probes are available with and without nerve stimulation capabilities, as well as hemispherical/blunt tips designed to minimize nerve/tissue trauma, and trocar ends for easy advancement through tissue. In general, even probes with trocar tips require a sharper introducer such as an intravenous angiocatheter to enable passage through the skin and muscle to the target nerve; so, it is unclear how beneficial hemispherical/blunt tips are in practice.[54–56,92] Ice balls are easiest to visualize with high-frequency linear transducers, but power Doppler may improve imaging with low-frequency linear-array transducers used for deeper structures.[109] Because of the hyperechoic border of the ice ball resulting from the higher acoustic impedance at the border between frozen and unfrozen tissues,[110–112] acoustic shadowing can limit visualization when the nerve is deeper than the ice ball.[84,113,114] After a freeze–thaw cycle, there are no ultrasonographic differences between treated and untreated tissue.[84] Consequently, a post-treatment "check" of the cryolesion is not currently feasible, and evaluation of the extent of nerve involvement must be made by direct visualization of the ice ball during treatment and physical exam after the procedure.

The relative costs for handheld *versus* console devices vary greatly. Although a console machine and reusable cannulas may require over $20,000 for the initial investment, the per-patient costs are negligible with only nitrous oxide required from a standard e-cylinder and any autoclave costs for sterilization. In contrast, the initial investment for a handheld device is usually a fraction of that for a console device (~$5,000), but the disposable cannulas (~$300 each) can quickly drive the total costs higher depending on the number of subjects treated. Therefore, the anticipated treatment volume often helps to direct operators toward one of these two machine designs, in addition to the many factors discussed previously.

Contraindications and Complications

Relative contraindications to percutaneous cryoneurolysis are similar to any percutaneous treatment with a needle, such as local or systemic infection, anticoagulation, bleeding diathesis, and immunosupression.[11] Specific contraindications to cryoneurolysis include cold urticaria,[115,116] Raynaud's disease,[117] cryofibrinogenemia,[118] cryoglobulinemia,[119] and paroxysmal cold hemoglobinuria.[22] Laboratory studies have demonstrated impaired nerve regeneration in diabetic animals,[120] and diabetes in patients can lead to impaired regeneration of axons and recovery after investigational nerve injury,[121] as well as focal neuropathies such as ulnar neuropathy and carpal tunnel syndrome.[122] Whether these findings are applicable to cryoneurolysis in patients with diabetes remains unknown.

There are few large studies on which to base estimates of complication rates, but overall, the literature is overwhelmingly positive.[11,79] Nonspecific risks include pain during and after the procedure, as well as superficial bleeding and bruising.[11] Because of a continuous flow of warm blood, large blood vessels are not at risk from ice ball involvement. For example, application of temperatures of nearly −200°C applied for up to 10 min did not result in vessel rupture, coagulation, or thrombosis.[123] For percutaneous cryoneurolysis, one suspected deep infection has been reported that eventually led to myonecrosis.[124] Transient or permanent

alopecia or changes in pigmentation may occur if the ice ball involves the skin.[125] For superficial areas, injecting a tumescent layer of local anesthetic or saline below the dermis can push the nerve deeper and increase the margin of safety.[55] Additionally, trident probes specifically designed for treating subdermal nerves are available with heated elements to protect the dermis and epidermis ("trident" probe, fig. 1).[108]

Of importance, various investigators have suspected a possible increase in longer-term neuropathic-like pain in patients who had intraoperative cryoneurolysis under direct vision,[25,42,44,50,60] although the limitations of these observations have been noted.[126] Indeed, two subsequent randomized, controlled trials did find a clinically relevant and statistically significant increased incidence of neuropathic pain 3 to 6 months after open thoracotomy with surgically applied cryoneurolysis.[40,43] However, the majority of randomized, controlled trials have not reported similar findings, and this discrepancy remains unresolved.[61] It is worth noting that preclinical studies clearly demonstrate hyperalgesia after an *incomplete* freeze lesion—but only hypoalgesia during the period of regeneration with complete nerve thickness involvement.[127] Additional preclinical investigations found that substantial nerve manipulation before cryoneurolysis was required to induce chronic pain conditions (personal written communication, Rochelle Wagner, Ph.D., June 29, 2017),[15] an observation possibly related to the "double-crush" theory first proposed by Upton and McComas.[128] In other words, when investigators sought to *intentionally* induce chronic pain in rodents, they succeeded exclusively when the target nerve was physically manipulated before treatment with cryoneurolysis. Although the precise etiology has yet to be elucidated, it is hypothesized that the physical manipulation produces an afferent barrage that sets up the central sensitization such that when axonal regeneration occurs after injury, the fiber activity is perceived as dysesthetic.[129]

These preclinical findings may help explain the inconsistent findings from the various clinical investigations in which a few detected an increased incidence of postoperative neuropathic pain, whereas the rest failed to do so.[49,50,58] The technique of exposing the target nerves intraoperatively before applying cryoneurolysis under direct vision varies dramatically among surgeons, from leaving the nerve *in situ* to having the nerve physically "separated from the adjacent intercostal artery and vein, supported with a lifting ligature, and then frozen with a cryosurgery probe" (see illustration, Nelson *et al.* 1974, page 281).[29] Significantly, the investigators with one of the highest incidences of postoperative neuralgias—20% identified 6 to 10 weeks after thoracotomy—clearly describe their technique in which each intercostal nerve was "***exposed*** paravertebrally, ***lifted*** with a nerve hook, and frozen at ***two close sites*** [emphasis added]…", suggesting both manipulation and double-crush.[42] Unfortunately, it is impossible to correlate technique and outcome because the majority of studies do not adequately describe the precise technique or degree of nerve involvement. However, when viewed in light of the preclinical data, it appears somewhat unsurprising that some healthcare providers report a high incidence of neuralgias in their practice (highest 38%),[60] whereas others do not (largest neuralgia-free series: 0% in over 1,500 patients).[126]

If intraoperative nerve manipulation is the cause of a possible increased incidence of neuropathic pain, then ultrasound-guided percutaneous cryoneurolysis should have no comparable risk. Indeed, to date, no incidence of neuropathic pain has been correlated with percutaneous administration.[79] Caution is still warranted because the number of percutaneous administrations is far fewer than for intraoperative application. Furthermore, replacing open-intraoperative with percutaneous-preoperative application can dramatically reduce operating room time by replacing serial with parallel case processing.[130] For example, although intraoperative cryoneurolysis decreased length of hospital stay after pectus excavatum repair—from 5 days to 3 days compared with epidural infusion—an additional 69 min of operative time, on average, was added for each case ($P < 0.001$)—an amount probably not viable or tolerated at many hospitals within the United States.[48]

Although direct comparisons with other postoperative techniques such as perineural local anesthetic infusion are unavailable, theoretical benefits of cryoneurolysis include an ultra-long duration of action; a lower risk of infection; no infusion pump and anesthetic reservoir carrying burden; no risk of local anesthetic toxicity, catheter dislodgement, or leakage; and no infusion management or catheter removal.[4,5] Radiofrequency ablation is a possible alternative long-acting modality,[131] although little data involving postoperative pain is currently available.[132–135] Unlike cryoneurolysis, traditional radiofrequency ablation may induce significant procedure pain requiring sedation,[136] may injure surrounding tissues and structures,[137] and is associated with neuroma formation.[136] Data for pulsed and cooled radiofrequency ablation to treat acute pain are not currently available.

Conclusions

Because of its prolonged duration of action measured in weeks to months, cryoneurolysis is an appropriate analgesic for a relatively small subset of surgical procedures (table 2). However, where applicable, it offers a unique option in treating acute pain conditions given its few contraindications, low risk profile, minimal per-patient cost, low patient burden (no infusion pump/catheter), and extended period of action far surpassing any local anesthetic-based peripheral nerve block (fig. 2). This decades-old—yet rarely utilized—analgesic modality might prove timely considering a temporal confluence of factors, including an understanding of the relationship of postsurgical opioid prescription to the opioid crisis; prevalence of advanced ultrasound capabilities among anesthesiologists; ubiquity of ultrasound equipment throughout healthcare systems; and growing appreciation of poorly controlled postoperative pain evolution into a

persistent, chronic condition. Multiple questions remain regarding ultrasound-guided percutaneous cryoneurolysis for the treatment of acute pain, not the least of which is determining whether the duration of action can be controlled by manipulating the administration protocol. Additional applications such as providing analgesia after iliac crest bone grafting, as well as various breast, intrathoracic and abdominal surgical procedures remain to be investigated. Data from randomized, controlled clinical trials are needed to conclusively demonstrate treatment benefits and better determine the incidence of adverse events.

Neuromodulation

Electrical "neuromodulation" is the use of electrical current to modify nerve activity.[138] This is scarcely a novel idea, having been described by the ancient Romans who treated various maladies such as headaches by delivering up to 220 volts using living torpedo fish.[139] The technique continued to be used into the 18th century with the development of multiple devices generating electrical current.[139] The early 1900s saw the first device specifically designed to use electricity to treat pain (among countless other ailments), the "Electreat."[140] However, electrical neuromodulation fell out of favor after the 1910 Flexner Report, which noted a lack of supporting scientific evidence and recommended the exclusion of electrotherapy in clinical practice.[141] It was not until 1967 that Sweet and Wall[142] used electrical stimulation to successfully treat pain emanating from a peripheral nerve and Shealy *et al.*[143] described the first application to the spinal cord.

Mechanism of Action

Numerous theories exist as to the exact mechanism of action,[144,145] but most commonly described is Melzack and Wall's "gate control theory."[146] This proposes that stimulation of large-diameter afferent nerve fibers close a "gate" that connects peripheral nerves and the spinal cord, thus interrupting the transmission of pain signals to the central nervous system.[146,147] Wall and Sweet[142] subsequently postulated delivering analgesia by stimulating primary afferent neurons, which was soon followed by commercially available pulse generators (stimulators) that were used—frequently off-label—to deliver peripheral nerve stimulation.[148] Unfortunately, these devices nearly always required multiple electrodes located immediately adjacent to the target peripheral nerve, thus requiring surgical implantation.[149] Moreover, lead removal frequently required additional surgery, often complicated by fibrous capsule formation adherent to the target nerve.[150] The invasive and time-consuming nature of surgical implantation and removal resulted in neuromodulation being used overwhelmingly for the treatment of chronic, *versus* acute, pain—and often as a last resort.[151–154]

The relatively rare application to postoperative pain occurred primarily with electrodes applied directly to the skin in the area of incision (transcutaneous electrical nerve stimulation).[155,156] Although demonstrated to be superior to placebo controls for various surgical procedures,[157–161] activation of pain fibers in the skin limits the tolerated current resulting in an analgesic "ceiling."[162] To increase current delivered to specific large—and frequently deeper—target nerves for acute pain relief, the current needs to theoretically bypass the skin without requiring an open surgical incision.[162] Beginning in 1978,[163] extremely small leads were developed that enable transcutaneous insertion *via* a needle (at times termed "injectable" leads).[162,164–175] Paired with ultrasound guidance, any peripheral nerve may now be targeted with a similar technique to that used for perineural catheter insertion.[5,176,177] Ultrasound-guided percutaneous peripheral nerve stimulation was first reported *in situ* by Huntoon and Burgher in 2009[178] using an epidural neurostimulation electrode for the treatment of neuropathic pain. Although multiple different lead designs and percutaneous approaches were reported subsequently, they were used nearly exclusively for chronic pain conditions.[170,179–201]

Application to Acute Pain

Recently, the U.S. Food and Drug Administration cleared the first percutaneous peripheral nerve stimulation lead and pulse generator system for use treating acute pain (fig. 3).[138] Because at the time of this writing this is the only system cleared to treat acute pain, much of the following section will involve this specific device (table 3), although the principles may be applicable to future lead and pulse generator designs. The leads consist of a 0.2-mm-diameter, seven-strand stainless steel wire core insulated with a fluoropolymer and wound into an open helical coil (0.6-mm diameter) with the distal tip forming an anchor (fig. 3). Unlike polyamide perineural catheters used for continuous peripheral nerve blocks, the leads are so flexible that they cannot be advanced/inserted themselves and are therefore preloaded into a 20-gauge introducer.[202] The introducer may be guided toward a target using real-time ultrasound visualization with the same in- or out-of-plane techniques frequently utilized for perineural catheter insertion.[203] When the introducer is withdrawn, the lead remains in place because of the small "anchor" at its terminal end. The pulse generators have a mass (30 g) and footprint (6.2 × 3.7 × 1.4 cm) small enough to allow the unit to be adhered directly to the patient. Replaceable/rechargeable batteries permit prolonged application, with a Food and Drug Administration–defined maximum of 60 indwelling days.[10] The 2-month duration offers the possibility of a perioperative analgesic modality that for most patients should significantly outlast the surgical pain being treated while also offering an option for patients whose pain has become chronic, lasting past the time of normal tissue healing.[138]

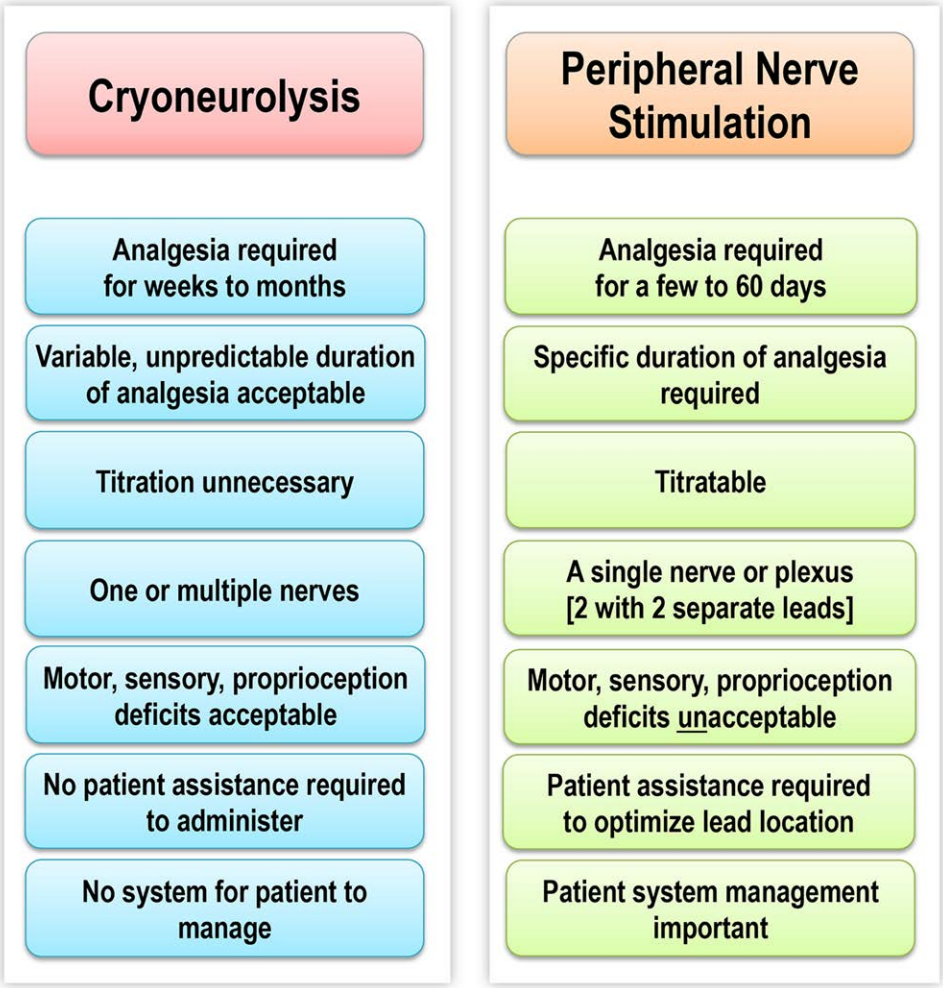

Fig. 2. Attribute comparison for two analgesic modalities: cryoneurolysis (*left panel*) and peripheral nerve stimulation (*right panel*).

The initial report involving acute pain examined five patients who experienced pain insufficiently treated with oral analgesics 6 to 58 days after total knee arthroplasty.[204] Percutaneous leads were inserted using ultrasound guidance 0.5 to 3.0 cm from the femoral and sciatic nerves. Pain at rest decreased from a mean of 5.0 to 0.2 on the Numeric Rating Scale almost immediately after electrical current was introduced, with four of five subjects having a complete resolution of pain. Pain during passive and active knee motion decreased approximately 30%, although maximum flexion was increased by only a few degrees. The leads were removed later that day. A second short series of patients (n = 5) published subsequently reported similar, although somewhat less dramatic, results.[205]

This research led to the first preoperative application of ultrasound-guided percutaneous peripheral nerve stimulation: seven subjects had both femoral (inguinal) and sciatic (subgluteal) leads inserted using ultrasound guidance up to 7 days before undergoing tricompartment knee arthroplasty.[206] In the preoperative holding area, subjects had a single-injection adductor canal block administered with ropivacaine 0.5% and epinephrine. Within 20 h after surgical stop, each lead was connected to a pulse generator, which delivered current for a median [interquartile range] of 38 [32 to 42] days, interrupted only for bathing and battery replacement. Six of seven subjects (86%) reported mild pain (Numeric Rating Scale < 4) both at rest and during ambulation through the first 4 postoperative weeks. One subject required no opioids, and four (57%) had discontinued opioid use within the first week. This pilot study lacked a control group, so the clinical significance of the magnitude of effects (if any) remains unknown. However, the series demonstrated the feasibility of postoperative stimulation for multiple weeks at home, and the results used to design and power subsequent ongoing randomized, controlled trials involving knee arthroplasty (NCT03286543 and NCT04341948).

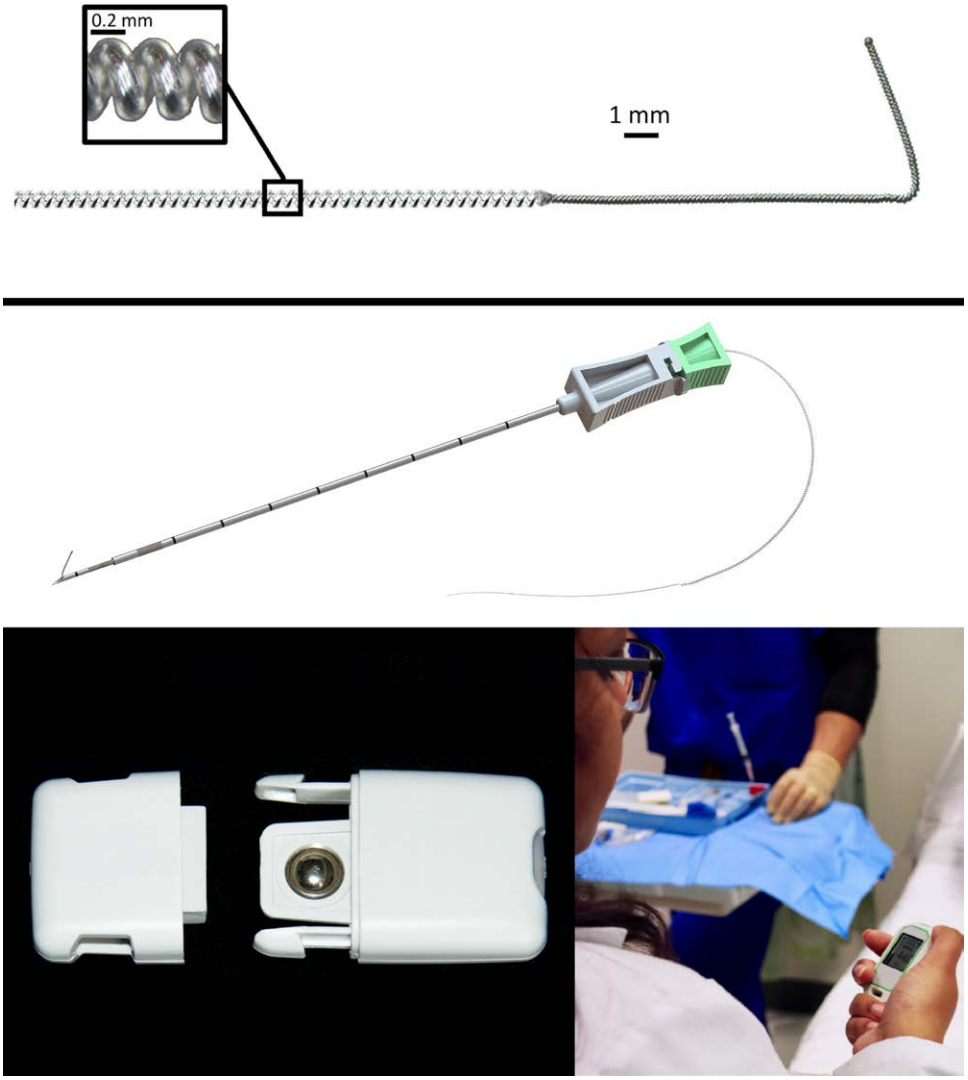

Fig. 3. A percutaneous peripheral nerve stimulation system approved by the U.S. Food and Drug Administration to treat acute pain (OnePass, SPR Therapeutics, USA). The insulated lead (MicroLead, SPR Therapeutics) is 0.2 mm in diameter wrapped into a helical coil 0.6 mm in diameter (*top panel*), which is percutaneously inserted using a preloaded introducer (*middle panel*). The rechargeable battery snaps into the pulse generator (SPRINT peripheral nerve stimulation system, SPR Therapeutics) and is controlled with a handheld remote control (*bottom panels*). Used with permission from Brian M. Ilfeld, M.D., M.S.

Three additional feasibility studies involved ambulatory procedures with a single lead inserted for each subject 1 to 7 days before surgery (table 3).[207–209] For hallux valgus osteotomy (bunion removal; n = 7) and anterior cruciate ligament reconstruction (n = 10), leads were inserted adjacent to the sciatic and femoral nerves, respectively.[207,208] For rotator cuff repair, the suprascapular nerve was targeted in the first two subjects, followed by the brachial plexus roots or trunks for the remainder (n = 14).[202] Preoperatively, all subjects had perineural catheters inserted using normal saline to be used only as a rescue analgesic. All subjects received a general anesthetic and had a pulse generator attached to their lead and activated within the recovery room. Two-thirds of subjects required perineural local anesthetic rescue even with maximum-tolerated stimulation, usually within the recovery room.[207–209] This is in contrast with the previously published series of patients with persistent pain multiple weeks or months after knee arthroplasty in whom dramatic analgesia was perceived within seconds of introducing electrical current *via* a femoral lead.[204,205] However, for the feasibility study subjects, nearly all experienced relatively little pain and extraordinarily low opioid requirements compared with historic controls in the 2 to 4 postoperative weeks. Subsequent

Table 3. Reported Percutaneous Peripheral Nerve Stimulation Applications for Acute Pain Management within the Peer-reviewed Literature (Exclusively Feasibility Studies)

	Surgical Procedure	Anatomic Lead Location(s)	Subjects	Treatment Duration	Primary Findings
Ilfeld *et al.*[204]	Total knee arthroplasty	Femoral and/or sciatic	5	< 1 day	Four subjects had complete resolution of pain immediately after stimulation begun
Ilfeld *et al.*[205]	Total knee arthroplasty	Femoral and/or sciatic	5	< 1 day	Four subjects had pain decrease by at least 50% immediately after stimulation begun
Ilfeld *et al.*[206]	Total knee arthroplasty	Femoral and sciatic	7	5–6 weeks	Six subjects had Numeric Rating Scale < 4 across first 2 weeks and 4 subjects ceased opioid use within 1st week
Ilfeld *et al.*[207]	Anterior cruciate ligament reconstruction	Femoral	10	2–4 weeks	Local anesthetic nerve block frequently required in the recovery room, but moderately low pain scores and opioid requirements subsequently
Ilfeld *et al.*[208]	Bunion removal	Sciatic	7	2–4 weeks	Local anesthetic nerve block frequently required in the recovery room, but very low pain scores and opioid requirements subsequently
Ilfeld *et al.*[209]	Rotator cuff repair	Suprascapular	2	2–4 weeks	Suprascapular leads did not appear to provide any reduction in pain or opioid requirements
		Brachial plexus roots or trunks	14		Local anesthetic nerve block frequently required in the recovery room, but very low pain scores and opioid requirements subsequently

experience (NCT03481725) suggests that a single-injection ropivacaine peripheral nerve block administered immediately preoperatively (but after lead insertion) results in a very smooth transition from the often-severe pain experienced in the recovery room to the more-moderate levels that follow, the latter which percutaneous peripheral nerve stimulation appears to treat adequately. The feasibility studies informed all aspects of perioperative percutaneous peripheral nerve stimulation technique and equipment design, beginning with lead insertion.

Lead Insertion

Although ultrasound visualization is used to guide the insertion device toward the target nerve, the ultimate location is determined by the patient reporting sensory changes—often described as a "pleasant massage"—in the general anatomic location of the planned surgery (*e.g.*, the foot for hallux valgus osteotomy) without discomfort or muscle contractions. In the first iteration of the peripheral nerve stimulation device, if an undesirable sensory or motor effect was elicited and remained unresolved with further needle advancement, an entirely new preloaded lead-needle combination was required because lead deployment occurred with needle withdrawal due to the lead's distal "anchor" (fig. 3). This resulted in a majority of participants requiring two to four lead-needle combinations and insertion times well over 15 min in most cases. These issues were resolved with a second-generation system that allows needle withdrawal and redirection/reinsertion without lead deployment, dramatically decreasing the required time and units and enabling insertion the day of surgery (fig. 3).[209] Because patients' descriptions of sensory changes help guide the final lead position, avoiding sedation is paramount: local anesthetic in a skin wheal at the needle entry point and 2 to 3 cm along the planned trajectory are nearly always adequate (although exceptions occur for brachial plexus leads because of the sensitivity of the neck muscles and fascia).[207–209]

The optimal distance from the lead tip to epineurium of the target nerve was consistently 1.0 to 1.5 cm (in contrast to 0 to 2 mm for conventional leads).[178] A relatively remote distance theoretically promotes selective stimulation of the desired larger-diameter myelinated sensory neurons without activating motor or smaller-diameter sensory neurons that induce muscle contraction and discomfort, respectively (fig. 4).[210] In addition, leads placed at this distance from the nerve are less sensitive to small changes in positioning caused by movement—critical to avoid unpleasant sensations with purposeful muscle contraction. For sciatic leads, optimal tip location was nearly uniformly posteriomedial to the nerve.[208] Three of five subjects (60%) with a lead inserted in the popliteal fossa just proximal to the sciatic bifurcation experienced cramping in their foot with stimulation, whereas of more than 50 percutaneous sciatic leads inserted at or proximal to the subgluteal region for that and previous investigations, none had induced foot cramps.[204–206,208] Whether this represents a spurious finding remains unknown, but considering that the relative intraneural fascicular orientation greatly impacts the functional results of stimulation,[211] the fascicular organization in the subgluteal location may be preferred to the popliteal region when the stimulation of sensory fibers is desired over motor and mixed fascicles.[212] For femoral leads, the optimal tip location was nearly uniformly immediately superficial to the fascia iliaca just medial to the nerve midpoint.[207] Although this location was frequently less than 1 cm from the epineurium, the increased impedance of the iliac fascia relative to muscle probably allowed for the decreased lead-nerve distance. Leads inserted deep to this fascia usually induced quadriceps femoris contractions.

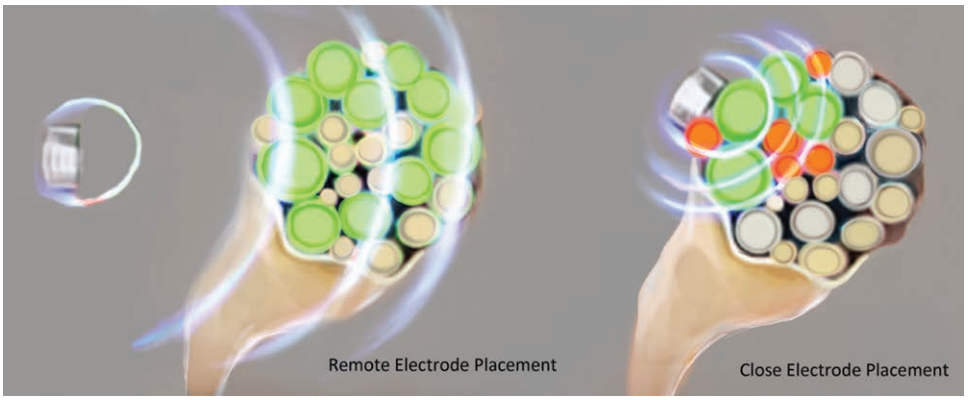

Fig. 4. The therapeutic window and the ability to preferentially activate the targeted large-diameter afferent fibers across the nerve's diameter—without activating pain or motor neurons—increase as the distance between the electrode and the nerve increases. Used with permission from Brian M. Ilfeld, M.D., M.S.

Unlike in the lower extremity, an optimal anatomic lead location for shoulder surgery could not be determined.[209] The leads of the first two subjects of the feasibility study were inserted adjacent to the suprascapular nerve in the suprascapular notch based on a published case used for the management of malignant neuropathic shoulder pain.[213] Unfortunately, these two subjects did not appear to gain any benefit from stimulation, although whether this was due to an inadequate implantation technique or other reason remains unknown.[209] The remaining participants received leads inserted through the middle scalene muscle with a trajectory nearly identical to an in-plane technique for interscalene perineural catheter insertion.[214,215] Those inserted just posterior to the superior trunk tended to result in cutaneous discomfort, whereas those placed adjacent to the C5 root frequently induced muscle contractions.[209] Although positioning the lead tip immediately posterior to the middle trunk did not always avoid triggering cutaneous fibers or motor nerves, it appears to be the location that is successful most often.

The pulse generator itself is attached to the skin with an adhesive mounting pad and should be located over clean, healthy skin on the ipsilateral side of the body to avoid the introduction of electrical current into the chest that may cause cardiac arrhythmias.

Stimulation Parameters

As described previously, within the first postoperative week there is a delay of approximately 1 h from the initiation of stimulation until maximum analgesia.[207–209] Therefore, continuous application of current is recommended (duty cycle = 100%) as opposed to activating the stimulator only when pain is experienced. At the time of this writing, the only Food and Drug Administration–cleared pulse generator for the treatment of acute pain (fig. 3; SPRINT peripheral nerve stimulation system, SPR Therapeutics, USA) provides a frequency of 12 to 100 Hz (higher usually optimal); an amplitude of 0.2 to 30 mA (higher usually optimal); and a pulse duration of 10 to 200 μs (lower usually optimal). Although the frequency is fixed after the initial programming, the amplitude and pulse duration may be adjusted by the patient within a provider-defined range with a small Bluetooth-connected remote control (fig. 3). This patient control is essential: although maximizing current theoretically maximizes analgesia, at some point before reaching the pulse generator's highest-possible current, uncomfortable sensations and/or muscle contractions will usually be induced. Consequently, optimizing analgesia requires setting the current at the maximum tolerated—and not simply the maximum available—but this level frequently varies with changes in positioning, activity level, and the simple waxing and waning of postoperative pain, making patient-enabled adjustments crucial.

Patient Instructions

If a single-injection peripheral nerve block is provided before surgery, it is impossible to determine the postoperative current requirements within the recovery room because of the insensate extremity. Therefore, the pulse generator is often set for a current below the maximum tolerated during lead insertion to avoid inducing pain upon block resolution. However, patients must be instructed to adjust the current to the maximum tolerated contemporaneously with block resolution, a maneuver that has proved challenging for a subset of patients (especially with nighttime resolution). In addition, any oral analgesic prescriptions should be filled even with a lack of pain (because of a dense surgical block) in case the peripheral nerve stimulation provides inadequate analgesia after block resolution. Each system comes with two rechargeable batteries, and although there is a battery-level indicator on the handheld

remotes, inadvertent battery exhaustion and subsequent surgical pain occurs frequently. This scenario may be easily avoided simply by having one battery recharging while the other is in use, and switching them at the same time daily. Patients may bathe as long as the lead insertion site is not submerged, but the pulse generator should be disconnected beforehand. Fortunately, a decrease in analgesia is not experienced for 2 to 3 h after a pause in stimulation—a phenomenon theorized to be related to prolonged alteration of supraspinal pain processing—so an increase in pain may be prevented by reattaching and restarting the pulse generator immediately after bathing.[216]

When lead insertion occurs on a day preceding surgery, providing system instructions at that time can be easier for patients to comprehend before the perioperative hours with its accompanying stress and sedation. On the day of surgery, both the patient and a caretaker should receive verbal and written instructions that include healthcare-provider contact information and a warning that magnetic resonance imaging use is hazardous with the lead/stimulator *in situ*. Patients should be cautioned to avoid strenuous physical activity and motion near the implant—an especially important instruction when leads are inserted on a day before surgery. Extra lead-site dressings and pulse generator mounting pads should be provided along with the second battery and battery charger for outpatients. Lead removal is accomplished simply with gentle traction, but is strongly recommended to be performed by a healthcare provider. Unlike polyamide perineural catheters,[217] the 0.2-mm-diameter wire lead is more easily fractured, and the helical coil unraveling during extraction can give the impression of a fracture and can be confusing in inexperienced hands. The pulse generators, batteries, and remotes are disposable and should not be reused.

Contraindications and Complications

The few absolute contraindications to percutaneous peripheral nerve stimulation include patients with a deep brain stimulation system, implanted active cardiac implant (*e.g.*, pacemaker or defibrillator), or other neurostimulator whose stimulus current path might overlap with that if the percutaneous peripheral nerve stimulation system. Relative contraindications include bleeding disorders, pharmacologic anticoagulation, severe adhesive allergies, or infection in the area of lead insertion.

With fewer than 1 infection every 32,000 indwelling days,[218] helically coiled leads have dramatically lower risk than percutaneous noncoiled leads or perineural/intravascular catheters.[2,219–221] The reason(s) for the extraordinary difference in infection rate—even between lead designs—remains unknown, but there are theoretical explanations that deserve future study. The helical open-coiled design permits fibrosis at the insertion site, leading to a superior bacteriostatic seal at the skin; and a solid anchor helping to prevent lead movement.[222] Decreasing lead movement theoretically decreases any "pistoning" effect that could draw pathogens subcutaneously.[222,223] In addition, the diameter of the lead wire (0.2 mm) and even of the entire helix itself (0.6 mm) have small diameters compared with cylindrical noncoiled leads (0.6 to 1.3 mm) and perineural catheters (0.8 to 1.0 mm) and therefore create a relatively smaller exit site.

Nerve injury has not been reported using percutaneous peripheral nerve stimulation. Leads are optimally implanted ~1 cm away from the epineurium in contrast to perineural catheters that are frequently inserted immediately adjacent to and within the same fascial plane as the target nerve.[4] Theoretically, the greater distance from the target nerve when using a lead decreases the possibility of neurologic injury caused by needle–nerve contact.[224] Because of the frequently prolonged duration of lead implantation (up to 60 days) and required dressing changes, skin irritation is the most common adverse event but can be easily mitigated by simply moving the mounting pad to different anatomic locations or replacing adhesive dressings with gauze and paper tape. Lead dislodgment may occur (8% in acute pain studies), but the incidence appears to be greatly lessened with the use of 2-octyl cyanoacrylate (surgical glue) at the lead insertion site (NCT03481725).[206–209]

The most concerning adverse event is lead fracture, occurring either during use or removal. Within postoperative patients discharged with a lead *in situ*, the overall fracture rate is 20%,[206–209] although this is more than halved (9%) when all patients—acute and chronic—are included.[209] It is notable that when leads were placed and subsequently removed the same day (n = 46), not one fractured (0%).[204–209] In contrast, of 49 leads implanted in the very same subjects but used after surgery, 10 subsequently fractured (20%).[206–209] Combined with preliminary evidence that sciatic leads implanted at the popliteal fossa fracture at a far higher rate than sciatic leads implanted in the subgluteal region,[208] we speculate that lead fracture is most likely related to applied tension caused by repeated flexion and extension of the surrounding musculature.

All fractured lead remnants have been left *in situ* with no negative sequelae reported in up to a 1-year period of assessment.[138] Importantly, magnetic resonance imaging may be performed safely in patients with retained lead fragments of up to 12.7 cm—the maximum possible—at 1.5 Tesla,[225] although most reported fractures have occurred at or near the tip of the lead, leaving a relatively short remnant of the 100-μm coated wire at a length of less than 1.6 cm.[225] Recent experience suggests that lead fracture may be reduced if resistance is encountered during withdraw by simply holding continuous traction and/or percutaneously injecting local anesthetic in the area of the lead to induce muscle relaxation (NCT03481725).

Conclusions

Because of its prolonged duration of action of up to 60 days, titratability, and low infection risk, percutaneous peripheral

nerve stimulation has significant potential as a nonopioid postoperative analgesic. As with continuous peripheral nerve blocks,[226,227] percutaneous peripheral nerve stimulation may be used to treat all major nerves,[178] as well as multiple nerves concurrently.[202,204–206] However, unlike perineural local anesthetic infusion,[228] percutaneous peripheral nerve stimulation does not induce sensory, motor, or proprioception deficits[208,209] and therefore possibly improves the ability to participate in physical therapy and reduces the risk of falling with lower extremity application.[1,229–231] Similarly, with percutaneous peripheral nerve stimulation, there is no risk of local anesthetic leakage or toxicity; the incidence of nerve injury and infection appear to be far lower, and patient burden is decreased without an infusion pump and local anesthetic reservoir to carry. Benefits of percutaneous peripheral nerve stimulation over cryoneurolysis include a lack of sensory and motor deficits, as well as titratability and complete control over the duration of treatment.[138] Conversely, cryoneurolysis may be easily applied to multiple target nerves (*e.g.*, intercostals) and, although no direct comparisons are currently available, appears to provide far more potent focused analgesia at a dramatically lower cost without the risk of lead dislodgement or retained lead fragments.[22]

Multiple questions remain regarding ultrasound-guided percutaneous peripheral nerve stimulation for the treatment of acute pain, not the least of which is determining the optimal equipment, lead insertion techniques, stimulation parameters, and potential applications such as treating pain after burns and percutaneous nephrolithotomy. The degree to which percutaneous peripheral nerve stimulation is used clinically will most likely depend on the ultimate cost of the available systems (~$4,000 per lead at the time of this writing), the ability to decrease the dislodgement/fracture rates, and—most importantly—validation and quantification of clinical benefits and risks with appropriately powered randomized, controlled trials (NCT03286543, NCT03481725, and NCT04341948).

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Competing Interests

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

James Darsie Morrison and Cold Anesthesia: A Technique of Antiquity and Modernity

For decades before the first clinical use of local anesthetics (1884), inhalational agents relieved the pain of dental procedures. In 1859, the Royal Scottish Society of the Arts (RSSA) awarded "Surgeon Dentist" James Darsie Morrison of Edinburgh (*right*) a silver medal for his application of an alternative anesthetic technique. The medal's obverse (*upper left*) displays a bust of Athena, goddess of wisdom and crafts, and symbol of the RSSA, whose mission was to promote scientific innovation. The award's reverse (*lower left*) praises Morrison for creating an "Apparatus for the Application / Of Cold for producing / Local Anaesthesia" (*right*). In ancient times, Hippocrates had noted the analgesic effects of snow. Today, the mechanisms of cold anesthesia are thought to include vasoconstriction, slowed nerve conduction, and impaired pain substance release. In 1859, Morrison, prefiguring modern cryoanalgesia, patented his award-winning thermoconductive device. His invention employed tubes of frosty liquid and chilled compressed air to numb the teeth and gums of patients.

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