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Percutaneous peripheral nerve stimulation and other alternatives for perineural catheters for postoperative analgesia

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A perineural catheter with a continuous infusion of local anesthetic is an excellent option for postoperative analgesia; however, its limitations include limited duration of action (i.e., 3–7 days) as well as a risk of infection and dislodgement. Furthermore, these blocks may cause dense sensory and motor blockades that under certain circumstances may not be ideal. There is novel evidence that ultrasound-guided percutaneous peripheral nerve stimulation (pPNS) may serve as an alternative approach free of the limitations associated with peripheral nerve blocks. In this review, we discuss the evidence for pPNS on postoperative acute pain management. Subsequently, we briefly discuss additional alternatives to continuous peripheral nerve blocks, including cryoanalgesia and liposomal bupivacaine.

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Introduction

Opioids are the mainstay treatment for postoperative analgesia following orthopedic surgery associated with moderate-to-severe pain. However, this is not an ideal option for analgesia as there are associated side effects such as nausea, vomiting, sedation, and respiratory depression. Furthermore, with the ongoing national opioid crisis [1], it is crucial that perioperative providers implement effective interventions for surgical patients that reduce opioid requirements and pain-related

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complications. A perineural catheter with a continuous infusion of local anesthetic is an excellent option; however, its limitations include limited duration of action (i.e., 3–7 days) as well as a risk of infection and dislodgement [2]. Furthermore, these blocks may cause dense sensory and motor blockades that under certain circumstances may not be ideal. There is novel evidence that ultrasound-guided percutaneous peripheral nerve stimulation (pPNS) may serve as an alternative approach free of the limitations associated with peripheral nerve blocks [3–9]. Furthermore, we briefly discuss additional alternatives to continuous peripheral nerve blocks, including cryoanalgesia and liposomal bupivacaine.

Peripheral nerve stimulation

The process of using electricity to induce analgesia originated by the ancient Romans using living torpedo fish, which was able to provide up to 220 V of current, to relieve pain [10]. The first device designed to provide "electroanalgesia" was described in the twentieth century [11] and has since then been adapted to clinical use for treatment of chronic pain via implanted spinal cord or peripheral nerve stimulators [12,13]. The mechanism of action at which nerve stimulation may provide analgesia is still unknown. The most commonly noted is the "gate control theory," whereby electrical activation of large-diameter myelinated afferent peripheral nerve fibers inhibits pain signals from the small-diameter pain fibers to the central nervous system [14].

The use of percutaneous peripheral nerve stimulation to treat postoperative acute pain is relatively novel and has been recently described for various surgical procedures including total knee arthroplasty [4,6], hallux valgus repair [3], rotator cuff repair [9], and anterior cruciate ligament repair [7]. Prior to these reports, its use in a fast-paced perioperative environment was limited primarily due to the invasive and time-consuming nature of placement and testing of PNS with the available technology [15]. Extremely, small insulated electrical leads were developed, which allowed more rapid placement via a percutaneous approach guided by ultrasound (Figs. 1 and 2) [16,17]. Clearance of such devices by the U.S. Food and Drug Administration now allow for the possibility of applying this technology in the perioperative setting [18–20].

There are various key differences in terms of ultrasound-guided placement of perineural catheters versus pPNS for acute pain. First, under ultrasound, pPNS leads are placed via an introducer; however, unlike traditional peripheral nerve block techniques, needle placement in a pPNS approach does not need to be immediately adjacent to the target nerve (only requires about 1–3 cm away). Once the lead is placed via introducer needle at the appropriate distance, nerve stimulation is tested. If sensations in the appropriate nerve distribution is elicited, the introducer needle may be removed and the lead remains in the patient. In one device (SPRINT, SPR Therapeutics, Cleveland, OH), the proximal portion of the lead is then attached to a small external stimulator, which can subsequently be placed easily onto the patient's skin (Figs. 1 and 2) [5].

Knee arthroplasty

Ultrasound-guided pPNS offers a newer approach to provide long-term analgesia for patients undergoing knee arthroplasty while avoiding the major limitations of opioids and continuous peripheral nerve blocks [5]. The risk of falls following joint replacement is a major concern and may be associated with the motor, sensory, and proprioception blockade provided by local anesthetics [21]. Furthermore, continuous peripheral nerve blocks are limited only to a few days while the pain associated with knee arthroplasty may last for weeks to months. Thus, peripheral neuromodulation has very important implications for this surgical group as it is not associated with motor and sensory deficits and may remain *in situ* for weeks to months with a dramatically lower risk of infection [22].

Recent preliminary studies provide potential evidence of the use of ultrasound-guided pPNS for acute postoperative pain following total knee arthroplasty [4,23]. In a pilot study, femoral and/or sciatic leads were placed in 5 subjects who experienced uncontrolled postoperative pain with oral analgesics between 8 and 58 days postoperatively following surgery [4]. After the leads were inserted in these patients, immediate analgesia was exhibited by all subjects: average resting pain decreased by approximately 90%, whereby 80% of patients reported complete analgesia. In a second case series

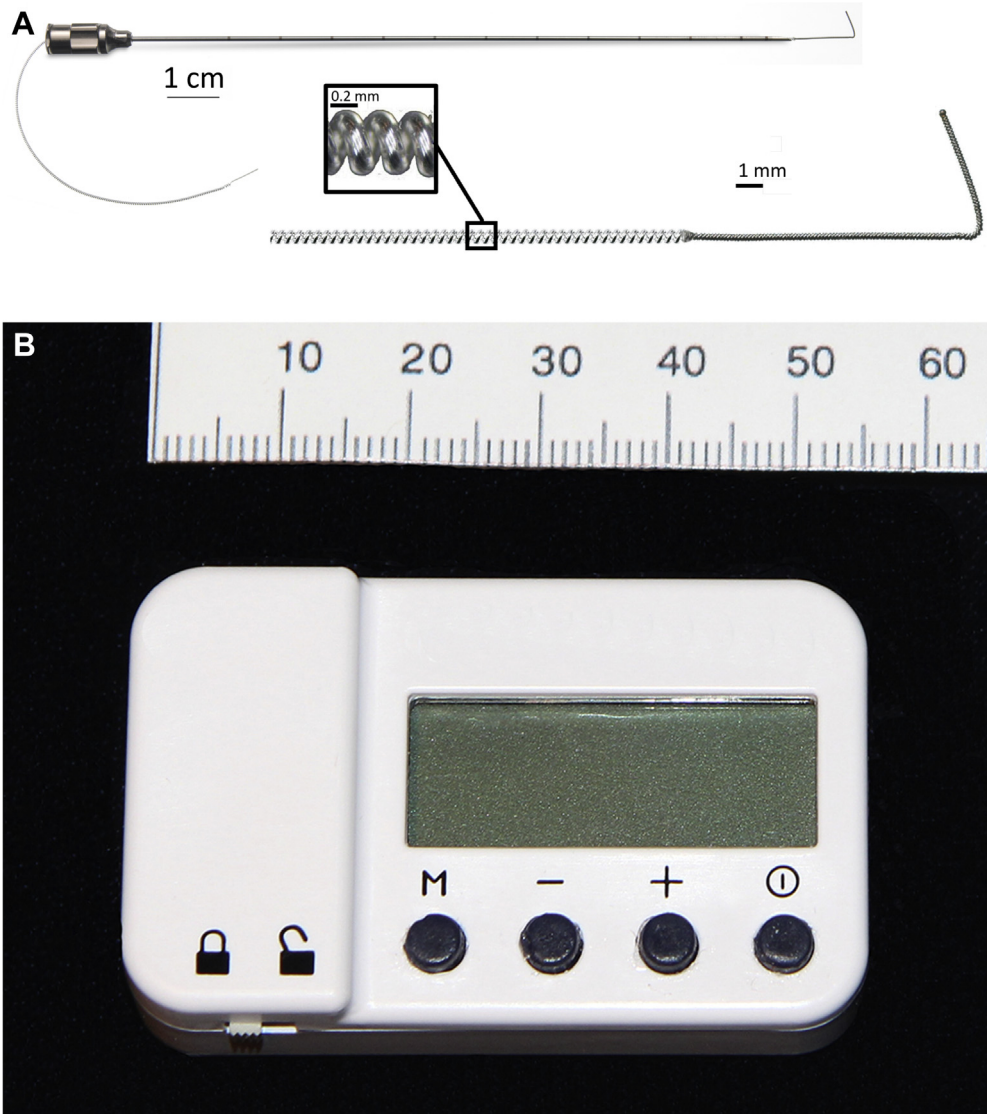

Fig. 1. The percutaneous peripheral nerve stimulation equipment used for this study: a 12.5 cm, 20 g needle with a pre-loaded helically coiled monopolar-insulated electrical lead (**Panel A**; MicroLead, SPR Therapeutics, Inc., Cleveland, OH); and, a pulse generator or "stimulator" (**Panel B**; SPR Therapeutics, Inc., Cleveland, OH; both illustrations used with permission from Brian M. Ilfeld, MD, MS).

involving another set of subjects, there were similar findings in patients who received total knee arthropasty [6].

A subsequent study evaluated pPNS in the *immediate postoperative period* following total knee arthroplasty [24]. This study included 7 patients in which femoral and sciatica leads were inserted prior to surgery and remained *in situ* for up to 6 weeks. Pain was subsequently well-controlled in 88% of patients for the first two weeks, in which 4 did not require opioids after this time period. Only 5 subjects had available data on opioid use, in which the median time to cessation of opioid use was 8 days postoperatively. This is an important improvement compared to other studies which report a

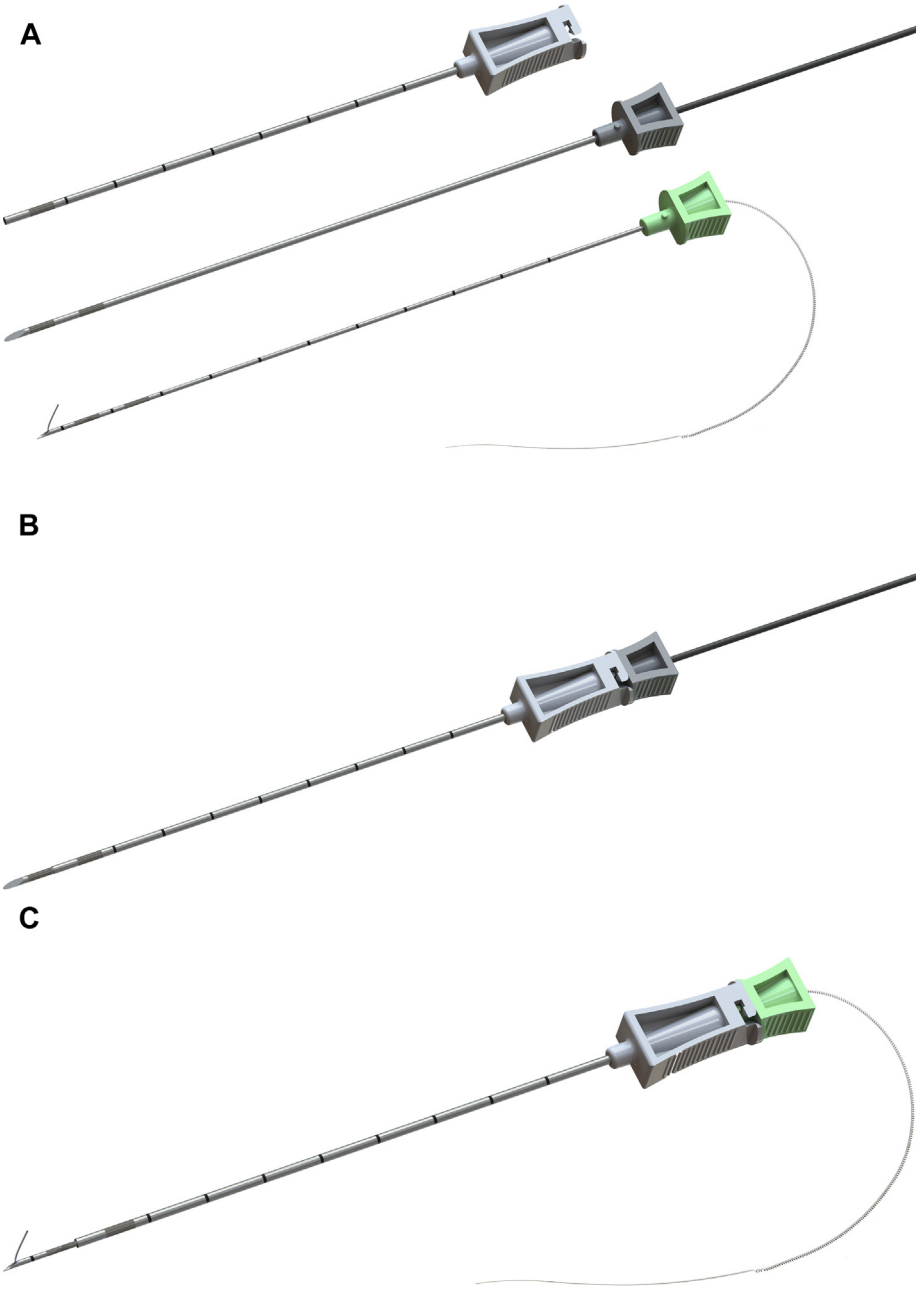

Fig. 2. A multicomponent lead implantation system with (from top to bottom) an introducing sleeve, stimulating probe, and needle with preloaded lead (**Panel A**; OnePass, SPR Therapeutics, Inc., Cleveland, OH; illustration used with permission from Brian M. Ilfeld, MD, MS). The stimulating probe is inserted and locked within the introducing sleeve (**Panel B**) and positioned to produce the desired patient response; the probe is removed and replaced with the preloaded needle and lead (**Panel C**); and the sleeve-needle withdrawn in tandem deploying the lead.

median time to opioid cessation at nearly 2 months [25–28] with a 1-month opioid-independence rate of 11–33% for patients having the same surgical procedure within the United States [29]. Furthermore, the average six-minute walk test distance was 97% and 124% of patients' preoperative distances at 2 weeks and 3 months, respectively. There were no falls, detected motor block, or infections reported.

Ambulatory foot surgery

To date, there has been one small clinical trial published investigating the use of ultrasound-guided pPNS for ambulatory foot surgery [3]. For this study, 7 patients undergoing hallux valgus ostoetomy were recruited. This was a randomized trial, in which patients either received 5 min of active stimulation first followed by 5 min of sham stimulation or 5 min of sham stimulation first followed by 5 min of active stimulation postoperatively. During the initial 5-min treatment period, those in the active stimulation group experienced an improvement in their pain over 5 min, while those in the sham group did not. Following this 10-min period, both cohorts were subjected to 30 min of active stimulation, in which pain scores decreased to approximately 50% of baseline. Three subjects required a local anesthetic bolus through their perineural sciatic nerve catheter during postoperative day 0–3. Throughout the study period (2–4 weeks after surgery), opioid use and dynamic and resting pain scores were low. Of note, no weakness in plantar flexion was noted. This proof-of-concept study demonstrated the promise of pPNS when stimulating the sciatic nerve for ambulatory foot surgery as its use provided analgesia and opioid reduction.

Rotator cuff repair

One study investigated the feasibility of percutaneous brachial plexus PNS to manage surgical pain following ambulatory rotator cuff repair during the immediate postoperative period [9]. For this study, 14 patients were recruited to receive preoperative placement of implanted leads to target either the suprascapular nerve or brachial plexus roots or trunks using ultrasound guidance. Postoperatively, patients received 5 min of either stimulation or sham followed by 5-min of a crossover period in a randomized fashion. Both cohorts received continuous stimulation thereafter until lead removal about 2–4 weeks postoperatively. The first two patients of the study received lead placement proximal to the suprascapular nerve, neither of which appeared to receive any appreciable postoperative analgesia; therefore, subsequent patients received lead placements through the middle scalene muscle posterior/lateral to the brachial plexus (roots and/or trunks). In the recovery room, neither of the cohort experienced any appreciable improvement in their pain scores during the first 40 min, whereby 7 of the 11 subjects required a single injection interscalene nerve block with local anesthetic. However, during postoperative days 1–14, the median pain score on the numerical rating scale was 1 or less, and opioid consumption averaged less than 1 tablet (oxycodone 5 mg) a day. This study demonstrated the feasibility of pPNS for the brachial plexus; however, it is important to note that while analgesia was not adequate during the immediate period (i.e., recovery room), it provided satisfactory results during the first two weeks following surgery. Furthermore, optimal placement of stimulator leads relative to the brachial plexus has yet to be determined. Further high-quality studies are required to address these questions.

Anterior cruciate ligament reconstruction

In addition, there is one study demonstrating the use of ultrasound-guided pPNS for management of acute postoperative pain following ambulatory anterior cruciate ligament reconstruction [7]. The trial was designed similarly to the reports previously described in this manuscript, in which one cohort was randomized to receive 5 min of active stimulation first followed by sham stimulation, while the other cohort received 5 min of sham stimulation first followed by active stimulation. Both cohorts then received ongoing active stimulation, and pain scores and opioid use were collected subsequently. In this study, 10 patients were recruited and received preoperative placement (days before surgery) of pPNS with leads adjacent to the femoral nerve (caudal to the inguinal crease) with leads remaining

from 14 to 28 days postoperatively. During the initial 5-min treatment period, those randomized to active stimulation experienced a 7% decrease in pain over that time period, while those in the sham group experienced a 4% increase in pain. The latter group subsequently had a 11% decrease in pain during the active stimulation crossover. Postoperatively, 80% of patients required additional continuous adductor canal nerve block for rescue analgesia during the first 2 days after surgery. After that, both pain scores and opioid use were minimal. This proof-of-concept study also demonstrated that utilization of pPNS for ambulatory anterior cruciate ligament reconstruction is feasible; however, larger clinical trials are required to adequately demonstrate its efficacy.

Risk factors and complications

There are minimal potential risks associated with the utilization of ultrasound-guided pPNS for acute postoperative pain. Of importance is that there is no large-scale clinical trial to further describe the incidence of complications with this intervention. One potential risk is lead infection; however, the risk is extremely low (fewer than 1 infection per 32,000 indwelling days) [22] when compared to that reported for perineural catheters [30]. Such low infectious rate of this foreign body is potentially due to the helical coil design, which allows tissue ingrowth between coils that seal the passage of bacteria through the skin. Furthermore, the stretching/compressing of the leads avoid pistoning that draws bacteria into the body with perineural catheters. There is also the risk of lead dislodgement and fracture, which was noted in a significant proportion of patients in initial studies looking at pPNS for acute postoperative pain management [3,6]. Nonetheless, the helical coil design of these leads permits long duration of lead retention from weeks to over a year [31–33].Note that, in more than 200 patients with a fractured intra-muscular lead over a 30-year period of time, the remnants were uniformly left *in situ* without any subsequent negative sequelae with patients followed for up to one year [5]. Furthermore, these remnants do not preclude subsequent magnetic resonance imaging [34]. Other theoretical risks of pPNS are nerve injury from either physical contact of the needle/lead to the nerve or from the nerve stimulation itself. However, after 50 years of clinical use, there have been no reports of nerve injury due to the electric current of neuromodulation [35].

Cryoanalgesia

Cryoanalgesia is a modality in which peripheral nerves are reversibly ablated by extremely cold temperatures, which provides analgesia in the distribution of the nerve until the nerve regenerates, often for up to several months. Initially, its clinical utilization has mainly been to treat chronic pain states [36]. In the acute pain arena, it has mainly been used intraoperatively via surgical exposure to the target nerve [37–49]. The majority of these examples target post-thoracotomy pain, in which cryoanalgesia was applied to intercostal nerves intraoperatively by the surgeon [38–41,43,44,46,47]. A less-invasive approach is now possible as described by a “blind” approach using landmarks [42] or by ultrasound-guidance [50,51]. With the advent of portable devices that may deliver cryoneurolysis, its use is more viable in the fast-paced perioperative environment [52]. Regardless, its safety and therapeutic profile have yet to be determined with adequately designed and powered trials. However, its potential advantages over continuous peripheral nerve block techniques include a much longer duration with a single application (weeks to months); avoidance of local anesthetic toxicity risk; a decreased risk of infection (none published to date); a lack of infusion pump malfunction, catheter migration/dislodgement, and leakage complications; and no burden of carrying an infusion pump and local anesthetic reservoir.

Liposomal bupivacaine

Local anesthetic may be encased in liposomes which, as they naturally break down following injection, release the medication over a period of multiple days. In 2011, the first formulation of liposomal bupivacaine (EXPAREL; Pacira Pharmaceuticals, Inc., USA) was approved by the U.S. Food and Drug Administration (FDA). It is now approved for use in surgical site infiltration as well as

transverse abdominis plane blocks and interscalene nerve blocks for shoulder surgery. Overall, the results have largely been negative in demonstrating the superiority of liposomal bupivacaine to nonliposomal bupivacaine for surgical infiltration. Thirteen published randomized controlled trials involved the use of liposomal bupivacaine infiltration of the knee joint for arthroplasty [53]. All but two of the studies reported negative results for their primary end point. Of the two positive trials favoring liposomal bupivacaine over non-liposomal bupivacaine, one lacked prospective registration or a defined primary endpoint [54]. In the another study, titled the Postsurgical Infiltration with exparel for Long Lasting Analgesia in total knee aRthroplasty (PILLAR) [55], the results would actually have been negative if the original statistical methods published prior to enrollment were followed [56,57]. Additional clinical trials investigating surgical infiltration of liposomal bupivacaine were negative for their primary end point for inguinal hernia repair [58–60] and laparoscopic urologic surgery [61]. Essentially, for surgical site infiltration, there is a lack of strong high-quality evidence from randomized controlled trials demonstrating superiority of liposomal bupivacaine to that of unencapsulated bupivacaine.

However, there are some promising results with the use of liposomal bupivacaine and single injection peripheral nerve blocks [62–64]. Liposomal bupivacaine, when added to standard bupivacaine for interscalene nerve blocks, decreased worst pain scores in those who underwent shoulder surgery [64]. There have been two prospective randomized controlled trials for subcostal transverse abdominis plane blocks, in which both reported decreased pain scores and opioid requirement for up to 72 h after robot-assisted hysterectomy and laparoscopic hand-assisted donor nephrectomy [62,63]. Confidence in these results is somewhat tempered; however, the registration of one of these trials was performed after the enrollment was complete and another did not specify a primary outcome measure and lacked any correction for multiple statistical comparisons.

When used in a femoral nerve block (currently an off-label indication), liposome bupivacaine demonstrated analgesic effects as long as 72 h compared to placebo (saline) [65]. However, greatly needed are future trials comparing liposomal bupivacaine to that of single-injection unencapsulated bupivacaine as well as continuous peripheral nerve blocks. Finally, Viscusi et al. demonstrated that when liposomal bupivacaine was injected as a single injection epidural block (off-label indication), there was longer duration of sensory blockade and shorter duration of motor blockade than that of nonliposomal bupivacaine [66].

In summary, there is still much needed evidence to demonstrate equivalency or superiority of liposomal bupivacaine compared to single-injection unencapsulated bupivacaine and/or continuous peripheral nerve blocks; and, cost-benefit analyses are needed.

Conclusions

Now is the time to develop novel and effective interventions that aid in the management of postoperative pain in patients undergoing surgeries associated with moderate-to-severe pain. In this review, we discussed the potential of the novel therapy of using ultrasound-guided pPNS to provide weeks of analgesia following various orthopedic surgeries. Before the widespread use of pPNS may be established, robust clinical trials demonstrating its efficacy are required. Ultrasound-guided percutaneous cryoanalgesia and liposomal bupivacaine also have promise; however, more high quality randomized controlled trials are recommended prior to widespread adoption.

Disclosures

Rodney Gabriel, MD, MAS: Dr. Gabriel's institution has received funding and product for his research from Myoscience and Epimed; infusion pump manufacturer Infutronics; perineural catheter manufacturer Ferrosan Medical; and a manufacturer of a peripheral nerve stimulation device, SPR Therapeutics.

Brian Ilfeld, MD, MS: Dr. Ilfeld's institution has received funding and product for his research from Myoscience and Epimed; infusion pump manufacturer Infutronics; perineural catheter manufacturer Ferrosan Medical; a manufacturer of a peripheral nerve stimulation device, SPR Therapeutics; and, a manufacturer of a long-acting bupivacaine formulation, Heron Pharmaceuticals.

Practice points

- Ultrasound-guided pPNS may serve as an alternative approach free of the limitations associated with continuous peripheral nerve blocks
- The use of pPNS to treat postoperative acute pain is relatively novel and has been recently described for various surgical procedures including total knee arthroplasty, hallux valgus repair, rotator cuff repair, and anterior cruciate ligament repair.
- Other potential alternative modalities to continuous peripheral nerve blocks for acute postoperative pain include percutaneous cryoanalgesia and liposomal bupivacaine.

Research agenda

- Now is the time to develop novel and effective interventions that aid in the management of postoperative pain in patients undergoing surgeries associated with moderate-to-severe pain.
- High-quality randomized controlled trials are now needed to assess the efficacy of pPNS for postoperative analgesia.

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