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Original Research

Use of Vascularized, Denervated Muscle Targets for Prevention and Treatment of Upper-Extremity Neuromas

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Purpose: Neuroma formation following upper-extremity peripheral nerve injury often results in persistent, debilitating neuropathic pain with a limited response to medical management. Vascularized, denervated muscle targets (VDMTs) offer a newly described surgical approach to address this challenging problem. Like targeted muscle reinnervation and regenerative peripheral nerve targets, VDMTs are used to redirect regenerating axons from an injured nerve into denervated muscle to prevent neuroma formation. By providing a vascularized muscle target that is reinnervated via direct neurotization, VDMTs offer some theoretical advantages in comparison with the other contemporary surgical options. In this study, we followed the short-term pain outcomes of patients who underwent VDMT surgery for neuroma prevention or treatment.
Methods: We performed a retrospective chart review of 9 patients (2 pediatric and 7 adult) who underwent VDMTs either for symptomatic upper-extremity neuromas or as a prophylactic measure to prevent primary neuroma formation. In-person and/or telephone interviews were conducted to assess their postoperative clinical outcomes, including the visual analog pain scale simple pain score.
Results: Of the 9 patients included in this study, 7 underwent VDMT surgery as a prophylactic measure against neuroma formation, and 2 presented with symptomatic neuromas that were treated with VDMTs. The average follow-up was 5.6 ± 4.1 months (range, 0.5–13.2 months). The average postoperative pain score of the 7 adult patients was 1.1 (range, 0–8).
Conclusions: This study demonstrated favorable short-term outcomes in a small cohort of patients treated with VDMTs in the upper extremity. Larger, prospective, and comparative studies with validated patient-reported and objective outcome measures and longer-term follow-ups are needed to further evaluate the benefits of VDMTs in upper-extremity neuroma management and prevention.
Type of study/level of evidence: Therapeutic III.

Peripheral nerve injuries have an incidence surpassing 200,000 annually in the United States.[1] Peripheral nerve injuries can result from a vast array of mechanisms, including transection, chronic irritation, compression, stretch, and iatrogenic surgical injuries. Whenever a nerve is injured and cannot be repaired, free nerve endings regenerating from the proximal nerve stump form aggregates of disorganized neural growth known as neuromas.[2] These neurons lacking end-organ interaction exhibit spontaneous activity and pain that can be exacerbated by mechanical stimuli, resulting in a considerable decrease in quality of life.[3] With the first reports on painful neuroma formation recorded in 1634 by Abroise Pare, this problem continues to plague patients and surgeons in the 21st century.[4] Simpler surgical techniques, such as direct excision of the neuroma alone, were originally posited as solutions to this problem; however, recurrence and continued neuropathic pain are both

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possible after these interventions. Burying the proximal end of an injured nerve in muscle can provide moderate benefits; however, innervated muscle will not accept additional innervation from an injured nerve implanted within it, and this approach results in neuroma recurrence within the muscle.[5] Based on an improved understanding of axonal regeneration and nerve physiology, more recent techniques have focused on the use of denervated muscle sources as a potential reinnervation target for the axons regenerating from the injured proximal nerve stump.

Targeted muscle reinnervation (TMR) involves coaptation of the injured nerve to a nearby motor nerve, such that the axons regenerating from the injured nerve are redirected into a denervated target muscle.[6] This procedure was originally developed to provide signal amplification and intuitive control of advanced prostheses for amputees, and was later found to help mitigate neuroma pain in this patient population.[7,8] Although TMR has been shown to be efficacious in preventing neuropathic pain, there is the concern that the substantial size mismatch that tends to be present between the injured proximal nerve stump and the much smaller recipient motor branch can result in axonal escape and neuroma formation at the site of coaptation. It also requires identification of a nearby recipient motor nerve that may not be readily available. Based on the same concept of using denervated muscle as a target for reinnervation, regenerative peripheral nerve interfaces (RPNIs) are constructed by implanting severed nerves into avascular, free muscle grafts.[9] These grafts then serve as denervated targets for an ingrowth of axons from the injured nerve(s). These biologic constructs have been shown to generate and amplify EMG signals from motor nerves, which can then be used for control of myoelectric limb prostheses.[10] Like all grafts, RPNIs initially subsist on diffusion of nutrients from their local wound bed before eventual revascularization. However, this process has size constraints, as RPNIs that are too large to be maintained by diffusion will undergo central necrosis.[11,12] All RPNIs, regardless of size, will undergo some degree of fibrosis and tissue resorption during the healing process. A wound bed that is compromised by radiation or infection also poses the risk of poor graft take. These considerations raise a concern regarding whether RPNI grafts maintain sufficient capacity to serve as reinnervation targets for all incoming axons from the injured nerve being treated.

Recently, vascularized, denervated muscle targets (VDMTs) have been described as an option for neuroma prevention and treatment.[13] This procedure involves first raising an island of muscle on a vascular leash, such that it is denervated while remaining vascularized. The injured nerve stump is then implanted within or wrapped with a denervated muscle flap.[13] This technique is similar to RPNI but obviates concerns regarding the viability and size constraints of avascular muscle grafts. By relying on direct neurotization of the muscle that fully envelops the transected end of the nerve being treated, VDMTs also avoid the concern of a donor-recipient nerve size mismatch in TMR. This series describes the use of this procedure in patients as either a prophylactic measure against neuroma formation or as a treatment for symptomatic neuromas in the upper extremity.

Materials and Methods

After obtaining institutional review board approval (Johns Hopkins University School of Medicine, S.H.T. and the Curtis National Hand Center, A.M.G), we performed a retrospective chart review of 9 patients (2 pediatric and 7 adult) who underwent VDMT surgery by the 2 senior authors between July 2019 and September 2021 either for symptomatic upper-extremity neuromas or as a prophylactic measure against neuroma formation.

The VDMT surgical technique has been published elsewhere.[14] In brief, the surgeon identifies candidate vascular branches entering muscles that are in close proximity to the injured nerve or neuroma and isolates them with vessel loops. After releasing the tourniquet and restoring perfusion to the extremity, these branches are then interrogated with a handheld Doppler ultrasound. The surgeon then designs small muscles flaps that may vary in size depending on the caliber of the nerve that is to be treated; general dimensions are usually $3 \times 3 \times 2$ cm for small, cutaneous nerves, with an increasing size of the muscle flap as the presumed axonal count of the nerve to be treated increases. Ultimately, the size of the construct is up to surgeon discretion and the state of the flap's vascular inflow. Care is taken to avoid harvesting these flaps from key areas that may compromise the functionality of the donor muscle (such as the musculotendinous junction). Any nerves traveling with the vascular leash are identified and divided, and the vascular leash is then electrically stimulated to ensure complete denervation of the muscle flap. The surgeon then performs neurolysis of the proximal stump of the injured nerve for several centimeters to allow for mobilization and tension-free transposition toward the VDMT. The most distal extent of the nerve is sharply resected until healthy appearing fascicles are visualized. The proximal stump is then buried into or wrapped with the VDMT and secured with fibrin glue under surgical loupe magnification. Epineurial sutures, often 8-0 nylon, can be used to secure the nerve stump to the surrounding VDMT if there is concern for tension with postoperative motion. Our postoperative care depends on the site of VDMT creation and our level of concern that the nascent construct could be disrupted by motion. In general, the senior authors (A.M.G and S.H.T) prefer a bulky, soft dressing that is to be kept on for approximately 1 week before the first follow-up, with orthosis fabrication used only when the VDMT is created in close proximity to a joint and when the patient has limited soft-tissue bulk.

After VDMT, we conducted in-person and/or telephone interviews with these patients to assess their postoperative clinical outcomes; in some instances, telephone interviews were necessitated by institutional policies to combat the coronavirus disease 2019 pandemic. A simple pain score (scale of 0–10, with 0 being no pain whatsoever and 10 being the worst pain experienced) was collected during follow-up visits.

Results

Table shows the demographic characteristics of the 9 patients included in this study. The average age was 42.8 years (range, 2–81 years). The average follow-up was 5.6 ± 4.1 months (range, 0.5–13.2 months). Six patients underwent amputations (5 transradial, 1 transhumeral). One (patient #1) presented with gangrene of multiple fingers secondary to severe peripheral vascular disease, which was treated with transradial amputation. One patient (patient #2) was diagnosed with giant cell tumor of the hand and chronic pain, which were treated with transradial amputation. Two patients (patients #3 and #4) underwent transradial amputations to treat ischemia-induced gangrenous changes secondary to coronavirus disease 2019 infection and prolonged hospitalization. Another patient (patient #5) underwent transhumeral amputation after a failed total elbow arthroplasty and multiple salvage attempts. One pediatric patient (patient #8) underwent transradial amputation for treatment of osteosarcoma of the radius. All of these patients had VDMT management of their major peripheral nerves at the time of amputation. Of these 6 patients, 2 (patients #1 and #5) experienced some degree of phantom limb pain (PLP).

Two patients presented with symptomatic neuroma of the radial sensory nerve; the etiologies of these injuries included

Table
Patient Demographics

Patient	Gender	Age at Surgery, y	Duration of Follow-Up, mo	Index Surgery	Rationale for VDMT	Nerves Used for VDMT	Muscles Used for VDMT	Pain Score at Final Follow-Up	Other Pertinent Findings
1	M	80	1.6	Transradial amputation for gangrenous fingers	Prophylaxis	radial, median, ulnar	FDS, FDP, FCU	0	Reports PLP completely resolved
2	M	57	0.5	Transradial amputation for giant cell tumor of the hand	Prophylaxis	radial, median, ulnar	FCR, FDP, FCU	0	Reports no PLP
3	M	56	6.5	Transradial amputation for ischemia-induced gangrene secondary to COVID-19 infection	Prophylaxis	radial, AIN, ulnar	FDP, PQ	0	Reports no PLP
4	F	50	2.1	Transradial amputation for ischemia-induced gangrene secondary to COVID-19 infection	Prophylaxis	radial, median, ulnar	FDS, FCU, PQ	0	Reports no PLP
5	F	68	3.2	Transhumeral amputation after failed elbow arthroplasty	Prophylaxis	median, radial, ulnar, LABC	triceps, coracobrachialis, biceps	8	Reports notable PLP, but denies any localized neuromatous pain
6	M	37	7.1	de Quervain tenosynovitis release complicated by infection and washout with injury to RSN	Symptomatic neuroma (15-month duration)	RSN	FCR	0	No longer experiences exquisite, localized pain in forearm at the neuroma site as previously experienced
7	M	2	7.5	Debridement of antecubital fossa wound after motor vehicle accident	Prophylaxis	PBCN	triceps	0	
8	M	10	8.4	Transradial amputation for osteosarcoma	Prophylaxis	Median, ulnar, and radial	PT	0	Reports no PLP
9	M	20	13.2	Radial forearm free flap complicated by injury to RSN	Symptomatic neuroma (11-month duration)	RSN	Brachioradialis	0	

AIN, anterior interosseus nerve; COVID-19, coronavirus disease 2019; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis; LABC, lateral antebrachial cutaneous nerve; PBCN, posterior brachial cutaneous nerve; PQ, pronator quadratus; PT, pronator teres; RSN, radial sensory nerve.

damage to the nerve after radial forearm flap harvest and after de Quervain tenosynovitis release complicated by a local infection necessitating washout (patients #9 and #6, respectively). Finally, 1 pediatric patient presented with an open wound of the antecubital fossa with an exposed posterior brachial cutaneous nerve after a motor vehicle collision (Fig.).

The average postoperative pain score of the 7 adult patients was 1.1 (range, 0–8). Six patients reported a pain score of 0 and 1 patient reported a pain score of 8. The latter reported that the pain is predominantly PLP.

Discussion

Symptomatic neuromas of the upper extremity after peripheral nerve injury can severely impact the patient's quality of life, psychosocial functioning, and ability to wear a prosthesis.[15] Although multimodal pharmacotherapeutic regimens, such as opioids and gabapentinoids, may be used for symptom management, medical management alone does not provide complete symptom relief and has its own limitations, including the potential for sedation, dependence, or overdose.[16] Thus, the effective prevention and treatment of neuromas remains a critical need to be addressed by the hand and peripheral nerve surgeon. In this study, we followed the short-term pain outcomes of patients who underwent VDMT surgery for neuroma prevention or treatment. We found that 7 out of 8 adult patients reported clinically considerable pain relief and both pediatric patients functioned without obvious pain; 1 adult patient reported PLP but did have improvements in localized neuroma pain.

Like TMR and RPNI, the goal of VDMT surgery is to redirect axons regenerating from a severed nerve in denervated muscle rather than allowing them to form a neuroma.[13] Vascularized, denervated muscle target surgery offers some theoretical advantages in comparison with TMR and RPNI. The size-mismatched nerve repairs that tend to occur in TMR raise concerns for axonal escape and neuroma formation at the site of the coaptation between the larger, proximal nerve stump and the smaller, distal donor motor nerve. This has led to some modifications in the original technique, such as performing the coaptation at or within the denervated muscle target.[17,18] However, VDMT obviates this issue by relying on direct neurotization of muscle that completely envelops the end of the injured nerve stump. Furthermore, unlike TMR, the use of VDMT surgery is not limited by the availability of a suitable locoregional motor nerve branch. In the upper extremity, there are numerous intramuscular perforators that can be used as the vascular pedicle for a muscle graft without compromising the functionality of the donor muscle.

Vascularized, denervated muscle targets share many similarities with RPNIs, in that they involve direct neurotization of a muscle target placed on the end of an injured nerve stump. However, an important consideration for RPNIs is the influence of the size of the muscle graft on overall viability. Since RPNIs are devascularized, they are initially sustained via diffusion of nutrients from the surrounding wound bed. During the process of engraftment, they undergo some degree of ischemia-induced fibrosis and resorption before neovascularization of the graft. Thicker grafts are susceptible to central necrosis. Previous work has shown that in rodent models, smaller muscle grafts are most successful as the central zones of

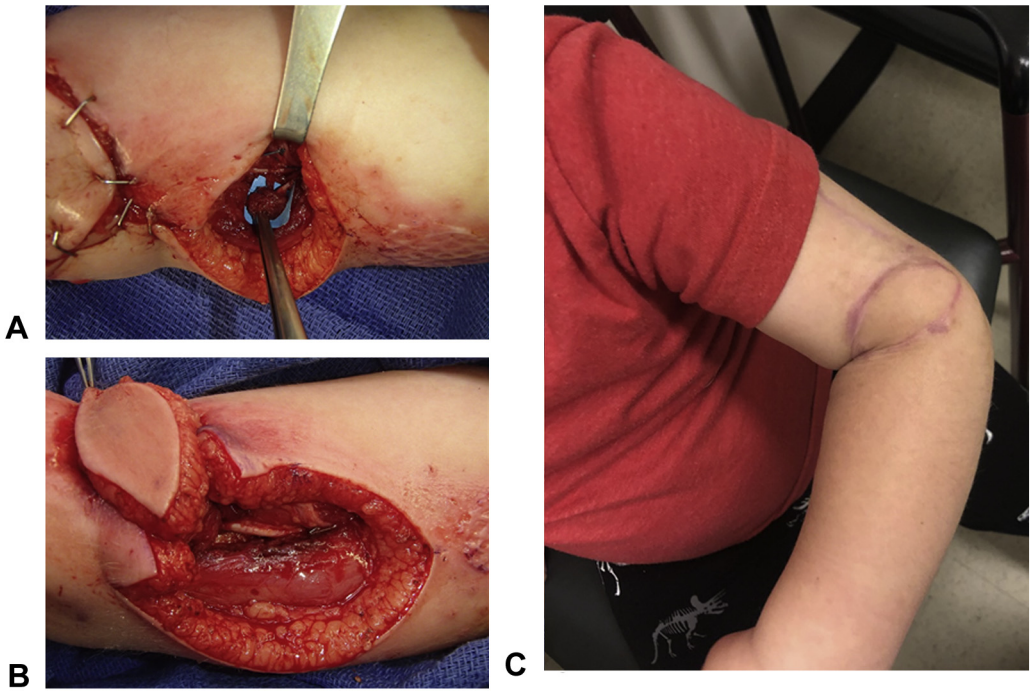

Figure. A Debridement of an antecubital fossa wound after a motor vehicle accident, with a subsequent soft-tissue defect and exposed posterior brachial cutaneous nerve; the VDMT creation used the triceps. **B** Pedicled, lateral arm flap for soft-tissue coverage. **C** The patient at the 7-month follow-up, with a well-healed flap and no evidence of symptomatic neuroma or pain.

these grafts and are more likely to be replaced by regenerating fibers.[11,19] Conversely, since VDMTs are perfused by a vascular pedicle, they can heal without the same degree of ischemia-induced fibrosis and do not have the same size limitations as RPNIs. The dimensions of a given VDMT are contingent on the orientation and amount of perfusion provided by its vascular pedicle.[13] Intraoperative assessment of perfusion can be performed; the margins of the VDMTs may be trimmed as necessary until bright red bleeding is noted. This raises a critical, unanswered question pertaining to the amount of viable muscle tissue required to adequately treat a nerve of a given caliber. Addressing this question will help to shed light on the indications and relative benefits of VDMTs in comparison to RPNIs.

Of the 9 patients included in this study, 6 underwent some level of amputation of the upper extremity (5 transradial, 1 transhumeral). Of these 6 patients, 2 experienced some degree of PLP in addition to localized neuroma pain. One patient (patient #5) reported persistent PLP after amputation and subsequent VDMT surgery. This patient underwent a failed total elbow arthroplasty and had multiple attempts at salvage and reconstruction before eventual transhumeral amputation. Another patient (patient #1) experienced almost complete resolution in their PLP over the course of their postoperative follow-up. Phantom limb pain is a complex, neurologic process that involves both the peripheral and central nervous systems.[20] Although the exact etiology is unclear, PLP is thought to be secondary to aberrant peripheral sensitization and dysfunctional cortical remodeling induced by afferent signaling from transected nerve ends.[8,21] Both TMR and RPNI offer some degree of efficacy in treating and preventing PLP, in addition to localized neuroma pain.[22,23] By providing a reinnervation target for transected peripheral nerves (whether distal motor nerves; devascularized, denervated muscle grafts; or vascularized, denervated muscle flaps), TMR, RPNI, and now VDMT all potentially prevent the aberrant signaling from the transected stumps of injured peripheral nerves that may contribute to the dysfunctional cortical remodeling that contributes to PLP. Although this study shows only the short-term outcomes for patients who underwent upper-extremity VDMT surgery, it is promising that 83% of patients with amputations experienced either no PLP or improvement in PLP symptoms. However, final conclusions about the use of VDMTs for the treatment of phantom pain cannot be made until longer-term follow-up has been achieved.

There are several limitations to our study. This is a small case series with short-term follow-ups. Additionally, there are inconsistencies across patients in the pre- and postoperative data points that were measured and how data were obtained. Furthermore, the outcomes of interest—namely, resolution of pain and numbness—were not measured using validated patient-reported outcome measures. However, the limited results from this study show that many patients who underwent VDMT surgery for neuroma prevention and treatment experienced near-complete or complete resolution of pain. Future, prospective studies with validated patient-reported outcome measures between distinct treatment arms, comparing VDMT to RPNI or TMR, are needed to firmly establish the role of this novel technique in treating and/or preventing neuromas.

This study examined the use of VDMTs for the treatment and prevention of neuroma formation in the upper extremities of 9 patients. Along with TMR and RPNI, VDMT is an addition to the armamentarium of the hand or peripheral nerve surgeon when faced with symptomatic neuromas in the upper extremity. Future, comparative studies with longer-term outcomes are needed to further examine the benefits of VDMTs for this patient population.

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