Topical Review

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Republication of "Treatment of Postsurgical Neuroma in Foot and Ankle Surgery"

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Commentary: Comprehensive review of foot and ankle peripheral neuromas the extant evidence for all major nonsurgical and and surgical treatments are discussed and well referenced.

The incidence of lower extremity postsurgical and posttraumatic neuroma is poorly described in the literature and may result from a number of insults to central or peripheral nerves. During traumatic injury, nerves can be injured by stretch, crush, or laceration mechanisms, which may result in aberrant axonal regeneration and neuroma formation. Unfortunately, iatrogenic and traumatic nerve injuries can be difficult to treat and have a profound impact on patient morbidity, functional outcomes, and chronic pain.

Nerve injury occurs on a spectrum of severity as described by Seddon in 1942 and modified by Sunderland in 1951.[43,47] When there is injury to axons resulting in discontinuity, a cascade of neurotrophic factors is released, resulting in sprouting of growth cones from the proximal nerve stump. These sprouting proximal nerve axons can become entangled in local surrounding tissue, forming a bulbous thickening termed neuroma (Figure 1). Surgical treatment of painful neuroma has been described in the literature as early as 1880.[19] Although our understanding of the pathophysiology of neuroma formation has evolved, options for treatment have not progressed at an equivalent pace.

Much of the literature regarding surgical treatment of painful neuroma is published in the upper extremity and hand literature; reports in the lower extremity are comparatively limited with reports ranging from 3.4% after ankle arthroscopy and up to 50% after lower extremity amputation.[12,15,17,25,38] The current review will focus on treatment of symptomatic peripheral neuroma in the lower extremity.

Diagnosis of Neuroma

Patients with symptomatic neuroma frequently have a history of surgery, trauma, laceration, crush injury, or stretch injury to the affected limb. Pain and symptoms associated with peripheral neuroma respect sensory nerve distributions; however, there can be increased pain in adjacent distributions because of the phenomenon of deafferentation of adjacent nerves. Some patients will have painful scars or palpable soft tissue masses due to scar tissue about the injured tissues or neuroma bulb. A positive Tinel sign, the sensation of tingling with palpation or percussion over the affected nerve (Figure 2), and temporary relief from diagnostic nerve block may aid in clinical diagnosis.[11] The Tinel sign may extend proximally because of decreased mechanical threshold for nerve stimulation; a phenomenon suggestive of nerve recovery. Ultrasonographic imaging is a useful adjunct to confirm the presence of neuroma bulb and guide anesthetic or steroid injections. MRI is helpful in cases of uncertain diagnosis or for surgical planning. The superficial peroneal and sural nerves are commonly encountered during surgical approaches to the foot and ankle. A cadaver dissection demonstrating their paths and distributions is shown in Figure 3. Recommendations for or against treatment options are graded according to the supporting level of evidence (Table 1). A summary of recommendations for the reviewed interventions is presented in Table 2.

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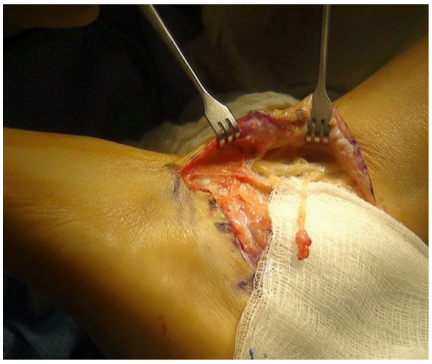

Figure 1. Operative photograph of a superficial peroneal nerve neuroma demonstrating dissection of neuroma in continuity of the superficial peroneal nerve. The disorganized sprouting of nerve growth cones led to a bulbous neuroma that was adherent to adjacent scar tissue. The patient presented with persistent neuropathic pain in the superficial peroneal nerve and hypersensitivity in the area overlying the neuroma. A positive Tinel sign was noted during examination.

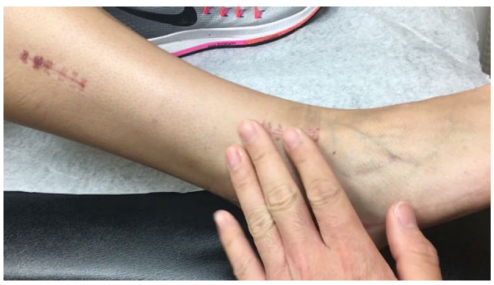

Figure 2. Peripheral neuroma can be diagnosed by the presence of a positive Tinel sign, the presence of paresthesias or lancinating pain elicited by palpation or percussion over a peripheral nerve. The diagnosis is further supported by temporary relief from diagnostic nerve block. Symptoms typically respect peripheral nerve distributions, but may extend into adjacent distributions as well.

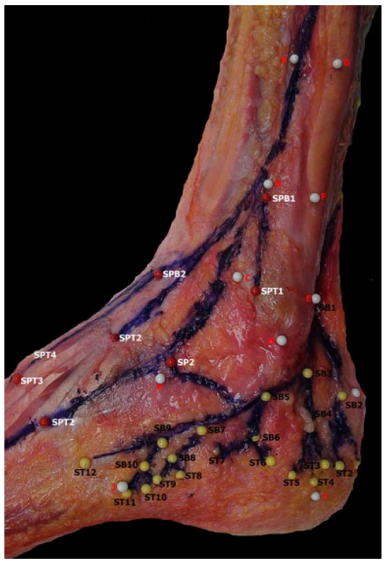

Figure 3. Cadaver preparation demonstrating the course of the superficial peroneal (branches labeled SP#) and sural nerve (branches labeled SB# and ST#), and their sensory branches. Superficial peroneal nerve and sural nerve are common sites of neuroma formation because of superficial location placing them at risk for trauma, and also surgical approaches to the ankle that require identification and dissection adjacent to the nerve branches.

Table 1. Grades of Recommendation and Levels of Evidence.

Grades of Recommendation for or Against Treatment Modalities
Grade A: Treatment options are supported by strong evidence (consistent with Level I or II studies)
Grade B: Treatment options are supported by fair evidence (consistent with Level III or IV studies)
Grade C: Treatment options are supported by either conflicting or poor-quality evidence (Level IV studies)
Grade I: When insufficient evidence exists to make a recommendation

Pathophysiology

Following injury to a peripheral nerve, a reparative process is activated by release of local neurotrophic factors including substance P, ciliary neurotrophic factor, nerve growth factor, calcitonin gene–related peptide, and local inflammatory cytokines. Neurotrophic factors released by the neuron cell body direct the initial healing response and stimulate the sprouting of axonal fibers from the proximal segment toward the distal segment, forming a growth cone. Schwann cells from the distal segment align themselves in bands that can help direct regeneration of the proximal segment, referred to as bands of Bugner, whereas macrophages are responsible for Wallerian degeneration of the distal stump. When the growth cone is able to reach the distal segment, there is bridging and regeneration of the nerve defect. If the defect is too large for the growth cone to reach the distal nerve segment or the growth cone becomes disorganized or entrapped in scar tissue, a disorganized arrangement of regeneration occurs leading to neuroma formation.[3,31] When intact nerve fibers sustain incomplete crush or traction injuries, injured nerve fibers attempt to heal in a similar fashion, and can escape the perineurium, leading to neuroma in continuity (Figure 1).

Outcomes Measurement

Comparison of patient outcomes between studies is complicated by lack of standardized outcome measurements, varied length of follow-up, and differences in methodology. There

Table 2. Summary of Assigned Grades of Recommendation for Each Intervention.

Intervention	Grade of Recommendation
Medications	Grade A
Desensitization therapy	Grade I
Peripheral nerve stimulation	Grade I
Simple neurectomy	Grade C
Neurectomy with implantation (muscle, bone, vein)	Grade B
Biologic therapies	Grade I
Containment	Grade C
Cryoablation	Grade I
Interpositional nerve graft	Grade C
Targeted nerve implantation/targeted muscle reinnervation	Grade C

remains no widely accepted standard for assessing outcomes following treatment of chronic neuropathic pain.[16,18,44,51] Farrar performed a meta-analysis examining the clinical significance of changes in the 11-point pain intensity numeric rating scale (PI-NRS) by association with changes in patient's global impression of change (PGIC), another patient-reported scale assessing functional change over time.[16] They reported close correlation between the 2 measures and that, on average, a decrease of 2 or more units on the PI-NRS resulted in a clinically important improvement.

Nonsurgical Treatment

Medications

Gabapentin and pregabalin are routinely used for diabetic neuropathy, post-herpetic neuralgia, and fibromyalgia. These medications act through modulation of Ca^{2+} influx into neurons, potentially decreasing nerve hyperexcitability. Although these medications have not been investigated specifically for painful neuroma, they have been investigated in placebo-controlled randomized controlled trials (Level I evidence) for treatment of posttraumatic and postsurgical neuropathic pain.[20,52] Among patients with neuropathic pain, significantly more patients experienced moderate pain relief (≥30% pain relief) and significantly decreased sleep interference scores after treatment with gabapentin for 5 weeks resulting in significantly improved health-related quality of life measures assessing vitality, emotional, and mental health.[20]

Tricyclic antidepressants are often used in recalcitrant pain and have been examined for neuromatous pain. Wilder-Smith et al demonstrated efficacy of amitriptyline and tramadol for decreasing postamputation neuropathic stump pain in treatment-naïve patients in a 2005 prospective randomized controlled trial (Level II evidence)[53] where they randomized 94 patients with postamputation neuropathic pain to treatment with amitriptyline, tramadol, or placebo for 1 month. A pain reduction of at least 10 points on a visual analog score (VAS) was reported by 25 of 30 patients in the amitriptyline arm, 22 of 33 in the tramadol treatment arm, and 2 of 31 in the placebo arm. Both medications also resulted in antinociceptive effect, with increased pain threshold to electrical stimulation.

Desensitization Therapy

Patients with neuropathic pain have been shown to have decreased thresholds for pain in the affected nerve distributions (eg, hyperexcitability), and therefore desensitization therapies attempt to modulate the threshold of painful stimuli in hypersensitive nerves, decreasing nociception. In 1949, Russel reported excellent results in 7 patients with postamputation neuromata by injecting local anesthetic or applying a tourniquet, followed by "gentle hammering with a wooden mallet or by means of a mechanical vibrator" about the painful stump for approximately 10 minutes, 1 to 2 times daily.[41] Russell and Spalding subsequently reported an additional 27 cases, making their total case series 33 patients.[42] Of these, 19 patients reported good or excellent results and an additional 5 patients reported improvement, whereas 9 patients were considered treatment failures. Desensitization and physical therapy are still commonly used to decrease hyperexcitability of affected nerves in treatment of neuropathic symptoms. These therapies have favorable risk-benefit profiles and are routinely included in nonoperative strategies for treating neuromatous pain, although there remains insufficient evidence to provide evidence-based recommendations.

Peripheral Nerve Stimulation

Peripheral nerve stimulation has been proposed to modulate axonal impulses at the site of neuroma. Meier et al reported a single case report of a young woman with neuromatous amputation stump pain recalcitrant to medications, therapy, and multiple attempts at surgical resection that had significant symptom relief with implantation of a subcutaneous electrode.[52] Although there is limited literature to support this modality, it may prove to be a useful option in cases of neuroma pain recalcitrant to nonoperative therapies and surgical resection.

Surgical Neurectomy and Transposition

Moszkowicz was one of the first to report muscle implantation as treatment for painful neuroma in 1918, since then numerous methods for surgical treatment of painful neuroma have been described, ranging from simple traction neurectomy, resection with proximal stump implantation, end-to-end anastomosis, or fascicular repair with interpositional

nerve grafting.[35] Clinical trials evaluating surgical treatment are small and often demonstrate variable outcome metrics. As such, there is no universally accepted standard of care for surgical treatment of painful neuroma.

Implantation of the stump into surrounding tissue beds, and away from the area of trauma, is thought to encourage more organized nerve fiber proliferation, leading to diminished size of resultant neuroma and reduction in associated dysesthesia.[40] Marcol et al examined the histologic and behavioral response of rats following transverse versus oblique nerve transection in rats, reporting a significant decrease in autotomy following oblique sciatic nerve transection, as compared to perpendicular transection.[27,33] On a cellular level, oblique transection of nerve tissue resulted in decreased histologic axonal degeneration and demyelination, as well as diminished Schwann cell proliferation and connective tissue growth at the site of injury.

Muscle Implantation

Following neuroma resection, implantation of the proximal nerve stump into muscle offers several technical advantages. First, there is no need for microsurgical technique, as in vein implantation, or for drilling bone to allow for bone implantation. Second, there is generally abundant muscle adjacent to peripheral neuromas in the lower extremity. Muscle fibers can be split to allow for tension-free transposition of the transected nerve end deep into the muscle belly, away from superficial scar tissue. Studies on neuroma excision with intramuscular implantation in the upper extremities have demonstrated promising findings with satisfactory to excellent results ranging from 59% to 94%.[11,23,50] However, there remains a paucity of literature on the implantation technique in the lower extremity.

In a 2009 retrospective case series, Ducic reported the largest series of saphenous neuroma resection and muscle implantation (Level IV evidence).[13,14] Neuroma resection and muscle implantation resulted in effective pain relief in 83% of patients at mean follow-up of 35 months.[20] Among below-knee amputation and above-knee amputation patients with debilitating neuromas in their studies, 12 of 15 were able to resume prosthesis wear and ambulation after resection and implantation, and 86% of patients reported at least 50% improvement in quality of life.[14] Of the 6 patients who failed treatment, all had complicated histories with multiple previous treatments including surgery. Furthermore, 4 of the 6 did not have preoperative diagnostic nerve block performed by the authors, highlighting the importance of strict surgical indications in patients with suspected neuromatous pain.

Chiodo and Miller reported a retrospective comparative study of 27 patients following neurectomy and proximal stump implantation into either bone or muscle (Level III evidence).[7] Following transection and implantation into muscle, 46% of patients reported clinical improvement, compared to 75% after resection and implantation into bone. The results of this study may be attributed to transposition into the small and superficially located peroneus brevis muscle and/or the lack of proximal fascial release during surgery, leaving a mechanism for local nerve compression despite proximal neurectomy.

Economides et al retrospectively compared 17 patients undergoing transfemoral amputation with nerve management through either traction neurectomy (11 patients) alone or a multimodal operative approach to prevent postamputation neuroma (6 patients) (Level III evidence).[15] The experimental arm underwent direct coaptation of the common peroneal to tibial nerve, collagen nerve wrapping, and submuscular transposition. At 6 months, 6 of 11 (54.5%) of the traction neurectomy group had developed a neuroma, compared to zero of 6 patients in the experimental treatment group.

Rungprai et al demonstrated significantly greater improvement in pain when measured using VAS (5.5 vs 3.7, $P = .002$) in patients undergoing neurectomy with intramuscular implantation (40 neuromas) compared to simple neurectomy alone (78 neuromas) for interdigital neuroma in a recent retrospective comparative study (Level III evidence). Although there was no difference in complications between the 2 groups in this study, operative time in the implantation group was significantly longer ($P = .001$).

Vein Implantation

Koch retrospectively reported short-term results of 8 patients with lower extremity neuroma treated with resection and vein implantation with microsurgery technique (level IV evidence).[29] Follow-up ranged from 8 to 37 months. All 8 patients noted immediate pain relief. One patient had symptom recurrence at 2 months and 3 patients reported recurrence of minor symptoms at final follow-up. Koch subsequently reported midterm results (range 19-64 months) from 8 patients with lower extremity and an additional 17 patients with upper extremity painful neuroma treated with neuroma resection and transposition into vein using microsurgical technique (Level IV evidence).[28] Although the 2 publications reported different outcome measures, they reported complete symptom resolution in 14 of 25 patients (56%). Mild symptoms recurred in 9 of 25 patients, while moderate to severe symptoms recurred in 2 of 25 patients at final follow-up. The authors suggested limiting the indication for vein implantation to superficial sensory nerves because of the limited availability of large veins for larger nerve transposition and the risk of venous thromboembolism in larger veins.

Balcin conducted a prospective randomized controlled trial of 20 patients with lower extremity painful neuroma. Subjects were randomized to proximal nerve transposition into vein or muscle (Level II evidence).[1] All patients

reported significant decreases in continuous, steady, and constant pain. However, reduction of pain intensity, assessed by VAS, was significantly greater in the vein implantation group compared to the muscle group.[40] The authors suggested that inhibition of neuroma formation was a result of an inhibitory effect of the endothelial layer, as well as a potential dilutional effect of blood flow decreasing the local concentration of nerve growth factors.

Biologic Therapies

Recent advances in biologic therapies has led to targeted antibodies with potential to modify local nerve growth signals, thereby preventing the disorganized axonal outgrowth that leads to development of painful neuroma. Nerve growth factor is secreted by local tissues, and binds with tropomysin-related kinase A. Activation of tropomysin-related kinase A results in increased expression of nociceptive receptors and neurotransmitters and results in increased sensitivity of adjacent nociceptive neurons. Jimenez-Andrade inoculated mice with prostate cancer cells followed by local injection with anti–nerve growth factor (anti-NGF). Compared to sham treatment, anti-NGF injection resulted in decreased tumor-induced axonal sprouting and nociceptive pain behavior.[26] Systemic and local applications of anti-NGF have been studied in humans and shown improvement in chronic pain associated with osteoarthritis of the hip and knee, chronic low back pain, and neuropathic pain associated with diabetic polyneuropathy and postherpetic neuralgia, but we are unaware of studies assessing anti-TNF in patients with painful neuromas.[6] Safety concerns raised in hip and knee OA patients due to reports of rapidly progressive joint destruction resulted in the FDA halting clinical studies in 2010; however, this FDA order was lifted in 2013 following an independent study on safety of anti-TNF antibody.

Cryoablation

Cryogenic nerve ablation has been proposed as an alternative to surgical neurectomy for patients with painful neuroma. Cryoablation results in demyelination and Wallerian degeneration of axons but leaves the perineurium and epineurium intact, limiting the potential for disorganized reorganization.[10]

Hodor presented a case report on percutaneous cryogenic neuroablation of an intermetatarsal neuroma in 1997, with complete relief from neuroma pain at final follow-up 6 months following the procedure.[24]

Caporusso reported a prospective case series (Level IV evidence) of 20 patients with 31 neuromas treated by percutaneous cryogenic neuroablation, the majority of which were intermetatarsal neuromas (28 of 31).[5] Patients in this series reported partial relief in 15 of 31 neuromas (45.2%), whereas 5 neuromas (16.1%) had pain unchanged from prior to treatment. Although 11 neuromas (38.7%) were pain free, more than one-third of patients indicated major reservations or complete dissatisfaction with the procedure.

Davies presented a case series of 6 patients who underwent open cryoablation of posttraumatic neuromas in the upper extremity (Level IV evidence).[10] Nerve tissue was directly visualized at time of cryoablation, and neuromas were treated with multiple applications of the cryoablation probe, without resection of neuroma at the time of treatment. Two patients reported an "excellent" outcome and 4 as "good." The authors advocate for an open approach to improve identification of the involved nerve and to confirm pathologic tissue is treated in its entirety.

Overall, the literature regarding cryoablation of painful neuromas in the lower extremity is limited to retrospective case series, and we were unable to identify any randomized controlled trials examining efficacy of cryoablation compared to other options.

Containment

Nerve capping was proposed as a way to prevent fascicular escape by controlling axonal outgrowth of the proximal nerve stump following neurectomy. Proximal end-to-end nerve anastomosis was reported at least as early as 1904 by Langley and Anderson. Proximal end-to-end anastomosis involves transection of the involved nerve proximal to the neuroma, with end-to-end anastomosis with another transected nerve or the involved nerve split and anastomosis of the resultant bundles. Outgrowth of the proximal axons is limited by the epineurium, and has been used with end-to-end and end-to-side anastomosis.

Other methods of capping have been investigated that do not require donor axons. In a 1976 case series, Tupper and Booth reported a subgroup analysis (Level IV evidence) of 17 patients with 32 neuromas undergoing revision neurectomy with silicone capping, with 8 patients reporting excellent results (25%) and 5 reporting satisfactory results (16%) after revision neurectomy and capping.[50] The authors concluded that silicone capping provided no benefit over simple neurectomy. Of 12 patients who underwent re-exploration as a result of unsatisfactory results in that series, the silicone cap was found to be dislodged from the neuroma.

Swanson reported a series (Level IV evidence) of 18 patients, with 38 neuromas, treated with neurectomy and silicon capping. Seventeen of 18 (94%) required revision surgery for disabling neuroma pain, with 15 revised patients experiencing symptomatic relief.[48]

Epineural grafts have been used to cap terminal neuromas, as well as to provide conduits to bridge gaps following resection of neuroma in continuity. Following promising results from a rodent model evaluating a modification of nerve capping, Martini and Fromm published a retrospective

case series (Level IV evidence) consisting of 36 patients with 68 neuromas.[34] At the time of microscopic neurectomy, nerve fascicles were shortened by 5 to 8 mm and Histoacryl glue was applied to the fascicles, after which the epineurium was then sutured closed to provide an epineural cap. With an average follow-up of 17 months (range 7-43), they reported complete relief or improvement in pain for 33 of 36 patients (92%).

Conduits are another treatment option that attempt to guide axon outgrowth to reduce neuroma formation. Gould reported a retrospective case series (Level IV evidence) of 50 patients (69 neuromas about the foot and ankle) treated with neuroma resection and nerve end capping with bovine collagen conduit.[21] Length of follow-up varied widely, ranging from 6 to 55 months, and final follow-up was performed by phone survey, eliminating the possibility of assessing clinical signs of neuromatous pain. The authors reported that 30 of 69 neuromas were painless (43%), whereas 10 had no improvement or were worse following surgery (15%). Although the authors report an overall satisfaction rate of 85%, the authors included all patients with pain score <8 of 10 as successful to achieve this outcome.

Autogenous vein grafts to bridge small gaps helps control axonal regrowth but is limited to 2 to 3 cm in humans.[8,9,39,49] Herbert and Filan published a series of 14 patients in whom nerve stumps were implanted into adjacent veins, which were then ligated distally.[22] At final follow-up, ranging 2 to 33 months, 9 were symptom free and 3 had minor residual symptoms (86% success). Two cases failed within a few weeks of surgery because of nerve pulling out of the vein graft; both patients had revision vein implantation with excellent results.

Nerve Repair

Neuroma excision with direct repair is frequently difficult because of creation of a nerve defect too large for tension-free direct repair. In this method, the nerve ends are mobilized and the neuroma is resected to healthy fascicles, taking note of external nerve markings to aid in proper orientation on repair. There is a paucity of evidence regarding epineural versus fascicular repair in the lower extremity. Repair under tension can lead to scar formation and nerve ischemia; in these cases, repair is augmented with autograft, allograft, or conduits for shorter defects in sensory nerves. Nerve autografts are currently the preferred method of gap repair; however, they are associated with donor site scarring, potential sensory deficits, and the possibility of new neuroma formation.[37] The sural nerve is the most common donor site; however, other cutaneous nerves such as the saphenous, lateral femoral cutaneous, and superficial peroneal are also potential donors in the lower extremity.[4,32,37]

Kon and Bloem reported on 18 patients with 42 neuromas of the fingers treated with microsurgical neurectomy and centrocentral anastomosis.[30] This microsurgical technique uses nerve allograft to connect proximal and distal nerve stumps or fascicular groups. The authors reported recurrent neuroma in 1 patient and persistent pain with percussion at the site of nerve union in 3 patients who reported some degree of pain interference with heavy work. All patients had diminished sensation in the affected digit, with 2-point discrimination in excess of 10 mm. Barbera and Albert-Pamplo subsequently reported a series of 22 patients with painful amputation neuroma of the lower extremity treated with centrocentral nerve anastomosis (Level IV evidence).[2] Complete pain relief was reported in 21 patients, with 18 patients able to wear lower extremity prosthesis at 4 weeks after treatment.

Souza and colleagues published a series of 22 patients with neuromas about the foot and ankle treated with resection and interpositional nerve allograft, with minimum follow-up of 6 months.[45] Although the authors reported improvement in PI-NRS, pain behavior, and pain interference, the authors elected to report mean results for PI-NRS, pain behavior, and pain interference, making comparison of individual results with other reported methods in the literature impossible.

Targeted Nerve Implantation/ Targeted Muscle Reinnervation

Targeted muscle reinnervation (TMR) is a nerve fascicle transfer procedure that seeks to reinnervate specific muscle units with the goal of improved prosthetic function. TMR requires dissection of a major motor nerve, with transfer to a distal motor unit target. Although TMR was initially investigated for improved prostheses use in amputees, it has been reported for treatment of chronic painful neuroma. Targeted nerve implantation (TNI) differs from TMR in that targeted nerve implantation uses a small distal motor neuron distribution as a target to prevent neuroma formation by providing a scaffold for guided, organized axon regeneration.

Souza and colleagues reported on 28 upper extremity amputees treated with neuroma excision and targeted muscle reinnervation (Level IV evidence).[46] Fifteen patients in this group reported neuroma pain prior to TMR; 14 of these had complete resolution of neuroma pain, with minimum follow-up of 6 months.

Pet et al published a retrospective series of patients undergoing targeted nerve implantation (TNI) for primary prevention of postamputation neuroma, as well as for secondary surgical treatment of known symptomatic postamputation neuroma (Level IV evidence).[36] Eleven of 12 patients (92%) with primary TNI and 20 of 23 patients (87%) with secondary TNI were clinically free of palpation-induced neuroma pain at minimum 8 months.[41] This retrospective case series suggested TNI results in equivalent or slightly better results compared to neurectomy with muscle or vein implantation, although TNI has the added complexity of requiring microsurgery for nerve dissection and coaptation.

Summary

- Peripheral neuromas of the lower extremity are frequently debilitating without a clear standard of treatment. The literature is largely limited to small case series and suffers from a lack of consistent methodology.
- Conservative measures can reduce nociceptive pain associated with neuroma, but rarely lead to complete relief.
- Biologics including anti–nerve growth factor show promise for preventing neuroma formation and decreasing nociceptive stimuli, but to our knowledge they have not been directly studied in patients with lower extremity neuromas.
- Many surgical options exist for addressing peripheral neuroma, with no high-quality studies demonstrating clear superiority of any method.
- Neurectomy and transposition away from site of injury to local muscle, vein, or bone has good results and does not require microsurgical technique.
- More advanced techniques such as interpositional nerve graft may offer improved outcomes, but require microsurgery and lack clear comparative studies to support evidence-based recommendations.

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