Background

Limb loss is a debilitating condition affecting 1.6 million Americans (1). Of these, approximately 80% go on to suffer phantom limb pain (PLP), a neuropathic condition characterized by throbbing, burning or electric shock-like sensations in the absent limb (2). A wide range of treatment options exist – pharmacologic agents such as anticonvulsants, antidepressants and opioids are commonly used but are often inadequate (3). Mirror therapy and transcutaneous electrical nerve stimulation units are effective alternatives (4-5). For those who fail these therapies, peripheral nerve stimulation (PNS) and perineural catheter placement (PC) are promising treatment options for PLP. We present a case of a 36-year-old male whose phantom limb pains were addressed with a 5-day perineural catheter placement (PC) and 60-day PNS lead placement (SPRINT, SPR Therapeutics, Cleveland, OH, USA).

Case

A 36-year-old male presented to the trauma bay in critical condition following a 15-foot fall from a telephone pole that subsequently fell on top of the patient resulting in traumatic partial amputation of the right upper extremity (RUE) and crush injury of the right lower extremity (RLE). Due to unsalvageable injuries, patient underwent right transhumeral amputation and partial right foot amputation involving toes 1 through 4. Patient's hospital course was prolonged by right transtibial amputation due to infection, and issues of difficult pain management throughout. In the initial period, patient experienced significant PLP of the RUE worse than the RLE despite a multimodal regimen including opioids, anticonvulsants, and antidepressants. The inpatient acute pain service team performed a single-shot (0.2% ropivacaine) brachial plexus block a week after the initial surgery, which provided significant

pain relief for 24 hours. A perineural catheter was placed subsequently and remained near the right brachial plexus for 5 days providing significant pain relief, and reduction in opioid requirements during this time. Patient was successfully moved onto a rehabilitation facility after a 23-day hospital stay.

Upon follow-up clinic visit, patient was suffering significant PLP of the RLE (worse than RUE). Diagnostic right sciatic nerve block and saphenous nerve block were performed providing 75-80% pain relief for up to 1.5 hours. This was followed by a 60-day PNS lead placement providing >50% pain relief from baseline.

As of today, patient continues to have >50% pain relief in his RLE nearly 9 months after the initial procedure. However, patient now suffers from worsened RUE PLP. A diagnostic right upper extremity brachial plexus block was performed in recent months achieving complete pain relief for several hours. We are currently waiting for approval from workers' compensation to proceed with RUE PNS lead placement.

Discussion

The pathophysiology of PLP is complex. Prevailing theories cite somatosensory reorganization at the cortical level, neuroma formation of injured peripheral nerves and aberrant signaling from the neuronal cell bodies as underlying mechanisms of PLP (6). PNS is a potential treatment option for PLP that works by directly applying electrical stimulation to the injured nerve thereby altering nociceptive signaling (7).

The data regarding the short-term efficacy of temporary PNS is generally positive, however, more data is needed to elucidate the long-term efficacy. A randomized controlled trial by Albright-Trainer et al., showed significant reduction in PLP, RLP and opioid consumption at

3 months for those who underwent PNS lead placement in the acute post-operative period following lower extremity amputation. The data collection and analysis are ongoing for 6-month and 12-month time points (8). Similarly, a randomized controlled trial by Gilmore et al., showed that 67% of subjects (6 of 9) who underwent a 60-day PNS trial went onto experience significant pain relief at 12-months compared to placebo (9). These findings suggest the effects of PNS could have long lasting effects. However, a more recent case series of 3 patients who underwent temporary PNS placement showed PLP returned within 1-3 months suggesting the positive effects of PNS may be short-lived in some (10).

Our patient underwent a 60-day RLE PNS lead placement approximately 2 months after the initial surgery and continues to experience sustained pain relief of >50% from baseline after 9 months from PNS lead placement. There are several proposed mechanisms of PNS. It involves direct stimulation of large diameter non-nociceptive Aβ nerve fibers, which interfere with neuronal signals from smaller nociceptive Aδ and C nerve fibers thereby preventing transmission of pain signals. Other proposed mechanisms by which PNS affects pain signaling are its ability to reduce hyperexcitability of injured neurons, suppress dorsal horn activity, alter neurotransmitter levels and modulate CNS activity (11). The wide-ranging effects of PNS on the nociceptive pathway could explain why many patients go on to experience sustained pain relief from PLP.

We hypothesize that early PNS lead placement could be an important component of long-term pain relief. There is evidence showing that hyperalgesia and allodynia originate from synaptic changes in the spinal dorsal horn contributing to lasting changes of the nociceptive pathway (12). Early intervention with PNS may mitigate some of the early synaptic changes, thereby, preventing PLP altogether.

The use of short-course PC for the treatment of PLP is another interesting component. Borghi et al., first reported the use of a perineural catheter to treat severe post-amputation PLP. After a 28-day course of continuous ropivacaine infusion, the patient went on to experience complete resolution of PLP at subsequent follow-up time points of 6, 12, 24, and 36 months (13). More recently, a randomized-controlled trial comparing a 6-day perineural catheter (continuous ropivacaine infusion) to placebo (normal saline) showed significant reduction in the intensity of PLP in the treatment group after 4 weeks (14). Our patient experienced significant pain relief after PC placement near the brachial plexus. Unfortunately, his pain returned almost immediately after catheter removal. Nonetheless, the evidence supporting the utility of perineural catheters seems promising. The use of perineural catheters can be a useful adjunct to manage PLP particularly in the inpatient setting where close monitoring is feasible.

Conclusion

Our case adds to a growing body of evidence that supports the utility of PNS. Future studies should explore whether early intervention with PNS could improve long-term outcomes.

Reference

1. Ziegler-Graham K, MacKenzie EJ, Ephraim PL, Travison TG, Brookmeyer R. Estimating the prevalence of limb loss in the United States: 2005 to 2050. *Arch Phys Med Rehabil*. 2008 Mar;89(3):422-9.
2. Ephraim PL, Wegener ST, MacKenzie EJ, Dillingham TR, Pezzin LE. Phantom pain, residual limb pain, and back pain in amputees: results of a national survey. *Arch Phys Med Rehabil*. 2005 Oct;86(10):1910-9.
3. Collins KL, Russell HG, Schumacher PJ, Robinson-Freeman KE, O'Conor EC, Gibney KD, Yambem O, Dykes RW, Waters RS, Tsao JW. A review of current theories and treatments for phantom limb pain. *J Clin Invest*. 2018 Jun 1;128(6):2168-2176.
4. Tilak M, Isaac SA, Fletcher J, Vasanthan LT, Subbaiah RS, Babu A, Bhide R, Tharion G. Mirror Therapy and Transcutaneous Electrical Nerve Stimulation for Management of Phantom Limb Pain in Amputees - A Single Blinded Randomized Controlled Trial. *Physiother Res Int*. 2016 Jun;21(2):109-15.
5. Kim SY, Kim YY. Mirror therapy for phantom limb pain. *Korean J Pain*. 2012 Oct;25(4):272-4.
6. Subedi B, Grossberg GT. Phantom limb pain: mechanisms and treatment approaches. *Pain Res Treat*. 2011;2011:864605.
7. Urits I, Seifert D, Seats A, Giacomazzi S, Kipp M, Orhurhu V, Kaye AD, Viswanath O. Treatment Strategies and Effective Management of Phantom Limb-Associated Pain. *Curr Pain Headache Rep*. 2019 Jul 29;23(9):64.
8. Albright-Trainer B, Phan T, Trainer RJ, Crosby ND, Murphy DP, Disalvo P, Amendola M, Lester DD. Peripheral nerve stimulation for the management of acute and subacute post-amputation pain: a randomized, controlled feasibility trial. *Pain Manag*. 2022 Apr;12(3):357-369.
9. Gilmore CA, Ilfeld BM, Rosenow JM, Li S, Desai MJ, Hunter CW, Rauck RL, Nader A, Mak J, Cohen SP, Crosby ND, Boggs JW. Percutaneous 60-day peripheral nerve stimulation implant provides sustained relief of chronic pain following amputation: 12-month follow-up of a randomized, double-blind, placebo-controlled trial. *Reg Anesth Pain Med*. 2019 Nov 17:rapm-2019-100937.
10. Pagan-Rosado R, Smith BJ, Smither FC, Pingree MJ, D'Souza RS. Peripheral Nerve Stimulation for the Treatment of Phantom Limb Pain: A Case Series. Case Rep *Anesthesiol*. 2023 Mar 6;2023:1558183.
11. Ong Sio LC, Hom B, Garg S, Abd-Elsayed A. Mechanism of Action of Peripheral Nerve Stimulation for Chronic Pain: A Narrative Review. *Int J Mol Sci*. 2023 Feb 25;24(5):4540.
12. Sandkühler J. Learning and memory in pain pathways. *Pain*. 2000 Nov;88(2):113-118.
13. Borghi B, Bugamelli S, Stagni G, Missiroli M, Genco R, Colizza MT. Perineural infusion of 0.5% ropivacaine for successful treatment of phantom limb syndrome: a case report. *Minerva Anestesiol*. 2009 Nov;75(11):661-4.
14. Ilfeld BM, Khatibi B, Maheshwari K, Madison SJ, Esa WAS, Mariano ER, Kent ML, Hanling S, Sessler DI, Eisenach JC, Cohen SP, Mascha EJ, Ma C, Padwal JA, Turan A; PAINfRE Investigators. Ambulatory continuous peripheral nerve blocks to treat postamputation phantom limb pain: a multicenter, randomized, quadruple-masked, placebo-controlled clinical trial. *Pain*. 2021 Mar 1;162(3):938-955.