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Authors

Gabriel, Rodney A

Ilfeld, Brian M

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Novel Methodologies in Regional Anesthesia for Knee Arthroplasty

Rodney A. Gabriel, MD, MAS (Clinical Research),
Brian M. Ilfeld, MD, MS (Clinical Investigation)*

KEYWORDS

• Knee arthroplasty • Cryoanalgesia • Cryoneurolysis • Neuromodulation
• Peripheral nerve stimulation

KEY POINTS

- Combined with the rising expertise of ultrasound imaging among anesthesiologists, ubiquitous availability of ultrasound devices, and availability of portable cryodevices, cryoanalgesia is now a realistic intervention for acute pain management.
- Although a single application of ultrasound-guided percutaneous cryoneurolysis provides weeks to months of analgesia, careful selection of candidates is required given the potential prolonged motor block if mixed motor-sensory nerves are targeted.
- Ultrasound-guided percutaneous peripheral nerve stimulation offers a novel intervention to provide post–knee arthroplasty analgesia without the major limitations of opioids and continuous peripheral nerve blockade.
- Before ultrasound-guided percutaneous cryoanalgesia and percutaneous peripheral nerve stimulation may be routinely practiced, robust clinical trials documenting their risks and benefits in managing acute and subacute postoperative pain should be conducted.

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Department of Anesthesiology, University of California, San Diego, 200 West Arbor Drive, MC 8770, San Diego, CA 92103, USA
* Corresponding author.
E-mail address: bilfeld@ucsd.edu

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INTRODUCTION

Maximizing analgesia is critical following joint arthroplasty because postoperative pain is a major barrier to adequate participation in physical therapy, which is in itself central to optimizing functional recovery. Both single-injection and continuous peripheral nerve blocks (PNB) provide pain control following knee arthroplasty[1] and are often considered the gold standard for postoperative analgesia.[2] However, limitations of these techniques have limited their general use,[3,4] and alternatives could improve the risk-benefit ratio and increase their application worldwide following knee arthroplasty.

One of the major issues of local anesthetic-based analgesics is their duration measured in only a few hours or days. The pain following total knee arthroplasty (TKA) usually far outlasts this analgesic duration. The duration of continuous PNB catheters is limited by the risk of infection and dislodgement.[5] Perineural infusions also induce motor, sensory, and proprioception deficits that potentially increase the risk of falling.[4] A further disadvantage of continuous PNB in ambulatory patients is the burden of carrying an infusion pump and local anesthetic reservoir bag. Percutaneous cryoneurolysis and peripheral nerve stimulation (PNS) are two modalities approved by the Food and Drug Administration (FDA) for use in treating acute pain; yet they have been nearly absent from the acute pain literature.[6–8] This article reviews these analgesic methods and their application to acute pain states, specifically for knee arthroplasty.

CRYOANALGESIA

Cryoanalgesia, also termed cryoablation, cryoneuroablation, or cryoneurolysis, is a method in which peripheral nerves are reversibly ablated by extremely cold temperatures leading to analgesia in the distribution of the nerve for multiple weeks to months. It was first reported in 1961 using liquid nitrogen to create temperatures at $-190^{\circ}C$ to ablate nerves.[9,10] Lloyd and colleagues[11] coined the term “cryoanalgesia” 15 years later after describing its use for the management of pain. Since then, its clinical application expanded mainly to treat various chronic pain conditions.[12] In the few cases cryoneurolysis was used to treat acute pain, it was almost exclusively applied intraoperatively by surgically exposing the target nerves and applying the cannula under direct visualization.[13–25] More recently, cryoneurolysis was administered using a blind percutaneous approach using landmarks,[18] and subsequently using a percutaneous ultrasound-guided approach.[6,7] Most studies have involved application to sensory-only nerves. Although mixed sensory-motor nerve treatment was reported without negative sequelae in preclinical[26,27] and clinical[28] settings, its safety and therapeutic profile have yet to be determined with adequately designed and powered trials.

Mechanism of Action

The modern cryoprobe consists of a hollow tube with a smaller inner tube. Highly pressurized gas (usually nitrous oxide or carbon dioxide) travels from the proximal part of the tube to its distal portion where it is released from a larger outer tube through a narrow annulus, allowing the gas to rapidly expand in the closed tip (**Fig. 1**). Because of the Joule-Thompson effect, a drop of temperature to approximately $-70^{\circ}C$ accompanies the drop in pressure, creating an ice ball at the tip of the probe.[29] The gas itself is vented back proximally through the outer tube. This mechanism ensures that no gas enters or remains in the patient’s tissues.

Wallerian degeneration (a breakdown of the axon) occurs distal to the point of treatment, resulting in a complete sensory, motor, and proprioception conduction block.

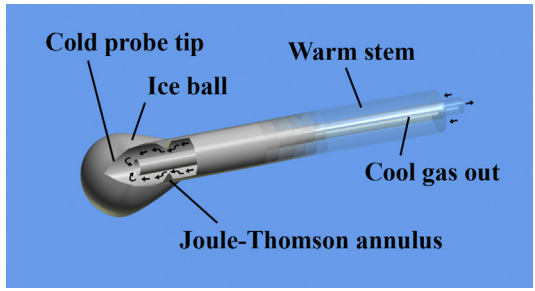

Fig. 1. A cryoneurolysis probe produces extremely cold temperature at its tip because of the Joule-Thomson effect, which results in gas flowing from a high to low pressure chamber. (*Courtesy of* B. Ilfeld, MD, MS, San Diego, CA.)

Fortunately, at temperatures warmer than −100°C, the endoneurium, perineurium, and epineurium all remain intact, permitting regeneration of the nerve of approximately 2 mm/d in a proximal-to-distal direction along the remaining nerve skeleton.[12] Cryoneurolysis using nitrous oxide or carbon dioxide has inherent safety because the freezing point of each is approximately −90°C and −80°C, and therefore each reaches a solid state before reaching −100°C, which is associated with neural and stromal destruction. Such extremely low temperatures can cause irreversible nerve injury, potentially leading to neuroma formation.[30]

Application to Acute Pain

Until recently, cryoanalgesia for acute pain management has been limited to invasive approaches that require surgical exposure of the target nerves.[24,25,31] Most of these examples target post-thoractomy pain, in which cryoanalgesia was applied to intercostal nerves by the surgeon intraoperatively.[14–17,19,20,22,23] However, technical advances now allow percutaneous administration, specifically hand-held devices with cryoprobes easily visualized with ultrasound-guidance and cleared by the FDA (**Fig. 2**).[29] Other portable devices exist that allow percutaneous administration with ultrasound guidance (**Fig. 3**). Combined with the rising expertise of ultrasound imaging among anesthesiologists and ubiquitous availability of ultrasound devices, cryoanalgesia is now a realistic intervention for acute pain management. Advantages over continuous PNB techniques include longer duration with a single application; avoidance of the risk of local anesthetic toxicity; theoretically decreased risk of infection; a lack of infusion pump malfunction, catheter migration/dislodgement, and leakage

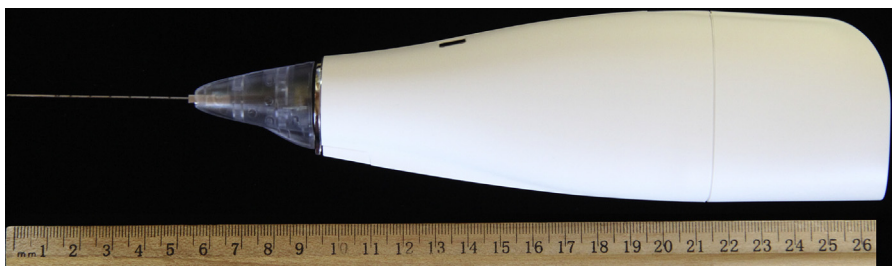

Fig. 2. A hand-held cryoneurolysis device with a 5.5-cm, 22 cryoprobe. (*Courtesy of* B. Ilfeld, MD, MS, San Diego, CA.)

Fig. 3. A portable cryoneurolysis device with built-in nerve stimulator (PainBlocker). (*Courtesy of* B. Ilfeld, MD, MS, San Diego, CA and Epimed, Dallas, TX.)

complications; and no burden of carrying an infusion pump and local anesthetic reservoir.

Dasa and colleagues[18] were the first to analyze the efficacy of a percutaneous approach to cryoanalgesia for management of post-TKA pain. Cryoneurolysis was performed at an office visit to the surgeon days before the scheduled surgery. A blind approach used landmarks to apply percutaneous cryoanalgesia along two treatment lines to treat the anterior femoral cutaneous nerve and the infrapatellar branch of the saphenous nerve (**Fig. 4**).[32] Both nerves provide purely sensory innervation to the anterior aspect of the knee and lie in a predictable and superficial location in the proximity of the knee capsule. The anterior femoral cutaneous nerve innervating the superior knee lies within the fascia above the quadriceps tendon as it crosses a horizontal line the width of the patella approximately 7 cm above the superior aspect of the patella. The infrapatellar branch of the saphenous nerve innervating the inferior knee lies along the joint capsule and crosses a vertical line from the inferior aspect of the patella to the tibial tubercle approximately 5 cm medial to the patella. Because of the superficial and predictable locations of each of these nerves, applying cryoanalgesia using landmark techniques is possible. To block these two nerves with cryoneurolysis, Dasa and colleagues[18] applied superficial treatment with a hand-held cryodevice to produce a 0.5-cm cold zone under the skin. A treatment cycle consisted of a period of cooling then warming of the probe, lasting approximately 50 seconds. Each treatment line required approximately six treatment cycles to cover the entire length (total procedural duration to freeze both nerves was 15 minutes).

Fig. 4. Treatment lines (*green bars*) used to apply cryoneurolysis via a "blind" superficial approach to target anterior femoral cutaneous nerve and the infrapatellar branch of the saphenous nerve. (*Courtesy of* B. Ilfeld, MD, MS, San Diego, CA.)

This retrospective study of 100 patients reported the use of preoperative cryoneurolysis was associated with a reduced incidence of prolonged hospitalization duration and opioid consumption up to 12 weeks postoperatively in patients undergoing TKA.[18] Similarly, this blind approach using landmark techniques was used to treat

nonsurgical pain associated with knee osteoarthritis.[33] In this randomized, double-blind, sham-controlled multicenter study, the infrapatellar branch of the saphenous nerve was targeted with cryoneurolysis. The study population consisted of 180 patients, in which those in the treatment group had statistically significant decreases from baseline Western Ontario and McMaster Osteoarthritis Index (an instrument measuring functioning) and pain scores at 30, 60, and 90 days after treatment when compared with the control group.

The use of ultrasound guidance combined with a percutaneous cryoprobe offer the ability to target far more peripheral nerves than the blind approach that is appropriate exclusively for cutaneous nerves. An ultrasound-guided percutaneous technique has been recently described but is currently limited to short series of cases.[6,7] Preoperative ultrasound-guided percutaneous cryoanalgesia for use in treating acute postoperative pain in the orthopedic population has also been reported.[7] Like the previously described reports, the infrapatellar branch was targeted by preoperative cryoneurolysis in patients planned for TKA. In contrast to prior studies, this approach used ultrasound-guidance to target the nerve versus a blind landmark technique. The case series also reports use of ultrasound guidance to visualize cryoprobe positioning and treatment of the suprascapular nerve just superior to the suprascapular notch for patients undergoing rotator cuff repair. All patients in this case series experienced excellent postoperative analgesia and had decreased opioid consumption compared with historical control subjects. No adverse events were reported.

In another report, ultrasound-guided percutaneous cryoanalgesia was used postoperatively or postinjury to treat the (1) intercostal nerve to provide multiple weeks of analgesia to a patient with refractory back pain associated with a surgical incision from a nephrolithotomy procedure; (2) subcostal and intercostal nerves to provide weeks of analgesia to a patient with hip pain following iliac crest bone grafting; and (3) the saphenous, sural, posterior tibial, and superficial peroneal nerves to help manage pain in a patient with burn injury to the foot.[6] In all cases, patients reported adequate analgesia for at least 2 weeks following treatment with no subsequent nerve injury or neuropathic pain. No other adverse events occurred in relation to cryoanalgesia.

Potential Risks

Compared with other invasive analgesic modalities, cryoanalgesia has few contraindications and risks. Relative contraindications include Reynaud syndrome, cryoglobulinemia, and cold urticaria.[34] The associated prolonged total sensory, motor, and proprioception block combined with an unpredictable duration of action (weeks to months) is not appropriate in most clinical scenarios involving acute pain with the one potential exception being the treatment of the anterior femoral cutaneous and infrapatellar branch of the saphenous nerve for knee surgery, such as knee arthroplasty.[18,32]

Similar to traditional needle-based percutaneous regional anesthesia techniques, potential complications of cryoneurolysis include bleeding, bruising, and infection. Additional risks include injury to the nerve or surrounding tissue if the cannula is retracted before resolution of the ice ball, and cutaneous discoloration if the ice ball reaches the skin.[29] Therefore, when treating superficial nerves it is important to use a cannula designed specifically for this area with heating units at and below the skin to protect against inadvertently involving the dermis and epidermis.

Of note, cryoneurolysis has been in clinical use for more than five decades without a single published case of permanent nerve injury or neuroma[28] and no evidence of long-term changes to nerve function.[26,30] However, two randomized, controlled

clinical trials reported an increase in neuropathic pain associated with cryoneurolysis when administered via the surgical incision during thoracotomy.[16,19] One study compared epidural infusion alone with a combination of epidural infusion and intercostal cryoanalgesia and identified a higher incidence of neuropathic-type pain (mainly allodynia) at 8 weeks, but resolving by 6 months.[16] Furthermore, this study reports that patients who had received cryoneurolysis had higher pain scores at various time points (12 hours, 2 days, and 8 weeks). Of note, the statistical significance for this analysis was not adjusted for multiple comparisons and these results are, therefore, inconclusive. The second investigation compared epidural infusion alone with intercostal cryoanalgesia alone.[19] They reported an increased incidence of allodynia for subjects who had received cryoneurolysis at 6 and 12 months. However, statistical significance was not adjusted for multiple comparisons. Furthermore, it remains unknown if the difference in treatments was caused by an increased risk of cryoneurolysis or a protective effect from the epidural infusion.

For both studies, cryoanalgesia was applied via surgical exposure and possible nerve retraction. This is significant because preclinical evidence suggests that any physical manipulation of the nerve at the time of cryoneurolysis may be a mitigating factor in producing a sustained chronic pain condition.[35] Although not perfectly understood, the nerve manipulation before the freeze is hypothesized to produce an afferent barrage that sets up the central sensitization such that when axonal regeneration occurs following cryoneurolysis, the fiber activity is perceived as dysesthetic.[36] Although this issue certainly deserves further investigation, it is relevant that most clinical reports identified no increased risk involving thoracotomy or any other surgical procedure,[6,7,18,20,21,23–25,31,37,38] and percutaneous application does not involve nerve manipulation. Lastly, preclinical data suggest that a partial nerve injury (inducing Wallerian degeneration of only a portion of nerve fibers) results in hyperalgesia, whereas a complete ablation does not.[35] It is therefore possible that incomplete neurolysis could explain why two trials found an association between cryoanalgesia and allodynia in contrast to most similar investigations.

Summary of Cryoanalgesia

There are currently far more unresolved questions than conclusive answers regarding the use of cryoneurolysis to treat post–knee arthroplasty pain. Remaining undetermined is the optimal number of cryoneurolysis applications for each target nerve, the duration of treatment, the duration of thawing before subsequently moving the cannula, and specific apparatus and cannula design. For example, there are preclinical data suggesting that the duration of analgesia/anesthesia is directly correlated with the duration of cryoneurolysis application (30–120 seconds),[22] suggesting that the ultimate treatment duration may be better controlled than currently realized. However, additional laboratory studies have demonstrated that partial nerve injury (inducing Wallerian degeneration of only a portion of nerve fibers) results in hyperalgesia.[35] Most importantly, outcome data from randomized, controlled clinical trials are required to identify and quantify any improvement in outcomes and associated risks. This technique should be compared with local anesthetic-based analgesic modalities; however, the optimal pain control method may involve a combination of PNBs and cryoneurolysis for short- and long-term analgesia, respectively. Nonetheless, the use of cryoanalgesia for TKA patients seems promising because of the combination of few contraindications, easy technical application, new portable cryoneurolysis devices and disposable cannulas, few apparent risks, and prolonged duration that in many cases outlasts the surgical pain itself.

PERIPHERAL NEUROMODULATION

The concept of using electricity to induce analgesia is not new, having originated with the ancient Romans using living torpedo fish.[39] Since the first device designed to provide electroanalgesia became available in the early twentieth century,[40] neuromodulation has mainly evolved for the management of chronic pain through implanted spinal cord and PNS devices.[41,42] Use of PNS to treat acute postoperative pain has been limited primarily because of the invasive and time-consuming nature of the available technology.[43] Although transcutaneous delivery of electrical current has been reported, the analgesic ceiling caused by triggering pain fibers in the skin significantly limits the degree of postoperative analgesia benefit.[44] The development and FDA clearance of a lead that is inserted percutaneously through a needle has now removed the limitation of invasive surgical implantation and extraction, thus opening the possibility of applying neuromodulation to treat postoperative pain (**Fig. 5**).

Extremely small, insulated electrical leads (**Fig. 6**) have been developed that allow rapid placement via a percutaneous approach through an introducer needle.[45,46] An ultrasound-guided percutaneous approach using these extremely small leads has been used for various chronic pain states[47,48]; but, its potential for acute postoperative pain management remains primarily unexplored. Using ultrasound, these leads are placed via an introducer needle proximal to nerve (about 1–2 cm away). Unlike traditional PNB techniques, needle placement does not need to be in contact with the nerve to ensure appropriate local anesthetic spread. Stimulation is subsequently tested and if appropriate paresthesias or motor stimulation is elicited, the introducer needle is removed and lead left remaining *in situ*. The proximal portion of the lead is then attached to a small external stimulator, which can easily be affixed to the patient's skin (**Fig. 7**).[8]

Mechanism of Action

The definitive mechanism of neuromodulation's effect on pain remains unknown, although multiple theories have been proposed. The most commonly noted is "gate control theory," in which electrical activation of large-diameter myelinated afferent peripheral nerve fibers inhibits pain signals from the small-diameter pain fibers to the central nervous system.[49] The resultant effect is analgesia while preserving motor, sensory, and proprioception.

Peripheral Nerve Stimulation and Acute Pain

Ultrasound-guided percutaneous PNS offers a novel intervention to provide post–knee arthroplasty analgesia without the major limitations of opioids and continuous PNB.[8] Just one example is the associated motor, sensory, and proprioception deficits

Fig. 5. A small diameter (0.2-mm), open-coiled, helical electrical lead with an anchoring wire preloaded within a 12.5-cm, 20-gauge insertion needle for percutaneous application. (*Courtesy of* B. Ilfeld, MD, MS, San Diego, CA.)

Fig. 6. A small diameter (0.2-mm), open-coiled, helical electrical lead. (*Courtesy of* B. Ilfeld, MD, MS, San Diego, CA.)

from the local anesthetic that may increase the risk of falling after joint replacement.[4] Therefore, neuromodulation has important potential implications for use in total joint surgeries because this intervention potentially may provide effective analgesia while also preserving complete motor function and proprioception, both of which are required to optimize postoperative rehabilitation and safety.

Recent preliminary studies provide data regarding the use of ultrasound-guided percutaneous lead placement and subsequent PNS in the management of acute postoperative pain following TKA.[50,51] In one pilot study, leads were placed in five subjects (femoral and/or sciatic nerve) who experienced uncontrolled postoperative pain with oral analgesics between 8 and 58 days following TKA.[50] Following lead insertion, pain scores were recorded before and after the stimulators were activated. Immediate analgesia was experienced by all subjects and decreased resting pain by an average

Fig. 7. Setup for a percutaneous peripheral nerve stimulator of the femoral nerve. (*Courtesy of* B. Ilfeld, MD, MS, San Diego, CA.)

of 93%, in which four of the five patients reported complete resolution of pain. Pain during passive and active knee motion was reduced by 27% and 30%, respectively, whereas maximum passive or active knee range-of-motion were only minimally affected. A second study involving another small series of subjects reported similar findings using an identical protocol between 8 and 97 days following TKA.[52]

Only a single report has been published describing the use of percutaneous PNS to treat pain in the immediate postoperative period.[53] Femoral and sciatic leads were inserted preoperatively in seven patients and remained for up to 6 weeks. During the first 2 weeks, pain was well controlled in 88% of the patients, four of whom did not require addition opioids after this time period. Of the five subjects with data on opioid use, the median time to complete opioid cessation was only 8 days, with 100% of subjects opioid-free 1 month following surgery. This is a dramatic improvement compared with the typical median time to cessation of nearly 2 months (vs 8 days)[54–57] with a 1-month opioid-independence rate of 11% to 33% (vs 100%) for patients having the same surgical procedure within the United States.[58] The average 6-minute-walk-test distance was 97% and 124% of patients' preoperative distances at 2 weeks and at 3 months, respectively. Importantly, there were no falls, motor block, or infections reported.

Potential Risks and Concerns

Potential risks associated with percutaneous PNS are, theoretically, minimal relative to current local anesthetic-based techniques; however, there have been no confirmatory large-scale clinical trials involving this novel modality. As with any implanted foreign body, there is a risk of infection. Yet the risk seems to be exceedingly low, with fewer than one infection per 3000 indwelling days,[59] orders of magnitude smaller than for perineural catheters.[60] This improvement is most likely because of the helical coil lead design, which encourages tissue ingrowth between the coils sealing the passage through the skin, and allowing stretching/compression of the lead avoiding "pistoning" that draws bacteria into the body (**Fig. 8**). Additional risks include migration, dislodgement, and fracture. As with infections, the helical coil lead design theoretically minimizes migration and dislodgement by allowing the lead to stretch and compress, unlike perineural catheters. As a result, the helical coil design permits long duration of lead retention from multiple weeks to more than a year.[61–63]

Fracture of the 2-mm diameter lead occurs in approximately 7.5% of subjects, usually during extraction, but sometimes simply during use.[8] In more than 200 patients with a fractured lead, the lead remnants were uniformly left *in situ* without any

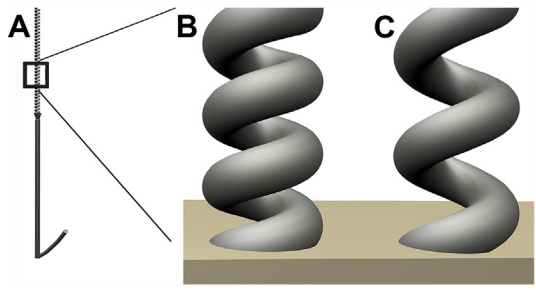

Fig. 8. Illustration showing how (*A*) electrical lead (*B*) when at rest and (*C*) when applied traction causes an opening of the helical coil, which prevents pistoning through the skin and dislodgment. (*Courtesy of* B. Ilfeld, MD, MS, San Diego, CA.)

subsequent negative sequelae.[8] Importantly, the remnants themselves do not preclude subsequent MRI.[64] Although not reported to date, there is the risk of nerve injury as with any invasive procedure. However, this risk is theoretically far lower than for local anesthetic-based PNBs considering the lead, and therefore insertion needle, do not require the lead and nerve to be in direct contact (unlike traditional PNB). Allowing for a remote distance from the nerve promotes selective stimulation of the required larger-diameter myelinated sensory neurons[65] without activating motor or smaller-diameter sensory neurons that induce muscle contraction and discomfort, respectively.[8] After 50 years of clinical use, we are unaware of any reports of nerve injury caused by the electric current of neuromodulation.[66] Many of the risks of continuous PNB do not apply to percutaneous PNS, such as local anesthetic toxicity and sensory, motor, and proprioception blockade (which may increase risk of falls). Finally, because the required external stimulator for percutaneous PNS is small and requires no medication bag to hold local anesthetic, this burden is no longer an issue with percutaneous PNS.

SUMMARY

With increased awareness of opioid overuse after surgery and the current worldwide opioid epidemic, it is timely to introduce and study novel interventions that may aid in long-term management of postsurgical pain to decrease opioid requirements. Also noteworthy is that during the first few days following knee arthroplasty, adequate analgesia improves ambulation, which is associated with shorter hospital length of stay and lower hospitalization costs.[67] Improved analgesia during the weeks to months following knee arthroplasty will theoretically aid in improved physical therapy participation and reduce opioid requirements at home.

Before ultrasound-guided percutaneous cryoanalgesia and percutaneous PNS may be more widely practiced, robust clinical trials demonstrating their efficacy in managing acute and subacute postoperative pain should be completed. Furthermore, other hospital metrics should be examined including hospital length of stay, opioid consumption, incidence of adverse events, and health care expenditures. Lastly, until the costs of percutaneous PNS systems are better defined, a cost-benefit analysis will remain inconclusive. Nevertheless, given the need to improve postoperative analgesia, decrease opioid requirements because of the current opioid epidemic, shorten hospitalization duration, improve postoperative functional outcomes, and lessen analgesic-associated patient risks, such as falling, ultrasound-guided percutaneous cryoanalgesia and PNS deserve further consideration and investigation.

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