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Nerve Transfer With Entubulated Nerve Allograft Transfers to Treat Recalcitrant Lower Extremity Neuromas

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ABSTRACT

Neuroma formation in the lower extremity can be debilitating to patients, especially when the neuromas are recurrent. The results of an advanced nerve reconstruction technique consisting of nerve transfer combined with nerve allograft and entubulation was evaluated in 4 patients with severe, debilitating, lower extremity neuromas. At a mean follow-up period of 26 months, the mean visual analog scale had improved from 9.5 preoperatively to 1.25 postoperatively ($p < .05$). These data suggest that techniques using a nerve allograft with a nerve conduit could be of great assistance in successfully managing debilitating neuromas of the lower extremity. Thus, further in-depth evaluation of these techniques is warranted.

Neuroma formation in the lower extremity can be an extremely debilitating painful condition, resulting in loss of work, limitation of activities of daily living, and an overall poor sense of patient well-being. The etiologies of neuroma formation can be idiopathic, post-traumatic, a sequelae of surgery around the nerves, or resection of nerve tumors (1). Currently, neuromas in continuity in the intact limb are by far most commonly managed by interfascicular dissection and partial resection scar within the sensory component of the nerve. Stump neuromas are typically managed by re-excision with the end capped or buried into muscle (neuromyodesis) or into bone (neuro-osteodesis).

During lower extremity amputation, the transected peripheral nerves have traditionally treated by “clean” nerve transection, allowing the transected nerve to retract proximally and, hopefully, settle within a bed of soft tissue. However, aberrant axon sprouting or pressure irritation might result in a painful stump neuroma.

In an effort to treat recurrent stump neuromas, the creation of a nerve “blind loop” or performing either a neuromyodesis or a neuro-osteodesis might be performed. However, in our experience, none of these techniques have been met with a 100% success rate when implemented to prevent or treat recurrent both neuromas in continuity and stump neuromas. More recently, the “nerve bypass” neurorrhaphy has been presented, but limits exist with the length of the nerve injury, the requirement for only a partial nerve injury, and the need for a recipient nerve to be in very close proximity to the injured nerve (2).

It has been well established that injured peripheral nerves can regenerate misguided axons and initiate a number of neuropathophysiologic mechanisms that result in magnification of pain impulses from neuromas (see below). This pathophysiology can be significantly compounded in neuromas that recur after failed primary surgical management. The present report describes the use of the concept of a “nerve transfer” that effectively creates a conduit neural tissue for sprouting transected axons in which to grow and assist in dampening abnormal pain impulses. Although described in the upper extremity, this technique for the management of lower extremity neuromas has not been fully explored (3). We hypothesized that an entubulated nerve allograft for either neuromas in continuity (Fig. 1) or stump neuromas (Fig. 2) would result in rapid nerve regeneration owing to the natural nerve skeleton framework, thus providing a satisfactory substitute for harvested autograft nerve. Entubulation restricts abnormal nerve sprouting beyond the repair, which might be a source of the recurrence of neuromas. Moreover, this technique might also provide more favorable conditions to decrease the abnormally high level of growth factors and pain/inflammatory mediators, dampening the perception of abnormal pain impulses within dorsal ganglion structures.

Surgical Technique

The examination for neuroma relies on the manual examination of the nerve in question: direct palpation, localized pain to percussion,

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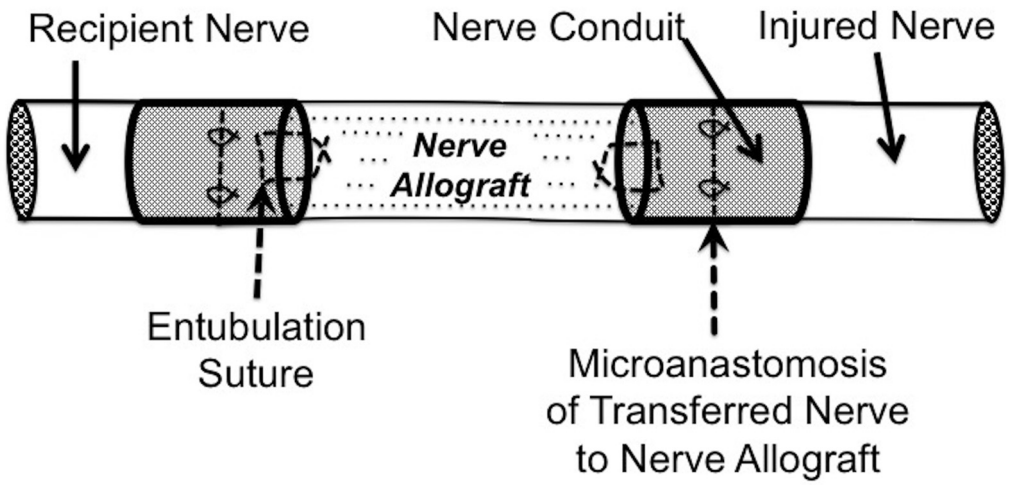

Fig. 1. Conceptual illustration of the reconstruction of a neuroma in continuity using nerve conduits and entubulation of an intercalary nerve allograft.

and generalized pain to the distribution of the involved nerve. Infiltration of local anesthesia with temporary relief of pain is a confirmatory test that supports the physical examination findings for neuroma.

The surgery is performed with the patient under general anesthesia without a central or peripheral nerve block. Muscle relaxation is not used, nor is a tourniquet, because nerve stimulation is required to distinguish the sensory component from the motor component of the recipient nerve. Sterile intraoperative ultrasound is used to facilitate exact location of the neuroma (Fig. 3*A*). Under loupe magnification, extensile incisions are placed in the region over the suspected neuroma. Neuroma resection is performed (Fig. 3*B*), resecting the neuroma to viable-appearing nerve tissue, typically exhibiting "mushrooming" of nerve fascicles that is also free of any scar tissue. If doubt arises, frozen section analysis can aid in defining a "clean" resection margin. The distal nerve is dissected free and mobilized to adequately be rerouted in a fashion that facilitates an end (distal nerve from which the neuroma was resected) to side (recipient nerve) anastomosis.

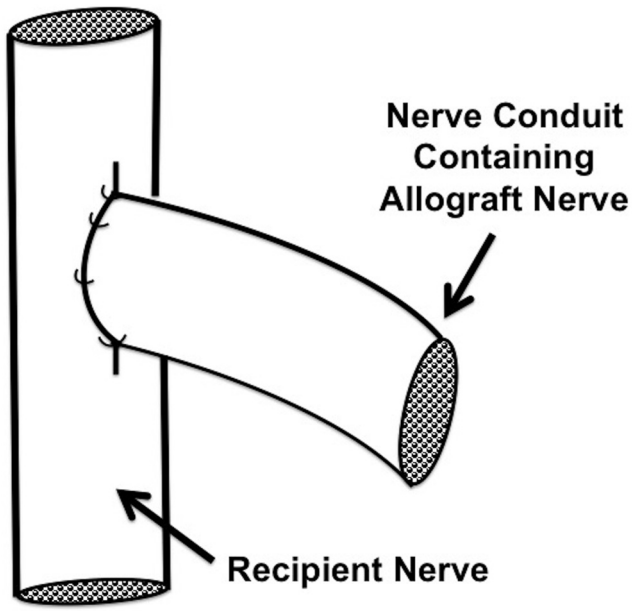

Fig. 2. Conceptual illustration of an end-to-side nerve transfer of the donor nerve sensory fascicles to recipient nerve sensory fascicles, using an entubulated nerve allograft.

A proximal mixed motor sensory nerve from which either the sensory branch containing the distal neuroma or an independent named sensory nerve is isolated with a sterile hand-held nerve stimulator. In cases in which an independent pure sensory nerve (ex-sural nerve) or a mixed motor/sensory nerve (ex-common peroneal or deep peroneal nerve) is involved with neuroma formation, the neuroma should be isolated and the nerve tissue excised to healthy margins (Figs. 3*B* and 4). The recipient nerve is mapped to ascertain the position of the sensory nerve fascicles with the aid of a sterile hand-held nerve stimulator (AcroVal® neurosensory and motor testing system; AcroMed, Alchua, FL). Once the sensory fascicles have been identified (usually on the outer side of the peripheral recipient nerve), an incision is made in the recipient epineurium of sufficient caliber to accept the diameter of the donor nerve. If the sensory fascicles happen to be positioned away from a direct route (i.e., the opposite side) of the recipient nerve, that nerve should be mobilized to allow easy access to the sensory fascicle site of the recipient nerve.

Typically, after neuroma resection (Fig. 4), a loss of length of the affected nerve results in a gap of variable length between the donor and the proposed recipient nerves (Fig. 3*B*). In an effort to maintain the normal sensory distribution to the lower extremity, a nerve allograft (Advance® nerve graft; AxoGen, Alchua, FL) is used to span the gap between the donor (neuroma-affected nerve) and recipient (normal nerve; Fig. 5).

Alternatively, an autologous sensory nerve, such as the sural nerve, can be harvested. If the donor nerve diameter is larger than the autograft, the nerve autograft is assembled using the cable technique, with the autograft cables all arranged in a retrograde orientation. However, we prefer to preserve the native nerve tissue and use the nerve allograft for nerve reconstruction.

High-power loupe magnification ($\times$3.5 to $\times$5) or the operating microscope is used for the nerve transfer procedure. For neuromas in continuity, the neuroma is resected and the native nerve trimmed sharply back to healthy-appearing fascicles (absence of scar and "mushrooming" of axons). The nerve allograft is anastomosed to both ends of the native nerve, using three to five 9-0 nylon sutures, by passing the microsurgical needle only through the epineurium only. The distal neural anastomosis is then drawn (entubulated) into a

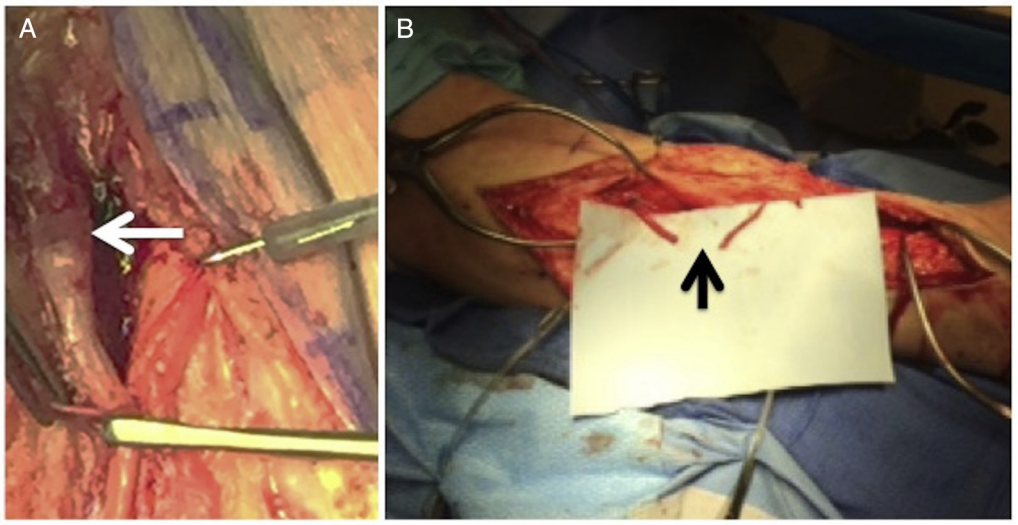

Fig. 3. (*A*) Neuroma *(white arrow)*. (*B*) Nerve after excision of neuroma back to healthy nerve tissue *(black arrow)*.

porcine submucosa nerve conduit of appropriate diameter (AxoGard® nerve connector; AxoGen) with either a one or two 9-0 nylon horizontal mattress sutures (entubulation). The proximal recipient nerve allograft nerve anastomosis is also entubulated (Figs. 1 and 5).

For stump neuromas, the end of the injured nerve is resected back to healthy fascicles. The end of the nerve allograft is drawn to the end of nerve conduit and anchored with an entubulation suture; the ends of the nerve allograft are placed in contact with the previously

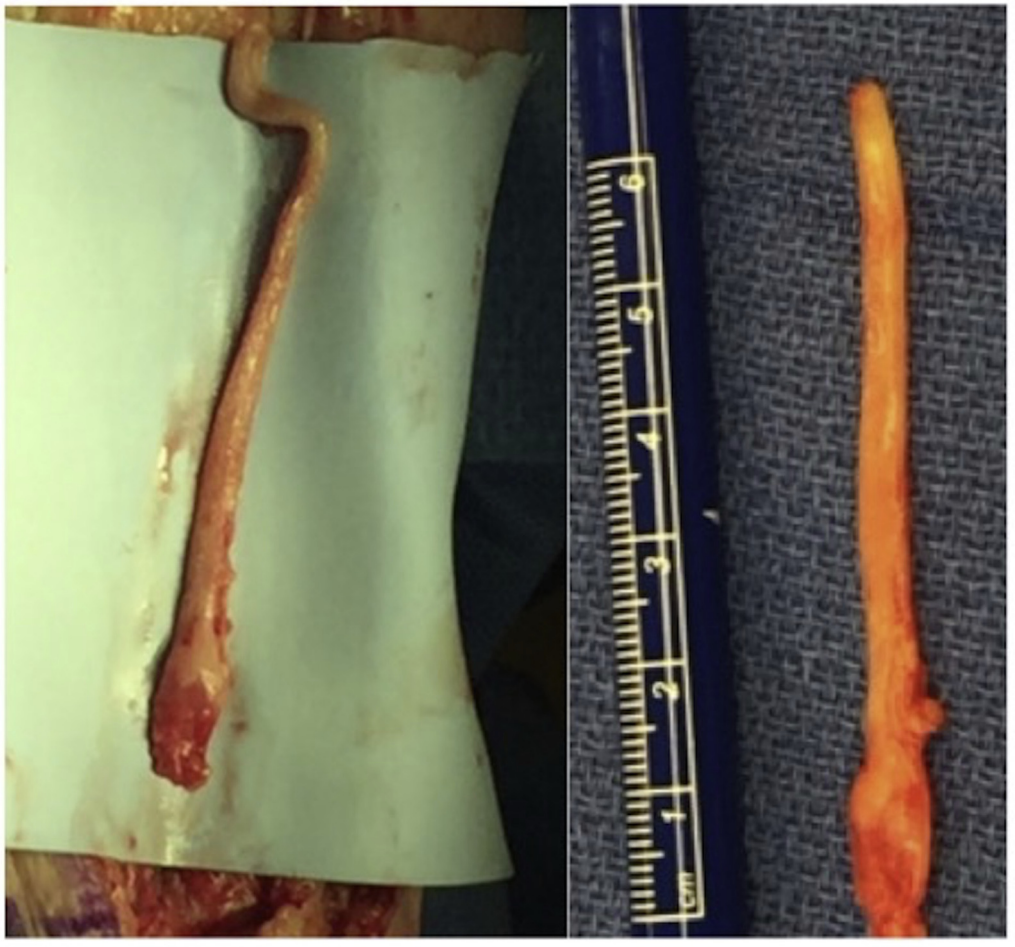

Fig. 4. Examples of stump neuromas, which also must be resected back to healthy nerve tissue.

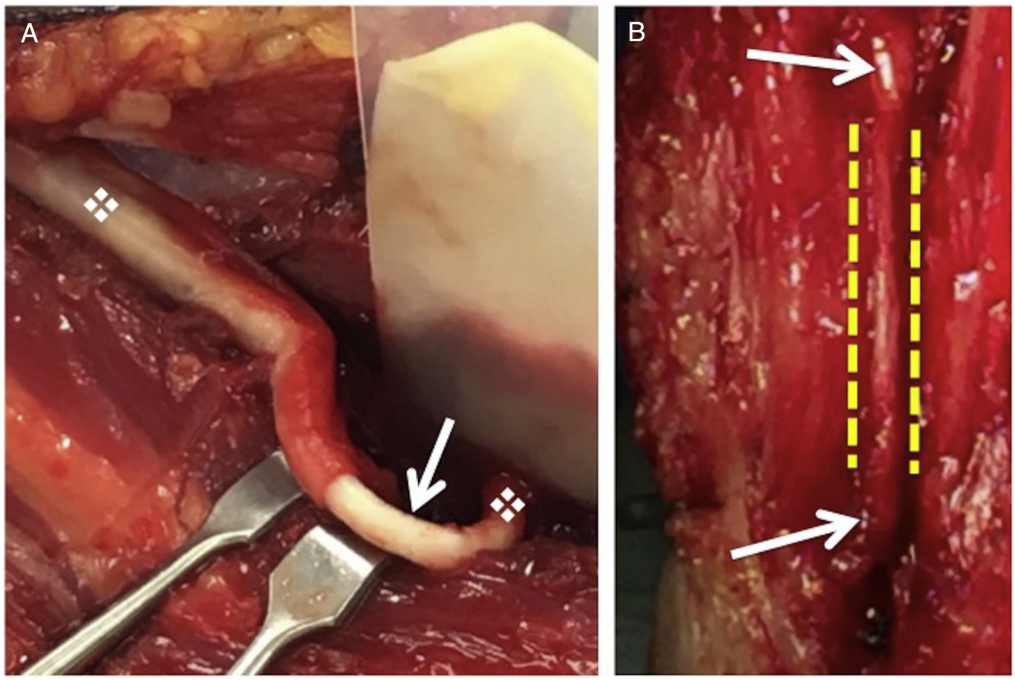

Fig. 5. (*A*) Final reconstruction of donor nerve allograft *(white arrow)* using nerve wrap *(diamonds)* as a conduit and an intercalary nerve allograft *(white arrow)*. (*B*) Example of final reconstruction of neuroma in continuity using conduits *(white arrows)* and an intercalary nerve allograft *(yellow dashed lines)*. Note that both were transected to the level of healthy nerve tissue, which was then transferred to the sensory component of the superficial peroneal nerve.

mapped sensory recipient nerve fascicles. The nerve conduit is sutured to the incised epineurium of the recipient nerve in an end-to-side fashion with 9-0 nylon (Fig. 2). The proximal end of the nerve allograft graft is also entubulated to the point of anastomosis with the recipient nerve. The nerve conduit is irrigated clear of blood and sterile normal saline or sterile water instilled. If a diameter mismatch exists, the nerve allograft can be wrapped with a protective nerve wrap (Axogard® nerve protector; AxoGen), which is longitudinally closed watertight with microsurgical suture (8-0 or 9-0 nylon). Fibrin glue can be applied to the nerve–conduit junction, along with protective nerve wraps, and to the nerve recipient–nerve transfer anastomosis to help seal any microgaps in the reconstruction. Closure is performed in layers, with the exception of closure of the deep fascia (to prevent undue compression). Skin closure is performed per surgeon choice. Drains are used as needed, just as is an incisional negative pressure dressing (Prevena™ Incision Management System; KCI, San Antonio, TX).

Postoperatively, just as in most peripheral nerve surgeries, patients are allowed touch-down weightbearing to tolerance for 1 week, and elevation is encouraged. Active range of motion and progressive weightbearing is begun at 1 week. In addition to any necessary narcotics, the surgeon can choose gabapentin immediately postoperatively, with the dosage quickly elevated to a maximum dose that is limited by patient tolerance to the side effects (typically 300 mg every 8 hours up to a maximum of 800 mg 3 times daily). Gabapentin can be continued for a period of 1 to 2 months, at which time, the patients are weaned off gabapentin.

Results

The present study was exempt from institutional review board approval owing to the small number of subjects (considered a small case series). Of the 4 patients, 3 were male and 1 was female; the mean patient age was 51 (range 42 to 74) years. None of the patients in the study cohort were diabetics or smokers. All patients underwent an end-to-end nerve transfer using a nerve autograft with an entubulation technique. No surgical site complications such as seroma, hematoma, infection, deep vein thrombosis, or incisional breakdown developed.

The mean final follow-up period was 26 (range 18 to 31) months. The mean preoperative visual analog scale (VAS) pain score was 9.5 (range 8 to 10). The mean postoperative VAS pain score was 1.25 (range 0 to 2). The difference in the VAS pain scores from preoperatively to the final postoperative follow-up visit was statistically significant ($p < .05$, 2-tailed paired Student's t test; Minitab 17 Statistical Software, State College, PA; Table).

Discussion

The musculoskeletal surgeon is quite often responsible for patients who develop neuromas after amputations, as surgical complication or a secondary complication such as a secondary complication, such as related to a prosthetic socket. Stump neuromas can occur even when an amputation is performed with flawless technique. It has been the observation of 1 of us (C.B.) that certain amputation techniques lend to the development of stump neuromas, namely the von Ertl bone–bridge transtibial amputation technique.

Measures to help prevent or reduce the incidence of stump neuromas and to manage existing stump neuromas have included free release of a transected nerve (during amputation), the creation of a nerve "blind loop," and performing neuromyodesis or neuro-osteodesis. Each has met with some degree of success, which could likely contribute to surgeon preference in selecting a technique to prevent or manage stump neuromas after amputation.

Probably the most vexing clinical scenarios are the development of a stump neuroma and attempting to prevent a second recurrence of a stump neuroma. This has resulted in the concept of allowing a resected end of a stump neuroma to incorporate into a regional

Table
Summary of patient data

Variable	Pt. No.			
	1	2	3	4
Age (yr)	45	44	74	42
Gender	Male	Female	Male	Male
Smoker	No	No	No	No
Diabetes	No	No	No	No
Neuroma etiology	Closed leg trauma	Sural nerve transection with stump neuroma during previous surgery	Transection of nerve during previous surgery	Nerve transection during previous surgery
Neuroma site	Neuroma in continuity of sural nerve	Stump neuroma of sural nerve	Stump neuroma of superficial peroneal nerve	Stump neuroma of superficial peroneal nerve
Previous failed treatment	Neurectomy, neuromyodesis	Sural neurectomy, neuromyodesis	Neurectomy, neuromyodesis, decompression	None
Nerve transfer technique	Nerve allograft, end-to-side entubulation	Nerve allograft, entubulated using nerve wrap (nerve–graft anastomosis junctions within nerve wrap)	Nerve allograft, end-to-side entubulation	Nerve allograft, end-to side entubulation
Recipient nerve	Superficial peroneal nerve	Superficial peroneal nerve	Deep peroneal nerve	Deep peroneal nerve
Preoperative VAS pain score*	10	10	10	8
Final follow-up VAS pain score*	2	1	0	2
Follow-up time (mo)	18	25	28	31

Abbreviations: Pt. No., patient number; VAS, visual analog scale.
* Mean preoperative and final VAS pain scores were statistically significant, $p < .05$.

secondary peripheral nerve. This offers the advantage of "like tissue" sprouting into "like tissue" and affords the opportunity of the nerve end to take advantage of the "cytoskeletal architecture" of the recipient nerve, the antegrade nutritional support, and mechanisms to "dampen" aberrant electrical transmissions along the path to the central nervous system. This last mechanism is exemplified by the pathophysiology of complex regional pain syndrome. In complex regional pain syndrome, for which a large number of pathophysiologic processes are present, it is notable that sympathetic sprouting, inflammation, and the overproduction of substance P result in pain (3). Overactivation of protein kinase C-mediated impulses along the injured nerve or nerves contributes to overexcitation of neurons at Rexed lamina I to IV levels in the dorsal horn of the spinal cord, resulting in pain perception. The findings from animal models have also suggested that the activation of mitogen-activated protein kinases in spinal glial cells results in peripheral injury and pain (4). Additionally, a lowering of the threshold of action potentials from C-fibers in neuromas to pass into the spinal cord level (by way of T-junctions) has been demonstrated in a murine animal model and thus appear to be a direct contributor to pain impulse generation from peripheral neuromas (5). We hypothesized that the use of a nerve transfer, accompanied by entubulation, would mitigate these neuropathologic responses to peripheral nerve injury, specifically the resection and "nerve-sparing" transfer of an injured peripheral nerve to an uninjured peripheral nerve. We prefer nerve conduits prepared from porcine submucosa, because porcine tissue is highly compatible with human tissue and has been shown to decrease adhesions and scar formation and enhance tissue gliding when reconstructing lower extremity tissues (6). Additionally, it has been our experience that nerve conduits made of materials other than porcine submucosa result in adhesions and dense scarring at the conduit–tissue bed interface, the important function of nerve gliding.

Using the nerve transfer technique an entubulated nerve allograft provides a potential mechanism to avoid the misguided sprouting of neurons that results in suboptimal functional results. Additionally, the use of entubulation might provide an environment to decrease inflammation, reduce pain-generating molecules, improve axoplasmic flow, and allow proper axon guidance by locally containing neural cell adhesion molecules and its polysialic acid moiety, which are essential growth factors facilitating proper guidance of axon growth (7).

The major limitation of the present study was the small subject size. Thus, we consider it a pilot study to be used as a platform for larger scale studies. Despite this, at a mean follow-up period of 26 months, the nerve transfer technique as described resulted in statistically significant improvements in VAS pain scores. We believe that the management of stump neuromas and neuromas in continuity managed as we have described can provide tremendous clinical improvement in pain for recurrent lower extremity neuromas.

In conclusion, painful neuromas of the lower extremity can result in major morbidities to the affected patients, resulting in disabilities for work, avocations, and simple activities of daily living. Although a number of neuroma operations are available to the surgeon, subjectively, these could be suboptimal for long-standing neuromas that have resulted in unrelenting pain and disability. The technique of nerve transfer proposes physiologic advantages to assist in overcoming the pathophysiologic processes that drive pain generation in the setting of peripheral neuromas. In select patients, nerve transfer is a valuable technique to manage painful neuromas of peripheral nerves in the lower extremity.

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