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CASE REPORTS / CASE SERIES

Neuromodulation using a hybrid technique of combined perineural local anesthetic and nerve stimulation in six challenging clinical scenarios

Neuromodulation à l'aide d'une technique hybride d'anesthésie locale périnerveuse combinée et de stimulation nerveuse dans six scénarios cliniques difficiles

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Abstract

Purpose *Postamputation pain is challenging because of complex mechanisms involving a multitude of pain pathways and psychological factors. This patient population also tends to have extensive comorbidities with or without a background of chronic pain. Electrical neuromodulation such as peripheral nerve stimulation has gained traction in the realm of chronic pain. Recently, the off-label use of hybrid perineural nerve stimulation in combination with locoregional block via the stimulating nerve block catheter has been described in single-center case reports.*

Clinical features *Herein, we present a case series of six patients from two different Canadian hospitals using such a hybrid technique in three different clinical scenarios. These scenarios were (1) local anesthetic dose minimization in the presence of multiple nerve block catheters, (2) analgesia augmentation when local anesthetic alone is insufficient, and (3) provision of an analgesic adjunct as part of a multimodal regimen. A stimulating sciatic nerve block catheter was inserted under ultrasound and nerve stimulation guidance for these cases. Patients tended to experience pain on the subsequent postoperative days whereby the off-label use of nerve stimulation successfully reduced their pain score and stabilized or decreased their opioid consumption or minimized the need to increase the local anesthetic dose when doing so could have precipitated local anesthetic toxicity.*

Conclusion *Our case series supports the feasibility of using a combination of low-frequency perineural stimulation and local anesthetic infusion via a single perineural nerve block catheter to manage challenging postamputation pain.*

Résumé

Objectif *La douleur post-amputation est difficile à soulager en raison de mécanismes complexes impliquant une multitude de voies de la douleur et de facteurs psychologiques. Cette population de patients a également tendance à présenter de nombreuses comorbidités, avec ou sans antécédents de douleur chronique. Les techniques de neuromodulation électrique, telle que la stimulation*

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nerveuse périphérique, sont de plus en plus populaires dans le domaine de la douleur chronique. Récemment, des présentations de cas monocentriques ont décrit l'utilisation hors indication d'une modalité hybride de stimulation nerveuse périneurale en combinaison avec un bloc locorégional via un cathéter de bloc nerveux stimulant.

Caractéristiques cliniques *Nous présentons ici une série de cas de six patients de deux hôpitaux canadiens différents utilisant une telle technique hybride dans trois cas cliniques différents. Ces cas étaient (1) la minimisation de la dose d'anesthésique local en présence de plusieurs cathéters de blocs nerveux, (2) l'augmentation de l'analgésie lorsque l'anesthésique local seul était insuffisant, et (3) la fourniture d'un adjuvant analgésique dans le cadre d'un régime multimodal. Un cathéter stimulant pour l'administration d'un bloc du nerf sciatique a été inséré sous échoguidage et guide de stimulation nerveuse pour ces cas. Les patients ont eu tendance à ressentir de la douleur les jours postopératoires suivants, et l'utilisation hors indication de la stimulation nerveuse a alors réussi à réduire leur score de douleur, à stabiliser ou diminuer leur consommation d'opioïdes, ou à réduire la nécessité d'augmenter la dose d'anesthésique local alors que cela aurait pu précipiter une toxicité anesthésique locale.*

Conclusion *Notre série de cas soutient la faisabilité de l'utilisation d'une technique combinée de stimulation périnerveuse à basse fréquence et de perfusion d'anesthésique local via un seul cathéter de bloc nerveux périneural pour prendre en charge la douleur post-amputation.*

Keywords hybrid technique · nerve stimulation · neuromodulation

A recent systematic review of the efficacy and safety of *high-frequency* peripheral nerve stimulation (PNS) in chronic pain indicates that the technique may be effective in managing postamputation pain.[1–3] Recently, we have reported success in using an off-label hybrid method of combining simultaneous perineural local anesthetic (LA) infusion with brief, intermittent *low-frequency* PNS in patients undergoing below-knee amputations (BKA).[4–7] Here, we report on six patients who received the hybrid technique as a rescue analgesia management for their postamputation at two Canadian hospitals. All patients had provided written informed consent and were aware of this off-label intervention's clearly stated unknown effectiveness and safety profile.

Case series

Written informed consent was obtained from all patients for publication. Patients undergoing BKA were perioperatively treated with stimulating sciatic nerve catheters (E-Cath® Stim Cath, PAJUNK® GmbH Medizintechnologie, Geisingen, Germany). A stimulating catheter was inserted preoperatively under ultrasound and nerve stimulator guidance with the motor response aiming at less than 1 mA to ensure the catheter was near the nerve. The Table summarizes the demographic features of these patients and other significant data. The following cases illustrate the benefits of PNS (one-hour trials of 2 Hz, 0.1 msec, 0.5 mA)[8] via their *in situ* sciatic-stimulating catheters in three challenging scenarios: (1) minimizing risks of local anesthetic systemic toxicity (LAST) with LA infusion via multiple nerve block catheters; (2) augmenting analgesia when LA alone insufficiently manages severe pain (numerical rating scale score [NRS] $>$ 7); and (3) provision of an analgesic adjunct as part of an opioid-sparing multimodal strategy.

Minimizing risks of local anesthetic systemic toxicity

Case 1 A 37-yr-old lady with obesity, diabetes, acute renal impairment, and alcohol abuse underwent bilateral BKA after having sustained frostbite. Bilateral nonstimulating femoral nerve catheters were placed preoperatively. Because of patient discomfort in positioning, only a right-sided proximal sciatic nerve block catheter was inserted preoperatively with an initial stimulating current of 0.2 mA that was increased up to 1 mA in 0.1-mA increments until the patient felt paresthesia in the foot. No motor response was noted at the time. The inner needle was removed and replaced by the inner stimulating catheter, and the current was increased to 1.5 mA for paresthesia. Despite LA injected preoperatively and postoperatively, the patient in the postanesthesia recovery unit (PACU) complained of severe pain mostly from the left stump (NRS of 8/10), where only the femoral nerve block catheter was present. A left popliteal nerve block catheter was inserted. Fifteen mL of LA (1% ropivacaine and 0.25% bupivacaine, mixed 1:1) was injected. To minimize the risk of LAST, LA infusion (1 mL every hour with two-hourly intermittent boluses of 15 mL of 0.2% ropivacaine via the sciatic nerve catheter and 10 mL of 0.2% ropivacaine via the femoral nerve catheter) was also commenced, with the bolus dose staggering an hour apart between the two nerve catheters. She was comfortable overnight. Nevertheless, despite an LA bolus the following morning, she complained of severe pain. She reported paresthesia below the knee without clear sensory changes when checked with ice. Due to concern about

Table 1 Patient demographics, comorbidities, and perioperative analgesic of patients in the case series

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (yr)	37	82	86	57	41	68
Sex	F	M	M	M	M	F
Weight (kg)	112	93	86	88	89	90
Height (cm)	170	175	183	184	186	165
Body mass index ($kg \cdot m^{-2}$)	38.7	30.5	25.8	25.8	25.6	33.2
ASA	2	3	4	3	3	3
Medical history	Diabetes, obesity, acute renal impairment, alcohol abuse	Diabetes, obesity, OSA, coronary artery disease, peripheral vascular disease	Hypertension, acute renal impairment, polycythemia	Diabetes, coronary artery disease, hypertension	Peripheral vascular disease, alcohol abuse, fatty liver disease, hypertension, anxiety, post-traumatic stress disorder, diabetes, peptic ulcer disease, dyslipidemia	Peripheral vascular disease, coronary artery disease, cerebral vascular disease, diabetes, chronic renal disease, hypertension, breast cancer
Chronic opioid use and other analgesics preoperatively	None	30 mg morphine milligram equivalence and gabapentin 300 mg TID	Tramadol long-acting 300 mg daily	No opioids but gabapentin preoperatively 300 mg TID	No opioid but only gabapentin	None

ASA = American Society of Anesthesiologists Physical Status classification; F = female; M = male; OSA = obstructive sleep apnea; TID = three times per day

reaching LA systemic toxicity, PNS (2 Hz, 0.1 msec, 0.5 mA) via bilateral sciatic-stimulating catheters as an off-label trial to manage her pain was discussed and agreed upon. After an hour, she reported a reduction of NRS from 8 to 4. Nevertheless, the effect was short lived and she requested PNS on postoperative day (POD) 2 as her pain intensity was increasing by late morning. The same stimulation setting was used for an hour, resulting in acceptable pain relief. Her morphine consumption was 45 mg on POD 1, 55 mg on POD 2, and 30 mg on POD 3. On POD 3, she described perioral paresthesia and signs of potential LAST. Local anesthetic infusion was discontinued. Nevertheless, nerve catheters were left *in situ* in anticipation of further PNS, although none was warranted. Her pain score at POD 5 was much less than her score preoperatively, and no opioid use was reported four months after her surgery.

Augmenting analgesia when local anesthetic alone is insufficient (cases 2, 3, and 4)

Case 2 An 82-yr-old diabetic man with persistent right leg pain required 6 mg hydromorphone daily and 300 mg gabapentin three times a day before BKA surgery. His other significant comorbidities included sleep apnea and coronary artery disease. A stimulating popliteal sciatic nerve block catheter was inserted. An intermittent bolus of 15 mL 0.2% ropivacaine every two hours via an infusion pump was commenced postoperatively. The next day, the patient cried secondary to significant pain and the sensory assessment was inconsistent. After reviewing the risks, he agreed to one-hour off-label PNS via the popliteal sciatic nerve block catheter. Following the PNS, he sat up, smiled, and reported less discomfort (NRS decreased from 10 to 6). He requested additional opioids three hours later. His pain score decreased (Figure), but his opioid use remained high (Electronic Supplementary Material, eAppendix). Following discussion, further one-hour perineural nerve stimulation was performed on POD 4 to reduce opioid requirement, and he requested an additional opioid six hours after. The catheter was removed the following day. His pain score returned to that preoperatively on POD 5. Four months after his surgery, his hydromorphone requirement increased by 2 mg daily compared with preoperatively.

Case 3 An 87-yr-old man with controlled hypertension and renal insufficiency underwent left BKA. Nonstimulating femoral and stimulating popliteal nerve catheters were inserted preoperatively under ultrasound ± nerve stimulation guidance. On POD 1, the patient

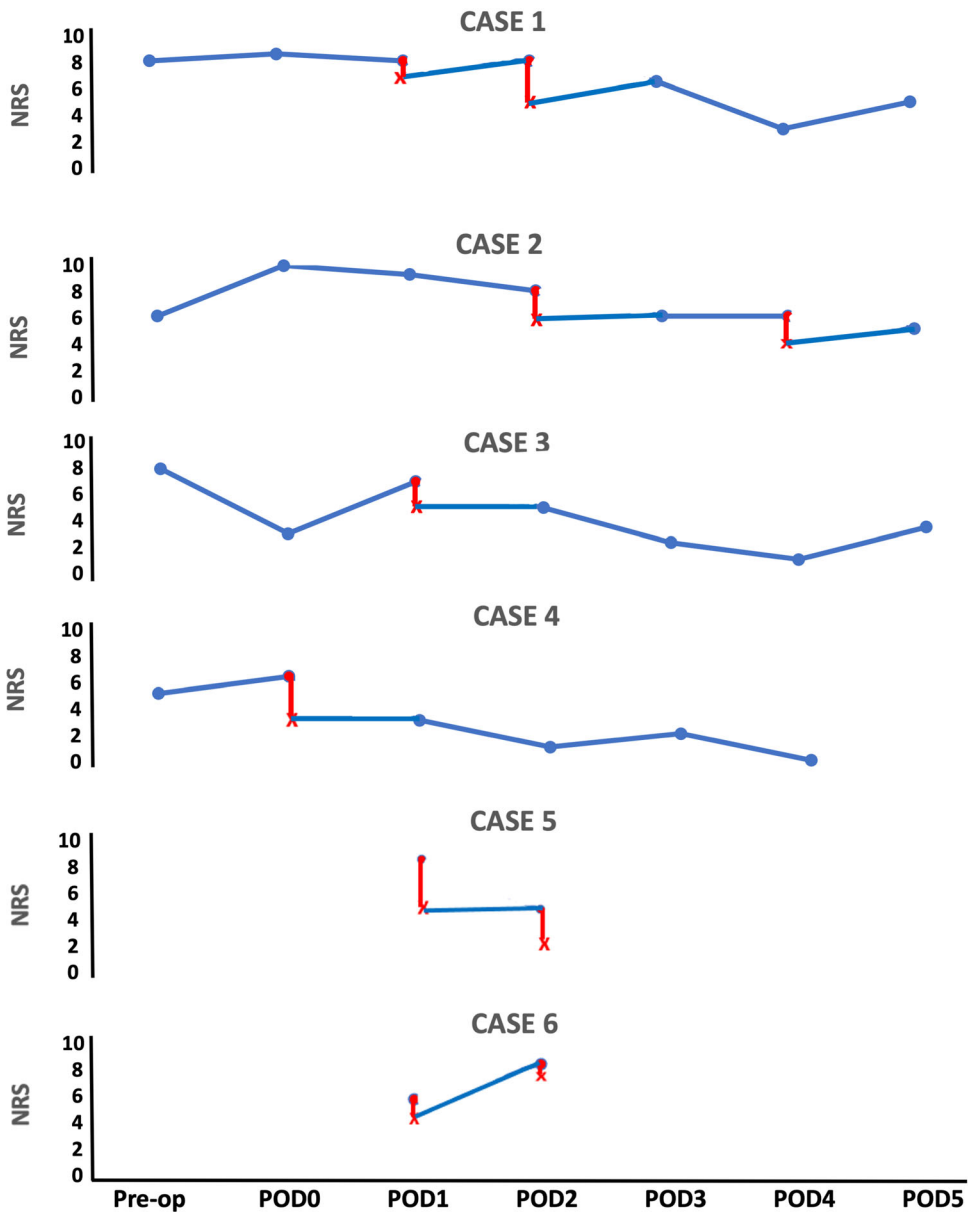

Figure Line graph showing the pain score (numeric rating scale) for six patients before and after nerve stimulation following below-knee amputation. ● Pain score before nerve stimulation. X Pain score after nerve stimulation

complained of significant stump pain not relieved by LA bolus despite decreased sensation with ice check. He did not want a higher dose of opioids to avoid confusion. Therefore, PNS was proposed and agreed as an off-label pain management option. Following PNS for an hour, he was comfortable with a reduced opioid consumption and an NRS pain score of 1–2. On POD 5, his pain score was much less than that preoperatively. He did not require opioids almost a year postoperatively despite taking long-acting tramadol 300 mg daily preoperatively.

Case 4 A 57-yr-old man with a history of type 1 diabetes, hypertension, and coronary artery disease underwent left BKA. Similar to the previous cases, a nonstimulating femoral catheter and a stimulating sciatic nerve block catheter were inserted preoperatively under ultrasound ± nerve stimulation guidance. On POD 1, his severe pain (NRS, 8) was not effectively controlled with LA bolus despite sensory block being present. He was reluctant to increase opioid consumption and agreed to try a one-hour PNS via the nerve block catheter as an off-label pain management option. Afterward, his NRS decreased to 2.

On POD 2, he only required minimal opioids and no opioid requirement afterwards. One year postoperatively, he required no opioid.

Provision of an analgesic adjunct as part of an opioid-sparing multimodal strategy (cases 5 and 6)

Case 5 A 41-yr-old gentleman who presented with extensive comorbidities (Table 1) and was taking gabapentin for neuropathic foot pain underwent BKA. Preoperatively, a stimulating sciatic nerve block catheter was inserted. Postoperatively, one-hour PNS was applied six hours apart twice on POD 1 and once on POD 2. This was done after discussion with the patient about this off-label pain management technique to reduce opioid consumption. An LA infusion with intermittent LA boluses was continued for two days postoperatively. Minimal opioid was required, and no immediate adverse effects were noted.

Case 6 A 68-yr-old lady with peripheral vascular disease underwent BKA (Table). After inserting a stimulating sciatic nerve catheter preoperatively, the patient underwent an uneventful general anesthetic for her surgery. Local anesthetic infusion with an intermittent bolus as described above was commenced postoperatively, and elective PNS was offered as an off-label pain management technique to reduce opioid demand. The patient received PNS twice, six hours apart, on POD 1 and once on POD 2 but declined another PNS later on POD 2 and did not request further opioids until 4.5 hr later. The nerve catheter was removed on POD 3.

Discussion

Our case series highlights the potential benefits of combining LA infusion with PNS to manage pain after BKA. The first case shows that PNS can augment nerve block catheters, minimizing the total dose of LA needed in four separate nerve block catheters concurrently and thereby reducing the potential for LAST, especially in those susceptible patients. Cases 2–4 illustrate that PNS can reduce opioid consumption in patients who have adverse effects from opioids or who are reluctant to use opioids. Peripheral nerve stimulation was electively applied once or twice a day as an opioid-sparing multimodal strategy in cases 5–6 without immediate adverse effects and was effective in reducing opioid consumption. The pain score of these individuals decreased with time, and all patients experienced instant pain alleviation following PNS. Opioid consumption either decreased during the remainder of the day or the subsequent day, and the duration until the next opioid dose was generally three to four hours (ranging between two and 13 hours) until the next opioid dose. In our case series, the intervention was guided by clinical judgment, and PNS was only tried when conventional multimodal analgesia was insufficient, except for cases 5 and 6, where PNS was used regularly to reduce opioid requirement. Within our limited case series of six patients, no patients required opioids for longer than four months postoperatively, except for one patient with chronic pain who needed a slightly higher dose (2 mg) of hydromorphone compared with his preoperative dose.

Peripheral nerve stimulation has been used to treat chronic pain and is gaining popularity as more evidence of its potential usefulness emerges. Percutaneous electrode insertion for PNS in chronic pain has been described as employing ultrasound-assisted, fluoroscopic-confirmed lead placement in recent decades.[9, 10] Recent meta-analyses of randomized controlled trials and observational studies found that PNS can effectively manage acute and chronic pain, with level II evidence in cluster headache and postamputation pain to name a few.[3] Nevertheless, the PNS procedures used in these trials are distinct from those described in our case series in terms of how the equipment used, the proximity of the electrode to the nerve, and the frequency and current applied.

The cases described herein featured a *hybrid* PNS approach involving a single perineural stimulating nerve block catheter in which the catheter tip is positioned perineurally and LA is injected adjacent to the nerve; additionally, intermittent PNS is applied perineurally via the same nerve block catheter using *low frequency and low current*, similar to the previous case reports.[4–7] Although the specific mechanism is unknown, low-frequency PNS (2 Hz, 1–2 mA, 0.15–0.2 msec on the median nerve) activated hypothalamic orexin neurons and resulted in analgesia independent of endogenous opioids in mice.[11] High-frequency transcutaneous electrical nerve stimulation (TENS) has also been shown to raise glutamate and aspartate concentrations in the spinal cord via opioidergic blockade.[12, 13] Supraspinal pathways have been implicated in triggering the spinal cord's descending noradrenergic, serotonergic, muscarinic, and dopaminergic systems.[14, 15] Since the electrical stimulating field can conduct and transmit beyond LA fluid, the most plausible mechanism for our hybrid technique is the use of LA to block distal notorious pain transmission of the nerve while simultaneously stimulating the unblocked nerve proximally with low frequency to release endogenous neurotransmitters via the central nervous system. From the long-term data in our case series, it is also plausible that nerve stimulation can minimize the need for chronic opioid use and prevent chronic neuropathic pain. In addition, preclinical studies have revealed that low-frequency PNS

can accelerate axon growth and nerve regeneration, which may play a role in analgesia.[16]

Selection bias and placebo effects may limit the merit of our findings. Further research is necessary to determine the optimal safe current, frequency, and duration of PNS. Consideration must also be given to the safety of the small surface area of the stimulating catheter tip that could result in a high charge density and the risk of adverse reactions in local tissue from extended stimulation duration. Fortunately, the concurrent administration of ionic LAs may disperse the electric current and protect adjacent tissues, as shown in animal models.[17] Without sufficient human safety data, PNS should be used sparingly and only during periods of poorly managed pain.

Conclusion

Our case series supports the feasibility of using the hybrid technique of combining perineural stimulation and LA infusion via a single perineural nerve block catheter to manage pain in patients with challenging postamputation. There is a minimal risk that off-label stimulation can cause functional deficit in below-knee amputees; therefore, additional research is necessary to determine the optimal configuration, efficacy, safety, and short- and long-term benefits of this concurrent technique in otherwise healthy patients.

Author contributions *Vivian Ip* contributed to all aspects of this manuscript, including study conception and design; acquisition, analysis, and interpretation of data; and drafting the article. *Yuvaraj Kotteeswaran* contributed to acquisition, analysis, and interpretation of data and drafting the article. *Savannah Prete* contributed to acquisition, analysis, and interpretation of data. Rakesh Sondekoppam and Ban Tsui contributed to study conception and design, interpretation of data, and drafting the article.

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