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Continuous Peripheral Nerve Blocks: An Update of the Published Evidence and Comparison with Novel, Alternative Analgesic Modalities

Brian M. Ilfeld, MD, MS

A continuous peripheral nerve block (CPNB) consists of a percutaneously inserted catheter with its tip adjacent to a target nerve/plexus through which local anesthetic may be administered, providing a prolonged block that may be titrated to the desired effect. In the decades after its first report in 1946, a plethora of data relating to CPNB was published, much of which was examined in a 2011 *Anesthesia & Analgesia* article. The current update is an evidence-based review of the CPNB literature published in the interim. Novel insertion sites include the adductor canal, interpectoral, quadratus lumborum, lesser palatine, ulnar, superficial, and deep peroneal nerves. Noteworthy new indications include providing analgesia after traumatic rib/femur fracture, manipulation for adhesive capsulitis, and treating abdominal wall pain during pregnancy. The preponderance of recently published evidence suggests benefits nearly exclusively in favor of catheter insertion using ultrasound guidance compared with electrical stimulation, although little new data are available to help guide practitioners regarding the specifics of ultrasound-guided catheter insertion (eg, optimal needle–nerve orientation). After some previous suggestions that automated, repeated bolus doses could provide benefits over a basal infusion, there is a dearth of supporting data published in the past few years. An increasing number of disposable infusion pumps does now allow a similar ability to adjust basal rates, bolus volume, and lockout times compared with their electronic, programmable counterparts, and a promising area of research is communicating with and controlling pumps remotely via the Internet. Large, prospective studies now document the relatively few major complications during ambulatory CPNB, although randomized, controlled studies demonstrating an actual shortening of hospitalization duration are few. Recent evidence suggests that, compared with femoral infusion, adductor canal catheters both induce less quadriceps femoris weakness and improve mobilization/ambulation, although the relative analgesia afforded by each remains in dispute. Newly published data demonstrate that the incidence and/or severity of chronic, persistent postsurgical pain may, at times, be decreased with a short-term postoperative CPNB. Few new CPNB-related complications have been identified, although large, prospective trials provide additional data regarding the incidence of adverse events. Lastly, a number of novel, alternative analgesic modalities are under development/investigation. Four such techniques are described and contrasted with CPNB, including single-injection peripheral nerve blocks with newer adjuvants, liposome bupivacaine used in wound infiltration and peripheral nerve blocks, cryoanalgesia with cryoneurolysis, and percutaneous peripheral nerve stimulation. (Anesth Analg 2016;XXX:00–00)

A continuous peripheral nerve block (CPNB) consists of a percutaneously inserted catheter with its tip adjacent to a target nerve/plexus through which local anesthetic may be administered. Such a "perineural local anesthetic infusion" provides a prolonged peripheral nerve block that may be titrated to the desired effect.[1] In the decades after its first report in 1946,[2] a plethora of data relating to CPNB was published, much of which was examined in a 2011 *Anesthesia & Analgesia* review.[1] The current update is an evidence-based review of the CPNB literature published in the interim. Because of publication limitations, the majority of information—including 364 citations—included in the previously published review is not repeated here.[1] Consequently, the current update is most likely best utilized in concert with the previous review article to provide a complete overview of CPNB. Because there are literally thousands of CPNB-related publications, only those that provide the highest quality data (eg, randomized controlled trials [RCTs]) and/or are the most influential (eg, unique case reports and observational studies) are included.

In addition, a variety of novel, alternative analgesic modalities are currently under development/testing. These techniques are also reviewed and compared/contrasted with CPNB.

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Parts of this report were previously presented annually since 2003 when I began giving presentations; this is a review article and therefore covers material that I have presented previously.

Reprints will not be available from the authors.

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INDICATIONS AND INSERTION LOCATIONS

The overwhelming majority of recently published CPNB data involves providing analgesia after surgical

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procedures. Noteworthy exceptions include case reports/series using CPNB to treat chronic pain such as cancer-related pain,[3–8] complex regional pain syndrome,[9–12] ischemia-induced pain,[13,14] ulcer-derived pain,[15] and phantom limb pain (Table 1).[16–18] Regarding the latter, the only available randomized data come from a very small pilot study (n = 3) but does strongly suggest that further research is warranted.[19] Another randomized, placebo-controlled pilot study (n = 4) provides evidence that a 3-day, continuous interscalene nerve block dramatically improves shoulder range of motion both during and up to 12 weeks after manipulation for adhesive capsulitis.[20] Also noteworthy, continuous paravertebral[21–23] and intercostal[24–26] catheters have been used to treat pain after traumatic rib fracture; and a randomized pilot study (n = 30) detected no differences between this CPNB technique and a thoracic epidural infusion with the exception of a greater incidence and degree of hypotension using epidural analgesia.[27] Lastly, continuous transversus abdominis plane (TAP) and femoral blocks have been used to treat abdominal wall pain during pregnancy[28] and femur fracture pain,[29,30] respectively.

Recently, case reports and small series using CPNB to induce sympathectomy to improve transplantation success have been published.[31,32] Similarly, a number of reports have been published, involving the use of continuous TAP blocks to treat postoperative pain after hernia repair,[33] renal transplantation,[34] and abdominal procedures.[35] Unfortunately, this catheter location remains unvalidated with the only (negative) randomized, placebo-controlled trial underpowered (n = 20),[33] and a different RCT comparing TAP and epidural catheters for upper abdominal surgery designed as a superiority trial yet detecting few differences between treatments (therefore, inconclusive).[36] Bilateral continuous paravertebral blocks have also been used for abdominal surgery in the presence of mild coagulopathy instead of an epidural because of concern of epidural hematoma formation.[37]

Novel insertion sites include catheters adjacent to the lesser palatine,[38] ulnar,[39] superficial peroneal,[40,41] and deep peroneal nerves.[40] New interfascial catheter sites have also been described: interpectoral[42,43] and quadratus lumborum[44–46] for breast and abdominal analgesia, respectively.

However, adductor canal catheters are by far the most examined and potentially influential anatomic site described recently (Table 1).[47] The adductor canal is an aponeurotic tunnel in the midthird of the thigh deep to the sartorius muscle that contains multiple afferent nerves innervating the knee, yet only a single efferent nerve innervating the medial part of the quadriceps femoris muscle.[48,49] Therefore, local anesthetic administered in the canal induces dramatically less quadriceps weakness compared with deposition adjacent to the femoral nerve at the inguinal crease.[50] Reflecting the concern regarding the association between continuous femoral nerve blocks and both falls[51–56] and physical therapy limitations,[57,58] adductor canal perineural infusion has garnered strong interest.[59,60] Although this catheter site has been validated with a number of randomized, placebo-controlled trials,[47,61–65] multiple issues remain in dispute[66–71] or are unclear/unknown[72,73] such as the relative analgesia afforded compared with a femoral infusion (see the following section on benefits).[50,57–59,74]

Although RCTs involving surgical pediatric populations remain the exception,[75,76] series of patients continue to be published.[77–83]

CATHETER INSERTION

Before the advent of ultrasound-guided regional anesthesia, CPNB-related clinical investigation focused on comparing nonstimulating and stimulating catheters inserted through an insulated needle used to localize a target nerve/plexus.[84,85] With the subsequent widespread adoption of ultrasound to place a needle adjacent to a target nerve/plexus, the emphasis has shifted to comparing needle/catheter insertion using ultrasound versus electrical current.[86] Since publication of the previous CPNB review,[1] the preponderance of new evidence suggests benefits nearly exclusively in favor of catheter insertion using ultrasound guidance compared with electrical stimulation (passed via either the needle or the catheter). Catheter insertion success is higher using ultrasound guidance compared with nerve stimulation for most insertion sites, yet requires less time for placement, induces less procedure-related discomfort, and carries a lower risk of vascular penetration.[87]

The data are somewhat conflicting on whether catheters inserted using ultrasound guidance provide superior analgesia during the perineural infusion itself.[87–92] Regarding this issue, the highest quality data are derived from an RCT involving over 450 subjects randomized to 3 different femoral catheter insertion techniques.[93] Using electrical current to guide the inserting needle and/or stimulating catheter failed to provide superior analgesia or decrease opioid requirements (and vice versa). In addition, using electric current with either the needle or the catheter required a longer insertion time and ultimately proved more costly. With the number of CPNB-related RCTs involving nerve stimulation appearing to fall precipitously within the past few years,[14,94–99] it subjectively appears there is now some consensus emerging regarding the ultrasound-versus-stimulation debate.[86] Nonetheless, using electric current to supplement ultrasound guidance for difficult to visualize (eg, deep)[100] or ambiguous (eg, inexperienced practitioners) neural targets may prove beneficial in challenging cases.[1]

Few RCTs have been published—recently or otherwise—to help guide practitioners regarding the specifics of ultrasound-guided catheter insertion.[1,101,102] For example, imaging the target nerve in the short axis (a cross-section) is far easier[103] and decreases total insertion time compared with imaging the long axis[103,104]; and nearly all publications report this transducer-to-nerve orientation. However, catheters may be inserted through a needle introduced either parallel or perpendicular to the target nerve.[105] Few RCTs compare these "in-" and "out-"of-plane techniques[106]; and of those that do, results may agree (femoral)[103,104] or conflict (interscalene).[107,108] Although publication limitations of this review article preclude an in-depth discussion of these issues,[109] readers are referred elsewhere for related information.[105,110]

Technologic innovations of the past few years offer possible improvements in CPNB application[110] and include self-coiling catheters that curl immediately on exiting the

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Table 1. Catheter Locations

Surgical Site	Major Approaches	Randomized and Controlled Study Design? (for Catheter Site)	Comments	Comparative CPNB Studies
Head and neck	Mandibular, maxillary, lesser palatine nerves, and cervical plexus	No[1,38,426]	Effectiveness of techniques unclear without RCT	
Shoulder and proximal humerus	Interscalene	Yes[20,98,99,108,116,119,130,131,145–147,153,163,164,173,176,195,427] No[4,5,8,16,77–81,159,162,168–172,175,428,429]	Recent RCT demonstrated a 2-d continuous interscalene block decreases pain 7 d after major shoulder surgery compared with a single-injection ropivacaine block[176]	A recent RCT demonstrated that a supraclavicular infusion is noninferior to an interscalene infusion and reduced the incidence of complete or partial hemidiaphragmatic paresis (analgesia was superior to the interscalene catheters in the recovery room)[427]
	Cervical paravertebral	No[6]	Little published since the widespread adoption of ultrasound-guided catheter insertion	
	Intersternocleidomastoid	No[1]	Little published since the widespread adoption of ultrasound-guided catheter insertion	
	Supraclavicular	Yes[427] No[77,165,430]	Relatively rare catheter site relative to the interscalene location for shoulder surgery[1]; however, the largest series to date was recently published (n = 498)[165]	
	Suprascapular	No[431]	Effectiveness of technique unclear without RCT	
Elbow, forearm, and hand	Supraclavicular	Yes[118] No[9,32,77,81,159,165]	Relatively rare catheter site relative to the infraclavicular and—historically—axillary locations[1]; however, the largest series to date was recently published (n = 271)[165]	Infraclavicular provides superior analgesia to both supraclavicular[432] and axillary[433] catheters for hand, forearm, and elbow surgery; 1 new RCT detected few differences between supraclavicular and infraclavicular infusions benefits but was underpowered for these secondary endpoints, and there were trends in favor of the infraclavicular location[434]
	Infraclavicular	Yes[173,434] No[19,77–80,102,127,173]	A recent RCT provided 60 h of infraclavicular infusion to all participants and randomized subjects to remain hospitalized for 1 vs 3 nights[173]; total hospital cost of care was 15% lower in the early discharge group and no other differences between treatment groups including elbow range of motion	
	Axillary	Yes[433] No[31,77,79–81,127,128,435]	Dramatic decrease in publications since the widespread adoption of ultrasound-guided catheter insertion	
	Median, ulnar nerves	No[39,436]	Effectiveness of techniques unclear without RCT	
Thorax and breast	Thoracic paravertebral	Yes[27,135,158,167,177,204,221,437] No[21–23,77,83,109,438]	For mastectomy, mixed evidence[439,440] with RCTs demonstrating no infusion benefits over placebo[221] and single-injection,[441] yet others demonstrating benefits both during[167,437] and after (up to 1 y) perineural infusion[177,221]	There are no studies comparing these CPNB techniques
	Intercostal	No[24–26]	Effectiveness of this technique unclear without RCT	
	Interpectoral	No[42,43]	Effectiveness of this relatively novel technique unclear without RCT	
Abdomen and inguinal region	Paravertebral	No[37,77,83,442,443]	New published data include pediatric patients[77,83,442]	
	Transversus abdominis plane	Yes[33,36] No[28,34,35,77,256,444]	Remains unvalidated with an RCT: one RCT was negative compared with placebo but was underpowered,[33] and a second RCT detected few differences between a continuous subcostal TAP and epidural infusion but was designed as a superiority study and the negative results should therefore be considered inconclusive and not equivalente[36]	
	Quadratus lumborum	No[44–46]	Effectiveness of this relatively novel technique unclear without RCT	

(Continued)

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Table 1. Continued

Surgical Site	Major Approaches	Randomized and Controlled Study Design? (for Catheter Site)	Comments	Comparative CPNB Studies
Hip, thigh, and leg	Posterior lumbar plexus Femoral	Yes[133,206] No[3,6,77–80,178] Yes[29,203] No[3,7,9,18,19,30,77–81,150,159,162]	Published RCTs dramatically diminished in numbers within the past few years, possibly indicating a general preference for other catheter locations	For hip arthroplasty, patients with femoral (vs posterior lumbar plexus) catheters: no difference in resting pain scores, but ambulation suffered; dynamic pain scores either higher or no difference; and increased opioid-related side effects and satisfaction[1]
	Fascia iliaca	Yes[445]	First study validating this technique for hip analgesia recently published[445]	
	Parasacral	No[1]	Effectiveness of this technique unclear without RCT involving hip, thigh, or leg surgery	
Knee (femoral nerve)	Posterior lumbar plexus	Yes[1] No[77–80,96]	Published RCTs dramatically diminished in numbers within the past few years, possibly indicating a general preference for other catheter locations	Compared with femoral infusion, adductor canal CPNB induces less quadriceps femoris muscle weakness[50] and ambulatory disability[57,58,74]; however, the evidence is mixed regarding comparable analgesia,[50,57,58,74] and further research is required to draw definitive conclusions
	Femoral	Yes[50,57–59,74,85,91,93,95,101,104,121,132,138,198,216,446,447] No[77–80,97,100,201,205,448–451]	Until recently, the most commonly published catheter location for knee surgery, but concerns regarding associated falls have raised interest in alternative catheter locations such as the adductor canal	
	Adductor canal	Yes[47,50,57–59,61–65,73,74,144] No[156,263,279,452–456]	Relatively recently validated with randomized, placebo-controlled trials,[47,61–65] but multiple issues remain in dispute[66–71] or unclear/unknown[72,73] such as relative analgesia afforded compared with a femoral infusion[50,57,58,74]	
	Fascia iliaca	Yes[1] No[77]	Dramatic decrease in publications since the widespread adoption of ultrasound-guided catheter insertion	
Knee (sciatic nerve), leg, ankle, and foot	Subgluteal/parasacral	Yes[94,96,97,126,201] No[77,78,82,128,159]	Three recent RCTs have investigated the effects of adding a continuous sciatic nerve block to a continuous femoral or posterior lumbar plexus (psoas compartment) block after total knee arthroplasty[96,97,201]; all demonstrated lower pain scores and decreased supplemental analgesic consumption,[96,97,201] and one detected a lower incidence of nausea and vomiting as well as improved knee flexion and ambulation[201]	No major analgesic differences found between subgluteal and popliteal[1]
	Popliteal	Yes[88,92,134,194,200] No[9,12–15,18,19,77–81,100,128,162,165,174,457,458]	A recent RCT provided 3 d of popliteal sciatic infusion to all participants (n = 120) and randomized subjects to remain hospitalized for 0 vs 2 nights after major orthopedic foot surgery[194]; total costs of care were decreased 79% in the early discharge group, and no other differences between treatments were detected, including pain scores, complications, and readmission rates	
	Tibial, superficial peroneal and deep peroneal nerves	No[11,40,41]	Effectiveness of these techniques unclear without RCT	
	Femoral/saphenous	Yes[1]	Femoral infusion in addition to—and not in place of—popliteal infusion for major ankle surgery	

Due to publication limitations, includes selected reports published subsequent to a previously published review article (Ilfeld[1]) and is not intended as an exhaustive list.

CPNB, continuous peripheral nerve block; RCT, randomized controlled trial.

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needle, theoretically decreasing the catheter tip-to-nerve distance[111–113]; a catheter attached to a needle that is passed adjacent to the target nerve and then exited out of the body on the other side of the transducer (remaining in plane the entire trajectory)[114,115]; a 6-hole catheter to theoretically improve local anesthetic spread (failed in 1 RCT)[116]; a perineural catheter that is introduced over an insertion needle to theoretically decrease the incidence of leakage (similar to an intravenous catheter)[30,117–120]; and a novel needle-over-cannula set to also decrease leakage (successful in 1 RCT).[121]

Because flexible perineural catheters usually deviate from the ultrasound plane of view after exiting a rigid in-plane needle, evaluating the crucial catheter tip-to-nerve distance can be difficult.[87] Various investigators have injected—under real-time ultrasound visualization—fluid, an agitated air/fluid admixture, or a small volume of air, although the relative benefits of each were previously uninvestigated.[1] The "air test" was recently evaluated within a porcine–bovine model, but unfortunately there was no benefit over simply visualizing the catheter without air injection.[122,123] Attempts to improve the echogenicity of perineural catheters have been somewhat equivocal[124,125] with 1 RCT detecting no differences in visibility between the experimental echogenic and the standard stimulating catheters.[126] Although visualizing catheter tip location using 3-dimensional ultrasound[127,128] and catheter stylet "pumping" combined with color Doppler are promising techniques,[129] neither has been validated.[110]

INFUSATES

Long-acting local anesthetic remains the primary analgesic infused during CPNB,[1] and there is minimal new information to help guide clinical practice: data suggest that ropivacaine, bupivacaine, and levobupivacaine provide similar analgesia[130] with the main differences being ropivacaine's shorter duration of action—presumably allowing easier titration yet added expense (at least within the United States).[1] New data do support previously available evidence[1] that total dose and not concentration/volume is the primary determinant of clinical effects for continuous interscalene,[131] femoral,[132] posterior lumbar plexus (psoas compartment),[133] and popliteal sciatic nerve blocks[134]; although it remains unclear whether this relationship is valid for other brachial plexus,[1] adductor canal,[57,58] TAP, and paravertebral perineural infusions.[135]

Although there is recently published preclinical evidence involving perineural pregabalin infusion[136] as well as the addition of clonidine, dexamethasone, and buprenorphine to perineural bupivacaine in a rat model,[137] these data are preliminary and there remains no medication other than local anesthetic approved for continuous perineural administration by the US Food and Drug Administration (FDA).[1] Randomized, controlled clinical trials have failed to detect benefits of adding clonidine or epinephrine to perineural infusions.[1] There are sporadic RCTs reporting benefits of various opioids in a perineural infusion[14,138–141]; however, all but 1[140] lacked an active systemic control group, precluding any determination on the importance of perineural (vs intravenous) administration. Unsurprisingly, the addition of opioids often resulted in an increased incidence of opioid-related side effects.[14,139] Regardless, considering the absence of safety data,[142] a dearth of evidence of perineural efficacy, reports of unacceptable side effects,[14,139] and lack of Federal regulatory approval,[143] no adjuvants can be recommended at this time; and CPNB with solely local anesthetic remains the infusate by general consensus as judged by published reports of the past 2 decades.[1]

LOCAL ANESTHETIC DELIVERY REGIMENS

The RCTs published in the past few years have done little to clarify the optimal mode of delivering perineural local anesthetic: as exclusively a basal infusion, solely repeated bolus doses, or a combination of the 2.[1] A large body of relatively older evidence suggests that providing a basal infusion improves baseline analgesia, decreases the incidence and severity of breakthrough pain, and decreases sleep disturbances and supplemental analgesic requirements for interscalene, infraclavicular, subgluteal, and popliteal sciatic infusions.[1] In contrast, recently published data indicate that few benefits—if any—are afforded with a basal infusion, as opposed to repeated boluses for catheters in these anatomic locations (Table 2).[94,144–147] Contrary new data also exist for femoral CPNB: although previous data suggested that the delivery mode is irrelevant for femoral infusions,[1] a recent RCT suggests that including a basal infusion improves analgesia for this catheter site.[95]

The conflicting results are most likely due to the heterogeneity of catheter designs (eg, nonstimulating vs stimulating), catheter insertion techniques (eg, ultrasound vs stimulating vs a combination), local anesthetic type (eg, ropivacaine vs bupivacaine) and concentration, basal infusion rates, bolus volumes, lockout times, surgical procedures, outcome measures evaluated, measurement sensitivity, and a multitude of other factors. Consequently, there is no evidence-based "ideal" delivery regimen,[148] although investigators have provided clinical recommendations.[143,149] Nevertheless, there are some clinical situations in which including bolus doses are theoretically beneficial such as to enable block reinforcement before potentially painful dressing changes[150] or physical therapy.[20] Virtually all RCTs providing patient-controlled boluses to 1 treatment group report a lower local anesthetic requirement, suggesting 3 possible benefits: (1) theoretically decreasing motor block by decreasing the required basal infusion rate (inadequately investigated to date)[51,151,152]; (2) decreasing the incidence of an insensate extremity[153]; and (3) increasing infusion/analgesia duration for outpatients discharged with a fixed local anesthetic reservoir volume.[154,155]

One technique variation has recently garnered increased interest: the use of mandatory/automatic bolus doses based on the theory that increasing the volume of local anesthetic introduced at a single time point might improve perineural spread compared with an equivalent volume/dose provided as a basal infusion.[13] Continuous adductor canal blocks appear to require a higher basal rate of local anesthetic than their femoral counterparts; and a recent study demonstrated that even with a relatively high rate of 8 mL/h, local anesthetic spread remains somewhat limited.[156] A subsequent investigation involving healthy volunteers found sensory perception and quadriceps femoris

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Table 2. Local Anesthetic Delivery Regimens for Continuous Peripheral Nerve Blocks

Catheter Location	Infusate(s)	Treatment Groups: n	Basal (mL/h)	Bolus (mL)	Lockout (min)	Primary Findings
Interscalene[147] • Arthroscopic rotator cuff repair • Ultrasound in-plane • Nonstimulating needle • Nonstimulating catheter	Ropivacaine 0.2% Control (no catheter)	33 33 33	4 0 —	0 4 —	— 60 —	Two groups receiving ropivacaine had lower pain scores and consumed less supplemental analgesics than the control group No differences between the basal and bolus treatment groups
Interscalene[146] • Arthroscopic rotator cuff repair • Ultrasound in-plane • Stimulating needle • Stimulating catheter	Ropivacaine 0.2%	32 32	4 0	4 4	60 30	Bolus group used a lower total volume of local anesthetic and experienced less motor block No other differences between the basal and the bolus treatment groups noted
Interscalene[153] • Arthroscopic or open rotator cuff repair • Ultrasound out-of-plane • Nonstimulating needle • Nonstimulating catheter	Ropivacaine 0.2%	38 43	2 5	5 5 mL every 6 h[a] 5	60 60	No differences detected between treatments with one exception: higher basal rate group required a temporary infusion cessation because of side effects (predominantly hand numbness)
Interscalene[145] • Major shoulder surgery • Ultrasound, out-of-plane • Stimulating needle • Nonstimulating catheter	Ropivacaine 0.2%	50 51	4 0	3 3 4 mL every h[a]	30 30	No differences detected between treatments
Paravertebral[158] • Thoracotomy • Nonstimulating catheter • Inserted by surgeon under direct vision	Bupivacaine 0.5% Bupivacaine 0.25%	40 40	0 5	15 mL every 6 h[a] 0	 —	Pain scores lower in bolus group, although statistically significant only at 48 and 72 h Higher total volume of local anesthetic consumed by the basal group
Adductor canal[144] • Healthy volunteers • Ultrasound, in plane • Nonstimulating needle • Nonstimulating catheter	Ropivacaine 0.2%	24 24	8 0	0 8 mL every 1 h[a]	— 	Equivalence between treatments to tolerance to cutaneous electrical current and quadriceps femoris maximum voluntary isometric contraction strength
Femoral[95] • Anterior cruciate ligament repair • Stimulating needle • Nonstimulating catheter	Bupivacaine 0.1%	16 19	5 0	5 5	30 15	Analgesia superior in basal + bolus group at rest and during mobilization
Sciatic[94] • Total knee arthroplasty • Anterior approach • Stimulating needle • Nonstimulating catheter • Femoral catheter and continuous infusion also used for both groups	Ropivacaine 0.2%	56 52	6 0	10 10	<30 min <30 min	Few differences between groups, other than the basal + bolus group consumed a higher total volume of local anesthetic

Due to publication limitations, includes selected randomized, controlled trials specifically investigating varying local anesthetic delivery method completed subsequent to a previously-published review article (Ilfeld[1]), and is not intended as an exhaustive list.
—, not included for this treatment group.
[a]Mandatory bolus doses administered (not as needed).

strength equivalent when administering ropivacaine 0.2% at 8 mL/h as either a continuous basal or hourly bolus doses.[144] Similar results were reported for interscalene,[145] femoral,[152] and popliteal catheters.[157] It would therefore be understandable to discount the concept of repeated bolus doses, except a new RCT did find analgesic benefit after thoracotomy in administering a relatively large volume of levobupivacaine (15 mL) via paravertebral catheters once every 6 hours compared with a continuous infusion.[158] Although this study was somewhat confounded by the use of 2 different concentrations of levobupivacaine, it does raise the possibility that the strategy previously used—a repeated hourly bolus

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equivalent to the volume from 1 hour of a basal infusion comparator—could be improved by scheduling larger bolus volumes over a longer period of time. Additional investigation at other catheter sites and administering a higher volume of local anesthetic is required (ClinicalTrials.gov, NCT02662023 and NCT02539628).

Lastly, evidence accumulates that prolonged ropivacaine infusions—even at relatively high doses >40 mg/h—have an extraordinarily low incidence of inducing toxicity signs, symptoms, or plasma levels.[159]

PORTABLE INFUSION PUMPS

Little has changed regarding portable infusion pumps since they were last reviewed[1,149,160] with 3 exceptions. First, more disposable pumps now allow a similar ability to adjust basal rates, bolus volume, and lockout times compared with their electronic, programmable counterparts.[161] Second, a number of portable pumps now have the capability of delivering repeated bolus doses at intervals set by the provider.[144] How useful this capability will prove to be remains under investigation (see the previous section).[13] However, the development with potentially the most influence on clinical care is the new ability of health care providers to remotely communicate directly with electronic infusion pumps via the Internet.[162] In a prospective cohort study of 59 hospitalized subjects undergoing CPNB over approximately 3 days, investigators were alerted by text message when the need for pump changes arose because of an insensate extremity, muscle weakness, or difficulty during physical therapy. The infusion pumps would query subjects and, based on the responses, then communicate directly with health care providers who could remotely control the device. The mean (standard deviation) time for pump setting adjustment from the initial alert was 15 (2) minutes with no associated adverse events, demonstrating at least the feasibility of this technique.

AMBULATORY PERINEURAL INFUSION

In contrast to the topic of portable infusion pumps, research involving ambulatory CPNB has been relatively prolific in recent years.[4,6,7,19,23,33,78,79,116,153,163–175] Originally, the objective of ambulatory perineural infusion was to simply improve analgesia for patients who were never intended to be hospitalized overnight.[149,155] Because enhanced pain control and its many derived benefits have been well documented in earlier RCTs (reviewed previously),[1] nearly[20,33,167,173,176,177] all recent investigation has centered on describing new applications or complications,[4,6–8,19,23,171,174,175] optimizing perineural techniques (few major revelations),[14,116,160] and reporting large series of cases (including over 1600 pediatric patie nts).[78,79,165,168,169,178] Although most series were retrospective in design, 1 large multicenter effort prospectively enrolled over 1500 patients receiving ambulatory continuous interscalene nerve blocks at home.[168] This study documented relatively few CPNB-related complications after discharge with a 1.5% catheter dislodgement rate and no catastrophic incidents. Whereas major problems outside the hospital are very rare,[174] they can prove more challenging to treat than in hospitalized patients.[171,174,179,180]

However, with the collective experience and thousands of published cases in the past 15 years, the main arguments against ambulatory CPNB has shifted from a lack of validation and the risks of complications[181] to instead the challenges of setting up and running an effective ambulatory service ("perineural catheter analgesia as a routine method after ambulatory surgery: effective but unrealistic").[182,183] This view is countered by others who contend that "rather than dismissing these techniques as too difficult, and settling for an unsubstantiated (but probably ineffective) alternative [wound infusion], future research should focus on facilitating the uptake of perineural infusions…."[184] Indeed, there are published accounts specifically addressing practitioners' successes[185] and challenges[186] in developing and implementing ambulatory infusion programs.[172,187]

A second goal of ambulatory infusion eventually developed: using improved pain control to allow patients—who would be expected to remain in the hospital—to be instead discharged earlier than otherwise possible.[188,20,175] Theoretical benefits include improved patient satisfaction, decreased risk of nosocomial infection and health care provider error, and decreasing health care-related costs.[170,189,190] Although multiple RCTs demonstrate that ambulatory CPNB reduces the time until discharge readiness,[1] only 2 have demonstrated a shortening of actual hospitalization duration.[191,192]

Nevertheless, with interest growing in the "perioperative surgical home," ambulatory CPNB is being viewed as a possible enabling intervention.[193] One recent example is an investigation that randomized subjects (n = 38) undergoing complex arthroscopic elbow surgery accompanied by a 60-hour continuous infraclavicular (brachial plexus) nerve block to either remain hospitalized for the 3-day standard of care or be allowed discharge as early as the morning after surgery (Table 3).[173] Both groups underwent continuous passive motion of the elbow for 14 days, and subjects discharged early had similar elbow range of motion after 2 weeks and 3 months compared with patients remaining hospitalized for at least 3 days. Furthermore, there were no statistically significant differences in pain scores, opioid requirements, patient satisfaction, and function-related questionnaires. Importantly, the cost of care for subjects remaining hospitalized was greater than for those allowed early discharge. Although there remains debate as to the significance of the degree of savings (15%),[193] these data are supported by an additional clinical trial that permitted a total avoidance of hospital admission.[194] This second investigation randomized subjects (n = 120) with a continuous popliteal nerve block having major orthopedic foot surgery to be discharged either after surgery or remain hospitalized for 2 nights (Table 3).[194] Total costs of care were decreased 79% in the early discharge group, and no other differences between treatments were detected, including pain scores, complications, and readmission rates. These savings are not applicable to practices within the United States because the surgical procedures under investigation—osteotomies and hallux valgus corrections—are already nearly exclusively performed as outpatients procedures, regardless of the presence of CPNB. However, the strong interest in these investigations may be an indication of the direction ambulatory infusion research—and practice worldwide—will take over the coming decade.

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Table 3. Randomized, Controlled Clinical Trials Involving At Least 1 Treatment Group With a Continuous Peripheral Nerve Block

First Author, Year	Surgical Procedure	Treatment Group	Control Group(s) During Catheter Utilization	Primary Positive Findings During Catheter Use (Treatment Group Superior Unless Otherwise Noted)
Interscalene catheters				
Fredrickson et al[163] (2010)	Minor arthroscopic shoulder	Ropivacaine 0.2% (n = 31) 2 mL/h + 5 mL PCB [60]	Catheters removed in recovery room (n = 30)	Lower resting and dynamic pain scores; less supplemental analgesic requirements
Malhotra et al[20] (2013)	Adhesive capsulitis manipulation	Ropivacaine 0.2% (n = 2) 8 mL/h + 4 mL PCB [30]	Normal saline (n = 2) 8 mL/h + 4 mL PCB [30]	Lower average and dynamic pain scores; lower opioid analgesics; fewer awakenings because of pain; greater shoulder range of motion on day 1 as well as weeks 6 and 12 (preliminary data from a pilot study—underpowered for definitive conclusions)
Salviz et al[176] (2013)	Arthroscopic rotator cuff repair	Ropivacaine 0.2% (n = 20) 5 mL/h + 5 mL PCB [60]	• Single injection only (n = 23) • No block or catheter (n = 20)	Catheter group with less pain, opioid requirements, and sleep disturbances; at 7 d (2-d infusion) only 26% of catheter group reported NRS ≥4 compared with 83% and 58% of single-injection and no block groups, respectively
Infraclavicular catheters				
Eng et al[173] (2015)	Complex arthroscopic elbow	Ropivacaine 0.2% 7 mL/h + 5 mL PCB [30] Discharge as early as postoperative day 1 (n = 19)	Ropivacaine 0.2% 7 mL/h + 5 mL PCB [30] Required to remain hospitalized 72 h (n = 19)	Total hospital cost of care was 15% lower in the early discharge group; no other differences between treatment groups including elbow range of motion
Paravertebral catheters				
Ilfeld et al[167,177] (2014) and (2015)	Mastectomy	Ropivacaine 0.4% (n = 30) 5 mL/h basal only	Normal saline (n = 30) 5 mL/h basal only	Lower resting and breakthrough pain scores; less pain-induced physical and emotional dysfunction during infusion; less chronic pain at 1 y
Karmakar et al[221] (2014)	Modified radical mastectomy	Ropivacaine 0.25% (n = 60) 0.1 mL/kg/h basal only	• Single injection only (n = 57) • No block or catheter (n = 60)	No differences among groups during infusion period nor chronic pain incidence at 3 or 6 mo, but at 3 and 6 mo, both infusion and single-injection group had less severe pain, exhibited fewer symptoms and signs of chronic pain, and experienced better physical and mental health-related quality of life
Pintaric et al[204] (2011)	Thoracotomy (open lung surgery)	Levobupivacaine 0.125% and morphine 30 μg/mL (n = 16) 0.1 mL/kg/h + 0.1 mL/kg PCB [60]	Epidural levobupivacaine and morphine at same concentration and rate/bolus as paravertebral catheters	Similar analgesia but greater hemodynamic stability than epidural analgesia with less required colloid volume and vasopressors to maintain target oxygen delivery index
Transversus abdominis plane (TAP) catheters				
Heil et al[33] (2014)	Abdominal or inguinal hernia repair	Ropivacaine 0.2% (n = 10) 10 mL/h basal only	Normal saline (n = 10) 10 mL/h basal only	No statistically significant difference in pain scores or supplemental analgesics (underpowered study because of curtailment of enrollment)
Niraj et al[36] (2011)	Open renal or hepatobiliary	Bupivacaine 0.375% (n = 29) 1 mg/kg each of bilateral catheters every 8 h	Epidural bupivacaine 0.125% with fentanyl 2 μg/mL (n = 33) 6–12 mL/h + 2 mL PCB [30]	No statistically significant differences in any outcomes between treatments except that the TAP group required a higher dose of rescue analgesics
Adductor canal catheters (placebo controlled)				
Andersen et al[64] (2013)	Total knee arthroplasty	Ropivacaine 0.75% (n = 20) 15 mL "twice daily"	Normal saline (n = 20) 15 mL "twice daily"	Lower average resting and breakthrough (maximum) pain scores and fewer sleep disturbances; ambulation possible in 100% vs 65% of subjects in the ropivacaine vs saline groups, respectively
Grevstad et al[65] (2015)	Severe pain on flexion after total knee arthroplasty	Ropivacaine 0.75% (n = 24) 30 mL single injection	Normal saline (n = 25) 30 mL single injection	Reduced pain during active flexion of the knee, but a large proportion (78%) still had at least moderate pain on flexion

(Continued)

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Table 3. Continued

First Author, Year	Surgical Procedure	Treatment Group	Control Group(s) During Catheter Utilization	Primary Positive Findings During Catheter Use (Treatment Group Superior Unless Otherwise Noted)
Hanson et al[61] (2014)	Total knee arthroplasty	Ropivacaine 0.2% (n = 36) 8 mL/h basal only	Sham catheter (n = 40)	Decreased resting and dynamic pain scores, lower required supplemental analgesics, greater quadriceps strength, greater ambulation distance, and higher satisfaction
Jaeger et al[47] (2012)	Total knee arthroplasty	Ropivacaine 0.75% (n = 21) 30 mL single injection	Normal saline (n = 20) 30 mL single injection	Decreased pain during hours 1–6 and less nausea
Jæger et al[63] (2014)	Revision total knee arthroplasty	Ropivacaine 0.75% (n = 14) 30 mL bolus; 6 h later 0.2% 15 mL bolus; then ropivacaine 0.2% 8 mL/h	Normal saline (n = 13) administered at the same time points and volumes as the ropivacaine group	Lower pain on knee flexion at 4 h (underpowered study for remainder of endpoints)
Jenstrup et al[62] (2012)	Total knee arthroplasty	Ropivacaine 0.75% (n = 34) 30 mL bolus; then 15 mL bolus at 6, 12, 18, and 24 h	Normal saline (n = 37) administered at the same time points and volumes as the ropivacaine group	Lower dynamic pain on flexion and supplemental analgesic requirements, superior ambulation, and mobilization at 24 h
Fisker et al[459] (2015)	Major ankle surgery	Continuous popliteal sciatic blocks for all subjects Ropivacaine 0.2% (n = 20) 5 mL/h basal only	Normal saline (n = 24) 5 mL/h basal only	No differences between treatment groups detected
Adductor canal catheters (versus femoral catheters)				
Elkassabany et al[59] (2016)	Total knee arthroplasty	Adductor ropivacaine 0.2% (n = 31) 8 mL/h basal only	Femoral ropivacaine 0.2% (n = 31) 8 mL/h basal only	Greater quadriceps femoris strength[a]
Jæger et al[50] (2013)	Total knee arthroplasty	Adductor ropivacaine 0.2% (n = 22) 8 mL/h basal only	Femoral ropivacaine 0.2% (n = 26) 8 mL/h basal only	Greater quadriceps femoris strength (52% vs 18% of baseline)
Machi et al[58] (2015)	Total knee arthroplasty	Adductor ropivacaine 0.2% (n = 39) 6–8 mL/h + 4 mL PCB [30]	Femoral ropivacaine 0.2% (n = 39) 4–8 mL/h + 4 mL PCB [30]	Improved ability to stand, sit, and ambulate, but higher dynamic pain scores than femoral infusion
Shah and Jain[74] (2014)	Total knee arthroplasty	Adductor ropivacaine 0.75% (n = 48) 30 mL, then ropivacaine 0.25% 30 mL every 4 h until postoperative day 2	Femoral ropivacaine 0.75% (n = 50) 30 mL, then ropivacaine 0.25% 30 mL every 4 h until postoperative day 2	Improved ability to stand, sit, and ambulate, as well as climb stairs; decreased time until actual discharge (3.1 vs 3.9 d)
Sztain et al[57] (2015)	Unicompartment knee arthroplasty	Adductor ropivacaine 0.2% (n = 15) 6–8 mL/h + 4 mL PCB [30]	Femoral ropivacaine 0.2% (n = 15) 2–6 mL/h + 4 mL PCB [30]	Fewer days until discharge readiness; improved ability to sit, stand, and ambulate; but higher resting pain scores than femoral infusion
Zhang et al[209] (2014)	Total knee arthroplasty	Adductor ropivacaine 0.2% (n = xx) 5 mL/h + 5 mL PCB [30]	Femoral ropivacaine 0.2% (n = x) 5 mL/h + 5 mL PCB [30]	Greater quadriceps femoris strength (52% vs 18% of baseline)
Femoral catheters				
Al-Zahrani et al[447] (2015)	Total knee arthroplasty	Femoral bupivacaine 0.2% (n = 25) 5 mL/h basal only (single-injection sciatic block 15 mL bupivacaine 0.25%)	Epidural bupivacaine 0.0625% + fentanyl 2 μg/mL (n = 25) 5–10 mL/h basal only	No differences between treatment groups detected
Sakai et al[198] (2013)	Total knee arthroplasty	Femoral ropivacaine 0.15% (n = 30) 4 mL/h basal only	Epidural ropivacaine 0.15% (n = 30) 4 mL/h basal only	Shorter time to achieve 120° knee flexion (8 vs 15 d), improved dynamic analgesia, and lower supplemental analgesic requirements
Baranović et al[196] (2011)	Total knee arthroplasty	Femoral levobupivacaine 0.25% (n = 35) 5–6 mL/h basal only	No catheter (n = 36)	Improved analgesia, improved knee flexion on postoperative day 2, lower intravenous morphine requirements, and dramatically lower opioid-related adverse events such as urinary retention, sedation, and nausea/vomiting

(*Continued*)

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Table 3. Continued

First Author, Year	Surgical Procedure	Treatment Group	Control Group(s) During Catheter Utilization	Primary Positive Findings During Catheter Use (Treatment Group Superior Unless Otherwise Noted)
Peng et al[216] (2014)	Total knee arthroplasty	Femoral ropivacaine 0.15% (n = 127) 5 mL/h + 5 mL [30]	No catheter (n = 123)	Less supplemental analgesics required and improved knee flexion during infusion, and lower incidence of chronic pain and improved knee flexion at 3 and 6 mo after surgery
Wu and Wong[197] (2014)	Total knee arthroplasty	Femoral levobupivacaine 0.08% (n = 30) 8–12 mL/h basal only	No catheter (n = 30)	Lower intravenous opioid requirements, fewer opioid-related side effects, improved satisfaction with analgesia, and increased ambulation ability
Sciatic catheters				
Elliot et al[200] (2010)	Hind foot or ankle surgery	Bupivacaine 0.25% (n = 27) 4 mL/h + 1 mL [60]	Normal saline (n = 27) 4 mL/h + 1 mL [60]	Lower pain scores and less supplemental analgesic requirements
Saporito et al[194] (2014)	Toes 2–5 osteotomy or hallux valgus correction	Ropivacaine 0.2% 5 mL/h + 5 mL PCB [60] Discharged day of surgery (n = 60)	Required to remain hospitalized 2 nights (n = 60)	Total costs of care were 79% lower in the early discharge group; no other differences between treatment groups including pain scores, complications, and readmission rates
Cappelleri et al[96] (2011)	Total knee arthroplasty	Continuous posterior lumbar plexus blocks for all subjects Subgluteal levobupivacaine 0.06% (n = 19) 0.1 mL/kg/h	Subgluteal normal saline (n = 19) 0.1 mL/kg/h	Lower resting and dynamic pain scores, less supplemental opioids, lower incidence of nausea and vomiting, improved knee flexion and ambulation
Sato et al[201] (2014)	Total knee arthroplasty	Continuous femoral nerve blocks for all subjects Subgluteal ropivacaine 0.2% (n = 30) 5 mL/h	Subgluteal normal saline (n = 30) 5 mL/h	Lower resting pain scores and less supplemental opioids
Wegener et al[97,220] (2011) and (2013)	Total knee arthroplasty	Continuous femoral nerve blocks for all subjects Parasacral levobupivacaine 0.125% (n = 30) 10 mL/h	• Parasacral single injection only (n = 30) • No block or catheter (n = 30)	Catheter group with lower dynamic pain scores compared with the other 2 treatment groups on postoperative days 1 and 2 during the infusion; and in a subset of the most initially disabled subjects preoperatively, joint stiffness was reduced at 3 and 12 mo, and dynamic pain reduced at 3 mo compared with the no block or catheter group

Due to publication limitations, includes selected reports published subsequent to a previously-published review article (Ilfeld[1]), and is not intended as an exhaustive list. In addition, investigations included in Table 2 are excluded.

NRS, numeric rating scale for pain (0–10, 0: no pain, 10: worst imaginable); PCB, patient-controlled bolus volume (lockout period in minutes).

[a]Infusions were discontinued morning of postoperative day 1 before endpoint evaluation.

BENEFITS

Novel indications for CPNB have been published within the past few years, suggesting benefits for an even wider array of morbidities.[13,15,20–24,28–36,47,61–65] New RCTs have provided evidence that adding a perineural infusion after a single-injection peripheral nerve block improves postoperative analgesia (and in most cases decreases supplemental analgesic requirements) using interscalene,[163,176,195] paravertebral,[167] adductor canal,[47,61–65] femoral,[196–199] and sciatic catheters (Table 3).[96,97,200,201] Compared with epidural infusions,[202] CPNB provides similar analgesia[203] but improves hemodynamic stability (presumably by inducing less sympathectomy)[27,204,205] and after knee arthroplasty shortens the time to achieve flexion goals, improves analgesia, and lowers supplemental analgesic requirements.[198] Compared with intrathecal morphine, continuous posterior lumbar plexus blocks provide similar analgesia with lower supplemental opioid requirements and incidence of pruritis.[206] Data continue to accumulate, demonstrating that CPNB provides superior analgesia compared with continuous wound infusions.[99,207,208]

Because of the association between continuous femoral nerve blocks and falling after knee arthroplasty,[51,52,54] the past 5 years have seen a plethora of research validating adductor canal catheter effectiveness after major knee surgery[47,61–65] based on the theory that any risk of falling will be decreased because of less induced quadriceps weakness compared with femoral infusion (Table 3).[50,59] Of the 6 RCTs directly comparing continuous adductor canal and femoral nerve blocks,[50,57–59,74,209] 3 demonstrated dramatic improvements for subjects with adductor catheters in the ability to stand, sit, ambulate, and climb stairs.[50,57,58,74] One study did not investigate ambulation[209]; but the 2 remaining RCTs failed to detect mobilization improvements using an adductor infusion—although they did document and quantify improved quadriceps femoris strength (52% vs 18% of baseline in one).[50,59] It is noteworthy that these 2 latter studies provided solely a fixed basal infusion (8 mL/h)

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without either patient-controlled or repeated provider-administered bolus doses,[50,59] which may have decreased adductor infusion effectiveness. In addition, 2 of the RCTs detected improved analgesia for subjects with femoral infusions at either rest (unicompartment arthroplasty)[57] or with movement (tricompartment arthroplasty),[58] whereas others failed to detect differences between the 2 catheter locations. Lastly, 1 of the investigations reported a decreased time until discharge favoring the adductor catheters (3.1 vs 3.9 days),[74] although there were issues raised regarding its protocol/findings[66–68] and a similar RCT detected no decrease in time until discharge readiness or actual discharge,[58] albeit with slightly different criteria. What does appear likely is that continuous adductor canal blocks are associated with greater mobilization ability while providing similar analgesia compared with their femoral counterparts.[60] What remains unclear is the ideal catheter insertion location/protocol,[70,71] optimal method of local anesthetic delivery (eg, basal infusion vs repeated bolus doses, basal rate, bolus volume), and if an optimized delivery regimen can shorten hospitalization duration.[144,210,211]

In an effort to further improve analgesia after total knee arthroplasty,[212,213] 3 recent RCTs have investigated the effects of adding a continuous sciatic nerve block to a continuous femoral or posterior lumbar plexus (psoas compartment) block.[96,97,201] All demonstrated lower pain scores and decreased supplemental analgesic consumption,[96,97,201] and 1 detected a lower incidence of nausea and vomiting as well as improved knee flexion and ambulation.[201] As has been previously opined, there are potential drawbacks to providing a continuous sciatic nerve block such as the extra time required to place a second catheter, an inability to fully evaluate sciatic nerve function postoperatively,[214] and interference with physical therapy goals (eg, foot drop, leg weakness).[215]

Although there are relatively few demonstrated benefits of CPNB after catheter removal,[1] there are significant additions to our knowledge base within recently published data. Two RCTs found that a 2- to 3-day postoperative continuous interscalene or femoral nerve block resulted in less pain,[176,216] opioid requirements,[176,216] and sleep disturbances[176] on postoperative day 7 compared with a control group after shoulder and knee procedures, respectively. Similarly, 2 RCTs add to the previous evidence that a continuous femoral nerve block after total knee arthroplasty improves joint flexion for up to 6 months.[198,216]

However, it is the possibility of decreasing persistent postsurgical pain that has perhaps garnered the most attention and optimism.[217,218] Four new RCTs add data to the single previous positive study that involved the addition of a femoral catheter to a popliteal infusion for major ankle surgery.[219] One study reported that providing a continuous femoral nerve block after total knee arthroplasty reduced chronic pain at 3 and 6 months,[216] and another involving the same surgical procedure found that providing a continuous sciatic nerve block in addition to a femoral infusion resulted in a reduction of dynamic pain at 3 months (no difference at 12 months for either trial).[220] Finally, 2 RCTs investigating continuous paravertebral blocks after mastectomy detected improvements in analgesia up to a full year after surgery,[177,221] including superior physical and mental health-related quality of life[221] and decreased pain-related physical and emotional dysfunction.[177]

COMPLICATIONS

Probably the largest change in the CPNB literature of the past 5 to 6 years is the proportion of reports involving ultrasound guidance versus nerve stimulation with the former now eclipsing the latter to an overwhelming degree. This is undoubtedly multifactorial; but a predominant reason is probably that the risk of inaccurate and/or difficult catheter insertion is, on average, decreased with the use of ultrasound guidance.[1,87] However, the incidence for all CPNB-related complications can vary dramatically, most likely because of heterogeneous catheter insertion equipment, techniques, anatomic locations, and infusion protocols. For example, the reported frequency of catheter failure over the past few years varies between 0.5% and 26%.[79,222] Accordingly, precise complication rates will not necessarily be widely applicable. This section reviews reports of adverse events published since the previous review article,[1] and readers are directed to that report for a complete examination of all possible complications.

Relatively few complications during insertion have been reported in recent years, perhaps because of the widespread adoption of ultrasound guidance (or possibly because all the adverse events had been previously published). However, new cases do include the inadvertent penetration of the epidural space[113,223] and a catastrophic incident involving an unidentified intrathecal placement bolused on the wards.[224,225] In addition, a single report describes the potential contamination of the surgical site caused by leakage from an interscalene catheter with the patient in a seated position.[226] In contrast, reports of adverse events occurring during infusion are more common, including those reported previously such as hoarseness,[227] dyspnea,[169,228] and respiratory distress[229] associated with continuous interscalene nerve blocks.[168] Although 1 healthy-volunteer study reported a catheter dislocation rate of 25% and 5% for femoral and interscalene catheters, respectively, over a period of 5 hours,[230] the incidence of dislodgement reported in both RCTs and large series is dramatically lower,[77,168]even for ambulatory pediatric patients.[79] Leakage at the catheter site continues to be an issue in a small minority of cases,[79,168] but 2-octyl cyanoacrylate glue can decrease this problem by a factor of 10.[231]

One case report describes a patient with an ambulatory popliteal sciatic block who fractured a metatarsal 2 days into the infusion, which was recognized only after the catheter was removed the next day.[174] In contrast, it is reassuring that there is 1 case of limb ischemia because of a surgically induced axillary artery injury and 3 reports of compartment syndrome all identified in a timely fashion by breakthrough pain not masked by the presence of a CPNB.[232–235]

Catheters have been accidentally cut during tunneling,[236] suture removal,[237] and for unknown reasons (most likely catheter withdrawal into the needle).[238] Although it is common to leave a fractured epidural catheter remnant in situ, health care providers should be cognizant that many perineural catheters contain coiled wire, which is

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at risk for heating during subsequent magnetic resonance imaging.[239] Catheter retention during withdrawal can also occur caused by a perineural loop,[165] knot,[240] kink,[241,242] or adherence.[171,179,243–247] Although multiple catheter designs have been involved with retained catheter reports,[240,242] it is notable that within the past few years, 1 specific stimulating catheter (StimuCath; Teleflex, Morrisville, NC) has been overwhelmingly the predominant model described: 9 publications reporting a total of 18 separate cases.[165,171,179,241,243–247] One investigator opined referring to these case reports, "While stimulating peripheral nerve catheters do have clinical utility, the expanding body of literature describing catheter entrapment is worrisome."[248]

Regarding infusion-induced local anesthetic toxicity, both older[1] and more recent evidence suggest that perineural infusion-induced local anesthetic toxicity is very rare.[159,249] Similarly, major hematoma formation is extraordinarily infrequent and usually occurs in the presence of anticoagulation and/or comorbidity such as myeloproliferative thrombocytosis.[250] There is limited new information regarding the concurrent use of anticoagulants and perineural catheters,[251–253] and no new recommendations from the American Society of Regional Anesthesia and Pain Medicine have been published since the previous review article.[254,255] Of note, some investigators have advocated replacing epidural with paravertebral or TAP catheters in certain situations[256] based on the theoretical premise that a hematoma in the peripheral nervous system carries less risk of catastrophic nerve injury.[35,37] Minimal information regarding CPNB-related infection has been published in recent years,[77,79,168] other than the identification of diabetes and obesity as risk factors for catheter-associated infection[257,258] and a few new cases of previously described related complications such as abscess formation.[259–262] Of note, although the incidence of infection increases with infusion duration, there remains no "maximum" time period for a perineural catheter (although there are various regulations regarding the maximum duration of local anesthetic contained within a reservoir); and the longest reported infusion of 88 days was recently published.[7]

In contrast, there has been a significant amount of data published in the past few years involving neurologic risk in the presence of a CPNB.[263] In most cases of postoperative neurologic symptoms (PONS), it is problematic assigning causality to the surgical procedure, CPNB, or simply perioperative injuries (eg, tourniquet or positioning injuries on an unrelated part of the body). Interpreting the available data is further complicated because of a lack of controls and/or randomization, which lead to multiple types of bias. An excellent example is a prospective, uncontrolled cohort study of patients with continuous popliteal sciatic nerve blocks (n = 151) after foot and ankle surgery reporting an alarming 41% incidence of PONS within 2 weeks, 24% at 34 weeks, and 4% after 48 weeks.[264] A similar retrospective study (n = 157) found a 1.9% incidence of unresolved PONS at 11 months.[265] These risks are an order of magnitude higher than previous estimates for popliteal infusions (0%–0.4%)[266,267] and are most likely because of numerous biases, beginning with selection bias.

Another relatively new retrospective investigation of 1182 continuous interscalene and femoral nerve blocks identified 4 (0.3%) patients with PONS at any time point, with 1 of these cases resolving by 6 months.[268] Of note, these investigators reported an increased incidence of PONS lasting >6 months among patients with continuous versus single-injection peripheral nerve blocks (0.24% vs 0.07%; $P = .08$).[268] It is important to be aware of the very high risk of selection bias from this retrospective, nonrandomized cohort (eg, larger surgical procedures—with inherently higher neurologic risk—more represented in the catheter group). The most reliable, recently published data are derived from 2 prospective investigations of over 2500 interscalene and femoral catheters, reporting a PONS incidence of 4.9% to 5.3% resolving by 6 months with all but 0.3% to 0.7% of these resolving by 11 months.[168,269] To emphasize, it is critical that practitioners are cognizant of the fact that these values approximate association and not necessarily causation: an unknown percentage of subjects with PONS would have experienced them without any regional analgesic because of the surgery itself or other factors. Unfortunately, the available data do not suggest that ultrasound guidance has a "meaningful impact on the incidence of PONS," so switching from a different insertion technique is not expected to decrease the rate of PONS.[270]

The risk of falling after knee and hip arthroplasty has become better appreciated within the previous decade.[271,272] Single-injection femoral nerve blocks do not appear to increase this risk[273]; but data from randomized, controlled trials suggest that a continuous femoral or psoas compartment block is associated with a 4 to 5 times increased risk of falling,[51,54,274] although some investigators have questioned this correlation.[275,276] Regardless of the relationship between CPNB and falls, this complication continues to occur even with the implementation of specific, intensive fall prevention programs.[52,56,277,278] Although replacing continuous femoral nerve blocks with adductor canal infusions have been proposed as a method to decrease the risk of falling because of decreases induced quadriceps weakness,[50,59] such an association has yet to be demonstrated.[59,279]

ALTERNATIVE MODALITIES

While perineural infusion has become accepted and now routine within anesthesiology, there are a number of novel, alternative analgesic modalities either currently available or under development/investigation. Although numerous analgesic possibilities are available,[99,207,280–282] publication limitations prohibit inclusion of every option.[182] The current article compares and contrasts 4 of the most novel analgesic alternatives to CPNB.

LOCAL ANESTHETIC ADJUVANTS

Single-injection peripheral nerve blocks have multiple benefits over their continuous infusion counterparts, including less time required for administration, management, follow-up; lower risk of infection; no risk of leakage, catheter dislodgement, or pump malfunction; and simply cost. Of course, the reason that CPNB is used despite these relative disadvantages is that the duration of treatment effects may be prolonged beyond the duration of a single-injection peripheral nerve block.[1] However, a single-injection block with a similar duration to what is possible with CPNB

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would provide the benefits of a 1-shot block without the drawbacks of a perineural catheter and infusion.[283] Toward this end, multiple medications—some in just the past few years—have been combined with (and without) local anesthetic, including opioids,[284–287] clonidine,[288,289] dexmedetomidine,[290,291] dexamethasone,[292–294] epinephrine, magnesium, midazolam, and tramadol.[295]

Unfortunately, most reported adjuvants prolong analgesia by fewer than 12 hours[295,296] with even the most effective—buprenorphine and dexamethasone—reliably providing <24 hours of pain control.[284–287,297] Many of the additives may increase the incidence of side effects such as pruritis,[298] nausea/vomiting,[287,298] hypotension,[288] bradycardia,[288,295] and sedation.[288,295] Optimal doses remain unknown,[299] and the risk of neurotoxicity remains a concern for multiple agents.[295] Importantly, because systemic administration may result in similar or even superior[300] prolongation of analgesic benefits versus perineural administration[291,301–303]—although there are exceptions[286,304]—and there is no adjuvant currently approved by the US FDA for perineural administration, the risk–benefit ratio of perineural administration remains in question at the time of this writing.

While there are no direct comparisons of CPNB and single-injection blocks including an adjuvant, it is unlikely that such studies will be conducted because most perineural catheters are inserted for use of at least 2 days,[1] and no adjuvant given by any route of administration has been shown to reliably extend analgesia even 1 full day. The 2 techniques do not, in fact, "compete" but are instead complementary, depending on the desired duration of block effects.

LIPOSOME LOCAL ANESTHETIC

Liposomes consist of 2 hydrophobic tails and a hydrophilic head[305] and can form vesicles to act as a medication "depot" (Figure 1).[306,307] After administration, the liposomes gradually break down, resulting in an extended release of medication.[308,309] Combining liposomes and a local anesthetic (lidocaine) was first proposed in 1979,[310] initially used in humans in 1988,[311] and first reported for postoperative analgesia in 1994.[310,312] Although multiple subsequent reports were published,[313–321] a liposome local anesthetic was not approved by the US FDA until 2011 (Exparel liposome bupivacaine; Pacira Pharmaceuticals, Parsippany, NJ) for administration at the surgical site to provide postoperative analgesia in adults.[307]

Two multicenter RCTs demonstrated superior postoperative analgesia of this approved medication compared with placebo wound infiltration after hemorrhoidectomy[322] and bunionectomy.[323] In contrast, when compared with bupivacaine HCl ("standard" bupivacaine), 10 of the 12 currently published RCTs were negative for their primary (and most secondary) analgesic end points.[324–330] Of the 2 positive RCTs versus bupivacaine HCl, 1 involved hemorrhoidectomy,[331] although another similar trial had negative results.[324] The second positive RCT involved submuscular augmentation mammaplasty in which mean pain scores were reduced by <1 on the 0 to 10 numeric rating scale and the investigators concluded, "…it is our assertion that the additional cost of liposomal bupivacaine is unjustified for this particular use."[332] Some of these 14 RCTs were dose–response studies, not powered to be a conclusive test of efficacy; and when combined with the placebo-controlled trials, there were some detected positive associations for secondary endpoints such as pain scores at individual time points,[333] opioid use (although differences were minimal),[333] and duration until first use of opioid analgesics.[324,333] However, considering the new medication costs an estimated 100 times that of bupivacaine HCl, it is incumbent on those proposing the conversion to produce data conclusively demonstrating superiority.[330] Various large RCTs currently ongoing should provide much-needed data to help practitioners make evidence-based decisions involving this analgesic modality (ClinicalTrials.gov NCT02713490, NCT02111746, NCT02197273).

There are no RCTs directly comparing CPNB with liposome bupivacaine wound infiltration.[334] The only direct comparison to a single-injection femoral nerve block after total knee arthroplasty suggests that liposome bupivacaine

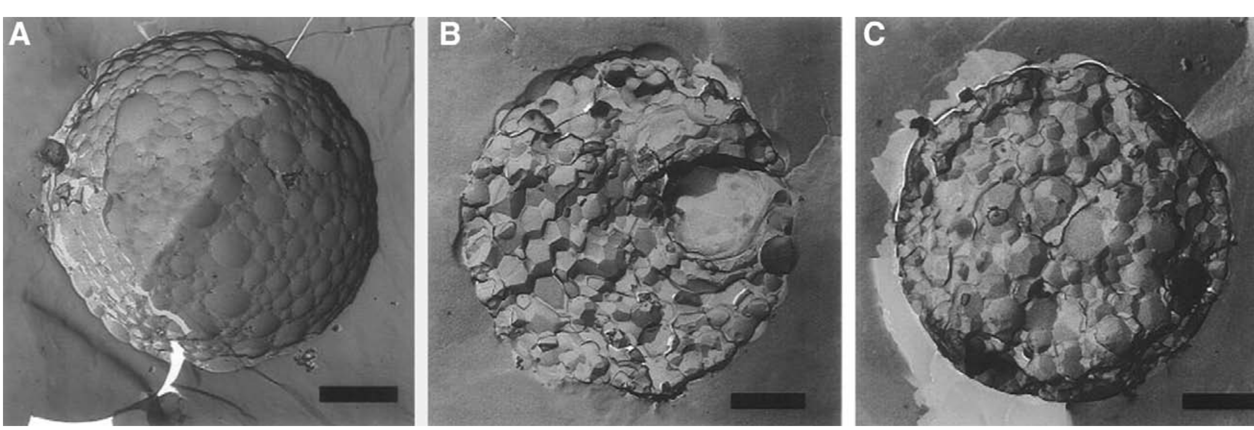

Figure 1. Liposome local anesthetic: (A) electron micrograph of a replica showing the outer surface of a multivesicular liposome. The abrupt change in the gray scale near the center of the multivesicular liposome is because of the shadowing effect of the freeze-fracture replica. The white region near the bottom is a crack in the replica, and (B and C) electron micrographs of freeze-fracture replicas showing cross sections through 2 multivesicular liposomes. The multivesicular liposomes are, on average, approximately 10 μm in diameter. The polyhedral interior compartments range from approximately 100 nm to several micrometers. The bars represent 2 μm. Reprinted with permission from Spector MS, Zasadzinski JA. Topology of multivesicular liposomes, a model biliquid foam. *Langmuir*. 1996;12:4704–4708. Copyright 1996 American Chemical Society.

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infiltration provides inferior analgesia during the duration of the peripheral nerve block without subsequent analgesic differences between the 2 treatments.[335] Considering that there are now 4 negative published RCTs comparing liposome bupivacaine with bupivacaine HCl infiltration after total knee arthroplasty,[324,326–328] and the literature is replete with positive studies involving CPNB,[1] the evidence certainly does not suggest even equivalence between these 2 modalities.

In contrast to wound infiltration, recently published data from 1 RCT strongly suggest that liposome bupivacaine within a single-injection subcostal TAP block provides statistically and clinically superior analgesia to bupivacaine HCl up to 3 days after robotic-assisted hysterectomy.[336] In a separate RCT, few differences were detected between a continuous subcostal TAP block and epidural infusion after open renal or hepatobiliary surgery,[36] although this investigation was designed as a superiority study and the negative findings should be viewed as inconclusive and not equivalent. Therefore, a randomized comparison of a TAP with liposome bupivacaine bolus compared with either an epidural infusion or a perineural local anesthetic TAP infusion appears warranted.[337,338] Of note, the US FDA recently revised the label for the single approved liposome bupivacaine formulation explicitly including, "infiltration into the transversus abdominis plane (TAP) which is a field block technique [is] covered by the approved indication for EXPAREL."

Although no liposome local anesthetic is currently approved for use within the epidural space[339] or peripheral nerve blocks, a great deal of related research has been completed (if not all published).[307] Both preclinical toxicology and clinical data indicate that liposome bupivacaine has a safety profile at least as favorable as bupivacaine HCl.[340–350] Although phase 1 to 3 clinical trials involving the use of liposome bupivacaine have been reported for intercostal and ankle blocks,[306,307,340] the most published data may be found for femoral nerve blocks.[351,352] No direct comparisons with CPNB are available, but liposome bupivacaine in a femoral nerve block produced over 72 hours of analgesia with an incomplete motor block in healthy volunteers[351] and demonstrated analgesic activity for up to 72 hours versus placebo in subjects after total knee arthroplasty (albeit extraordinarily minimal analgesic differences after 24 hours).[352] Further sizable RCTs involving adductor canal, brachial plexus, and femoral nerve blocks with liposome bupivacaine are ongoing (ClinicalTrials.gov NCT02607579, NCT02713230, NCT02713178).

Theoretical benefits over CPNB include the avoidance of catheter insertion (eg, less procedure time, no catheter management/removal), the lack of an infusion pump and anesthetic reservoir to purchase/carry, a lower risk of infection, and no risk of catheter dislodgement or leakage.[353] It is emphasized that at the time of this writing, there are no liposome bupivacaine local anesthetics approved for use in the epidural space[339] or peripheral nerve blocks (other than the possible exception of TAP blocks, depending on how this block is categorized).

CRYOANALGESIA

Cryoneurolysis is the application of exceptionally low temperatures to reversibly ablate peripheral nerves, resulting in temporary analgesia termed "cryoanalgesia."[354] The first cryosurgical apparatus was described in 1961,[355] and modern cryoprobes transmit a gas (usually nitrous oxide or carbon dioxide) at high pressure down their length, through a minute opening, and into the sealed distal tip at a lower pressure (Figure 2A).[356] Explained by the Joule-Thomson effect, a large drop in temperature occurs when the gas moves from a high to low pressure inducing brisk expansion and absorption of heat.[357] The gas is returned out of the body through a larger diameter (low pressure) cylinder in the middle of the shaft. This closed circuit ensures that all gas exits the body. The intense cold temperature at the probe tip produces Wallerian degeneration—a reversible breakdown of the nerve axon—subsequently inhibiting transmission of afferent and efferent signals. However, because the temperature resulting in irreversible degeneration—approximately −100°C—is colder than the boiling point of the gas (carbon dioxide: −79°C;

Figure 2. Cryoanalgesia: (A) the Joule-Thomson effect producing very cold temperatures resulting from gas flowing from a high- to low-pressure chamber (used with permission from B.M.I.), and (B) a portable cryoneurolytic device (Iovera; Myoscience, Fremont, CA). Inset: 3-needle tip for cryoneurolysis of superficial nerves.

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nitrous oxide: −88°C), the remaining endoneurium, perineurium, and epineurium remain intact and the axon regenerates at a rate of approximately 1 to 2 mm/d.[356]

Cryoneurolysis has been used via the surgical incision to treat acute pain after thoracotomy,[358–374] tonsillectomy,[375] and herniorrhaphy.[376,377] Alternatively, ultrasound may be used to guide[378,379] a percutaneously inserted probe to a peripheral nerve to provide analgesia and has been described for various chronic pain conditions.[380–385] The combination of ultrasound and newly designed, FDA-approved handheld cryoneurolysis devices[386,387] may now make percutaneous cryoanalgesia a valuable postoperative analgesic alternative to CPNB (Figure 2B).[354] The largest limiting factors when applying this technique to acute pain states are (1) the inhibition of efferent signals effectively paralyzing innervated muscles; and (2) the relatively unpredictable duration of action measured in multiple weeks and often months. Therefore, the modality has historically been used to target sensory-only nerves,[388] although mixed motor–sensory nerves have been cryoablated to treat spasticity,[389] and preclinical studies found no lasting changes to the structure or function of motor nerves after remyelination.[386,387]

Surgical procedures possibly amenable to cryoneurolysis include iliac crest bone harvesting (superficial superior cluneal nerves), total knee arthroplasty (anterior femoral cutaneous and infrapatellar saphenous nerves), various thumb surgeries (superficial branch of the radial nerve), rotator cuff repair (suprascapular nerve), and digit/limb amputations, among others.[354,356] Although there are available cryoneurolysis devices currently approved by the US FDA for relief of pain, the use of cryoanalgesia to treat acute pain requires a great deal of further investigation with both RCTs and large series. It remains undetermined whether the duration of denervation can be shortened (eg, decreasing the freezing interval or number of cycles) and the incidence of adverse events such as neuralgias after thoracotomy.[372–374] Direct comparisons with CPNB are unavailable, but some theoretical benefits of cryoneurolysis include an ultralong duration of action, no catheter management/removal, the lack of an infusion pump and anesthetic reservoir to carry, a lower risk of infection, and no risk of local anesthetic toxicity, catheter dislodgement, or leakage.

PERCUTANEOUS PERIPHERAL NERVE STIMULATION

Electric current applied in both the central and the peripheral nervous systems induces analgesia. There are numerous theories regarding the mechanism of action,[390] but most are usually based on "gate control theory" by Melzack and Wall[391]: current activates large-diameter myelinated afferent peripheral nerves which then—within the spinal cord—impede pain signal transmission from small-diameter pain fibers to the central nervous system.[392,393] Implanted spinal cord and peripheral nerve stimulators have since been used to treat multiple chronic pain states.[394–398] In contrast, the use of peripheral nerve stimulation to treat acute/postoperative pain is extraordinarily rare,[399–401] in no small part because of cutaneous pain fiber activation with transcutaneous electrical nerve stimulation[392] and the invasive requirement of surgically implanting/removing peripheral nerve electrodes/leads.[402,403]

Electrical leads are now available with a diameter small enough to allow passage through a needle, allowing percutaneous insertion (Figure 3A).[404–409] Precise placement is possible using ultrasound guidance[410,411] and has been reported to treat chronic pain.[412–415] More recently, postoperative pain was treated using ultrasound-guided percutaneous peripheral nerve stimulation.[416–416c] In one report, femoral—and in 2 cases sciatic—leads were inserted in subjects (n = 5) 8 to 58 days after total knee arthroplasty.[416] Percutaneous peripheral nerve stimulation decreased pain an average of 93% at

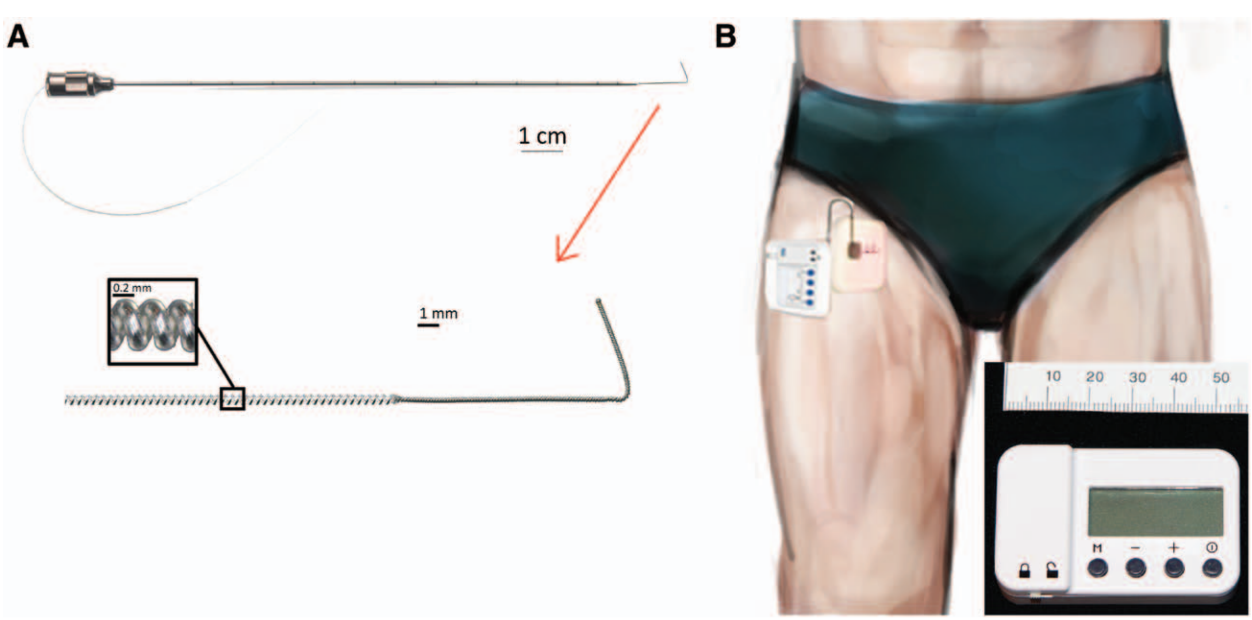

Figure 3. Percutaneous peripheral nerve stimulation: (A) a preloaded, small-diameter (0.2 mm), open-coiled, helical electrical lead with an anchoring wire preloaded within the 12.5-cm, 20-g insertion needle (MicroLead; SPR Therapeutics, Cleveland, OH) and (inset) a small-diameter (0.2 mm), open-coiled, helical electrical lead with an anchoring wire (MicroLead; SPR Therapeutics); and (B) a stimulator small enough to be simply adhered to the skin during use (SPR Therapeutics) (both used with permission from B.M.I.).

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rest (reduced from a mean of 5.0 to 0.2 on a 0–10 numeric rating scale) with 4 of 5 subjects experiencing complete resolution of pain. During passive and active knee motion, pain decreased an average of 27% and 30%, respectively. Neither maximum passive nor active knee range of motion was consistently affected in this small cohort of subjects.

There are no direct comparisons with CPNB, but theoretical benefits of percutaneous peripheral nerve stimulation are numerous.[416d] Leads function optimally when inserted 0.5 to 3.0 cm from a target peripheral nerve, negating the importance of location within a particular facial plane. Electrical generators are now so minute that their footprint is smaller than a business card and may be literally adhered to a patient's limb, so there is no large portable infusion pump or local anesthetic reservoir to carry (Figure 3B). Helically coiled leads are designed to minimize the risks of migration and fracture and decrease the infection risk to approximately 0.03 per 1000 indwelling days (or 1 infection for approximately every 33,000 indwelling days).[416c] These characteristics permit a dramatically long duration of lead retention—well over a year in some cases[417–419]—raising the possibility of preoperative insertion and continued postoperative stimulation for the entire interval of surgically related pain.[417–421] There are theoretically no induced sensory, proprioception, or motor deficits, enabling full engagement in physical therapy and likely lacking any association with an increased falling risk. Obviously, there is no risk of local anesthetic toxicity or leakage. Conversely, practical implementation of percutaneous peripheral nerve stimulation to treat acute pain states is dependent on multiple factors that are currently undetermined: the time required for lead insertion, clinical efficacy and applicability, adverse event rate, the cost of leads and electrical generators, the maximum provided analgesia, and the future commercial availability of US FDA-approved equipment specifically approved for the treatment of acute pain.[415,422]

CONCLUSIONS

Although the recently published evidence presented in this review helps to clarify questions previously unanswered, many unknown aspects of CPNB persist. Although the data demonstrating perineural local anesthetic infusion's many benefits continue to grow in quality, breadth, and depth, both older[280,282,298,423] and novel[307,352,354,424] analgesic alternatives must be considered and investigated. Only through persistent, unbiased investigation will we be able to optimize analgesia for patients, whether from CPNB or an alternative modality.[425]

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Contribution: This author helped design the study, conduct the study, and write the manuscript.
Attestation: Brian M. Ilfeld approved the final manuscript.
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