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Targeted muscle reinnervation for the management of pain in the setting of major limb amputation

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Abstract

The life altering nature of major limb amputations may be further complicated by neuroma formation in up to 60% of the estimated 2 million major limb amputees in the United States. This can be a source of pain and functional limitation of the residual limb. Pain associated with neuromas may limit prosthetic limb use, require reoperation, lead to opioid dependence, and dramatically reduce quality of life. A number of management options have been described including excision alone, excision with repair, excision with transposition, and targeted muscle reinnervation. Targeted muscle reinnervation has been shown to reduce phantom limb and neuroma pain for patients with upper and lower extremity amputations. It may be performed at the time of initial amputation to prevent pain development or secondarily for the treatment of established pain. Encouraging outcomes have been reported, and targeted muscle reinnervation is emerging as a leading surgical technique for pain prevention in patients undergoing major limb amputations and pain management in patients with pre-existing amputations.

Keywords

Neuroma, pain, TMR, amputation, neuroma, nerve transfer, nerve, chronic pain, residual limb pain, stump pain, phantom limb pain

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Background

Major limb amputations are life altering events for patients. Beyond the deficits in form and function, there is a risk of significant post-amputation pain that can manifest itself in the weeks, months, and years following the amputation. This pain decreases quality of life, increases the risk of depression, negatively affects interpersonal relationships, and impacts the ability to return to work.¹ It has been reported that 70%–80% of the greater than 2 million major limb amputees in the United States deal with chronic pain of varying etiologies.^{1,2} The commonly reported amputation-related pain etiologies can be categorized as residual limb pain (RLP), phantom limb pain (PLP), and neuroma pain.

RLP, commonly referred to as “stump pain,” is localized intense pain that impacts prosthetic use and is a frequent cause of revision surgery.³ There are several etiologies of RLP including organic causes such as soft tissue inflammation, infection, osteomyelitis, and heterotopic ossification, but symptomatic neuromas are most often the underlying

cause. It is important to differentiate the etiology of RLP when recommending management. The mechanisms of PLP, or the perceived notion of pain in the amputated limb, are not entirely understood. However, both PLP and neuroma-related RLP are related to the transection of major nerves—a necessary step of any amputation. When a peripheral nerve is severed, it will invariably attempt to regenerate. Nerve regeneration is guided both by the intrinsic pathway in the nerve and by signals from the distal target that it innervates. When these distal targets are unavailable, as is the case with a major limb amputation, there is a greater

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risk of aberrant and inappropriate axonal regeneration leading to the formation of amputation site neuromas.

A neuroma consists of uncontrolled axonal growth entwined with myofibroblasts, Schwann cells, and endothelial cells. Up to 60% of patients with a nerve injury can develop a painful neuroma.^{4,5} Traditional amputation techniques addressed major nerves with traction neurectomy at the time of limb amputation. In this technique, traction is applied to the nerve as it is transected as proximal as possible so that the severed end will retract under viable proximal soft tissue. Despite traction neurectomy being a standard part of amputation technique, amputation site pain and neuroma formation are still a significant problem that impact overall quality of life after limb amputation.

The scope of this issue should not be underestimated. There are approximately 185,000 major limb amputations performed each year and approximately 2 million amputees currently living in the United States.⁶ This population is projected to rise to 3.6 million by 2050.⁷ Phantom limb pain and RLP following major amputations are unfortunately quite common, with a prevalence of at least 30%–50%.⁸ These numbers are likely under reported. Following major limb amputations, there is a 40%–50% reoperation rate, with neuromas being the second most common reason for reoperation.^{9,10} Beyond the pain itself, neuromas often make the use of a prosthetic uncomfortable or intolerable, which impacts the functional quality of a patient's life.⁶

As our understanding of the peripheral nervous system has improved, it has become clear that severed nerves will invariably attempt to regenerate from the site of neurectomy to reach a distal target.¹¹ In the case of traditional amputation, no distal target is available, leaving a high risk situation for neuroma formation. This can have significant consequences for both the peripheral and the central nervous systems, as patients can theoretically eventually develop centralization of their pain symptoms.⁶ Management of neuroma-associated pain is multifactorial. There can be several contributing factors including mechanical pain, centralized pain, depression and psychosocial issues. Surgical intervention addresses the mechanical aspect of a patient's pain.

With the substantial morbidity seen following major limb amputations secondary to neuroma pain, strategies are needed to both prevent and treat neuromas. Over 100 surgical techniques have been reported for the surgical treatment of neuromas, with no consensus on the best treatment. A comparative meta-analysis stratified patients into 5 groups according to the treatment they received: excision and transposition (63%), excision only (35%), excision and repair (20%), neurolysis and coverage (19%), and excision and cap (4%).¹² This study concluded that surgical treatment resulted in a meaningful reduction in pain in 77% of the patients with no significant differences between surgical techniques. In stratified analysis for confounding variables, excision and transposition and neurolysis with coverage were statistically more effective when neuroma pain was present for greater

than 24 months prior to surgery or when the patient had already had one or more prior operations compared to excision and repair or excision alone, respectively.¹² These findings suggest that surgery can be an effective intervention for the management of neuroma pain. However, there remains much room for improvement.

Clinical and anatomic applications of targeted muscle reinnervation

Targeted muscle reinnervation (TMR) offers a new approach to neuroma management—as a result a paradigm shift regarding the surgical management of neuromas is currently taking place. It has been known for decades that placing a severed nerve end into muscle capitalizes on our understanding that microenvironment matters for nerve regeneration.¹³ Placement of transected sensory nerves in muscle yields small, organized nerve fibers with no myofibroblasts, neuroma formation, or connections to the skin.¹³ In TMR, this is taken a step further and the severed nerves are coapted to end motor targets (the entry point of a nerve branch into muscle) of an innervated muscle, giving the severed nerves analogous tissue and a functional target to reinnervate. In other words, TMR gives the regenerating fascicles “somewhere to go and something to do,” not just “somewhere to go.”¹⁴ TMR that is performed months to years after the index amputation surgery, when the patient has established neuroma pain, is referred to as “secondary” TMR. The successful clinical results seen with secondary TMR led to the development of “primary” TMR, performed at the time of limb amputation, in an effort to prevent development of PLP and neuroma pain. The objectives of primary TMR are the *prevention* of symptomatic neuromas and PLP, while the objective of secondary TMR is the *treatment* of symptomatic neuroma and PLP.

TMR in the upper limb

Introduced clinically in 2004, TMR was originally designed to improve prosthetic function after upper extremity amputation by innervating residual muscles to create additional electromyographic signals to operate a myoelectric prosthesis.¹⁵ Substantial clinical success was demonstrated with several initial case reports.^{16–18} Notably, the amplification of myoelectric signals for advanced bioprosthetic limbs in the upper extremity occurs regardless of the timing of TMR, that is, whether it is performed as primary or secondary TMR.¹⁸ In addition to good functional outcomes, it was noted that many patients who underwent TMR had subjective improvement in their pain.¹⁸ This led to studies investigating TMR as a clinical strategy to treat established neuromas of amputated limbs. TMR in the upper limb is now commonly employed to optimize control of myoelectric prostheses, but is also utilized for prevention or treatment of neuroma pain.^{19–23} Among patients with upper limb amputations, those with transradial amputations are most likely to report phantom

pain and the use of neuropathic pain medication.²⁴ The specific nerve transfers for TMR in the upper limb may vary depending on the exact level of amputation and quality of the remaining soft tissue.^{21,25} In the initial description of TMR for shoulder disarticulation, a cadaveric dissection demonstrated that the median, musculocutaneous, radial, and ulnar nerves could be identified several centimeters proximal to the glenohumeral joint.¹⁵ In addition, these nerves were able to reach the pectoralis motor targets (where the respective pectoral nerve branches are entering the muscle), and the segmental innervation of the pectoralis major proved to be favorable for TMR.¹⁵

TMR in the Lower Limb

TMR of the lower extremity is often performed in below knee and above knee amputations and is used to prevent or treat neuroma and PLP.¹⁸ Current mainstream lower extremity prosthetics do not require the myoelectric signals that their upper extremity counterparts do. Thus, performing TMR in the lower extremity, whether it be primary or secondary, is typically aiming to prevent and treat neuroma formation and pain only.

An anatomic dissection series was recently performed to identify a roadmap for the identification of end motor targets for TMR in a below knee amputation.²⁶ In this study, the major branch points of motor nerves and the motor entry points to the muscles of the leg were dissected in five cadaver specimens. This dissection series demonstrated that the tibialis anterior and the extensor digitorum longus were both acceptable targets in the anterior compartment. The peroneus longus had the most optimal motor entry points in the lateral compartment. In the superficial posterior compartment, the gastrocnemius and soleus muscles were both acceptable targets. The flexor digitorum longus was considered the best target located in the deep posterior compartment of the lower leg. This study provided a helpful road map to locate motor entry points in which to perform TMR in the lower extremity and aid in intra-operative decision making.²⁶

A similar anatomic dissection series was performed to identify motor targets in the setting of a transfemoral (“above-knee”) amputation.²⁷ Five lower limbs were dissected and the motor points of the 13 muscles of the thigh were assessed. At this level, the tibial and the common peroneal nerves are the main nerves to be transferred into motor end points of nearby muscles for TMR. In this dissection series, the motor points to the biceps femoris and the semimembranosus were found to be the most easily coapted to the common peroneal and tibial nerves, respectively. The motor end points were in close proximity to these nerves and consistently located over a smaller territory along the thigh. The gracilis, adductor longus, vastus lateralis and vastus intermedius were considered as alternative motor endpoints based on their proximity to the tibial and common peroneal nerves, but have more widespread motor end point distributions. The other muscles of

the thigh, notably the rectus femoris, sartorius, vastus medialis, adductor brevis and adductor magnus muscles had motor points removed from the tibial and the common peroneal nerves that would necessitate a more difficult nerve coaptation. Therefore, these motor points are less ideal for TMR in a transfemoral amputation.²⁷

Surgical technique

The amputation is performed per the surgeon’s preferred technique, accounting for soft tissue needs. Note that for secondary TMR cases, marking the site of any Tinel signs pre-operatively may help to locate neuromas.²¹ If the amputation is performed under tourniquet control, nerve stimulation to identify end motor targets should be performed within 20–30 min for reliable stimulation. Otherwise, the tourniquet must be released both for the purpose of hemostasis as well as allowing sufficient time for the nerves to recover from the ischemic palsy for stimulation. The use of a hand-held nerve stimulator allows identification of motor nerve branches entering the target muscle, known as the “end motor targets.” When performing TMR, paralytic agents and nerve blocks should be avoided until the nerve transfers are completed. The major peripheral nerves are identified and transected, leaving a substantial length to later perform TMR. Significantly more length needs to be left on the proximal nerves compared to a traditional amputation as the length is needed to facilitate the nerve transfer component of TMR. End motor targets are identified on neighboring innervated yet now de-functioned muscles. Ideal muscles for TMR are those that have lost their insertion sites as part of the amputation procedure (“defunctioned”) or have function that is redundant and have a motor innervation point that is in close proximity to the donor nerve.^{22,25} The major peripheral nerves that were previously transected are then coapted to the defunctioned muscle just proximal to the entry point of the motor branch into the muscle. End-to-end coaptation is performed from the transected peripheral nerve stump to the recipient motor nerve branch, typically using 8-0 nylon epineurial sutures. Fibrin glue may be utilized to augment the nerve coaptation as well.²⁵ If there is significant size discrepancy, muscle surrounding the motor nerve recipient is dissected to create a cuff of muscle tissue around the nerve coaptation with 5-0 suture. This theoretically optimizes ingrowth of the nerve transfer into both the target motor nerve as well as directly neurotizing the muscle. Different combinations of nerve transfer have been described, but any combination of nerve transfers will provide the amputated nerve with a target muscle. This is uniformly how TMR is approached, and the technique can be applied at almost any level of amputation. Recent reports have even described this technique in digital amputation.²⁸

For transradial amputations, TMR is typically performed for the median, ulnar and radial nerves. Common nerve transfers for transradial amputation TMR are listed in Table 1. At

Table 1. Recipient motor branches frequently utilized for targeted muscle reinnervation for each major nerve of the upper extremity by amputation level.

| Donor nerve | Recipient motor nerve branches |
|---------------------------------|---|
| Transradial amputations | |
| Median nerve | Flexor digitorum superficialis, flexor digitorum profundus, brachioradialis, extensor carpi radialis longus, flexor capri radialis, palmaris longus |
| Ulnar nerve | Flexor carpi ulnaris, flexor pollicis longus, extensor carpi radialis brevis, palmaris longus |
| Superficial radial nerve | Flexor digitorum profundus |
| Transhumeral amputations | |
| Median nerve | Short head of biceps |
| Ulnar nerve | Brachialis |
| Radial nerve | Lateral head of the triceps |
| Shoulder disarticulation | |
| Musculocutaneous nerve | Clavicular head of pectoralis major |
| Median nerve | Segment of sternal head of pectoralis major |
| Ulnar nerve | Segment of sternal head of pectoralis major |
| Radial nerve | Thoracodorsal nerve |

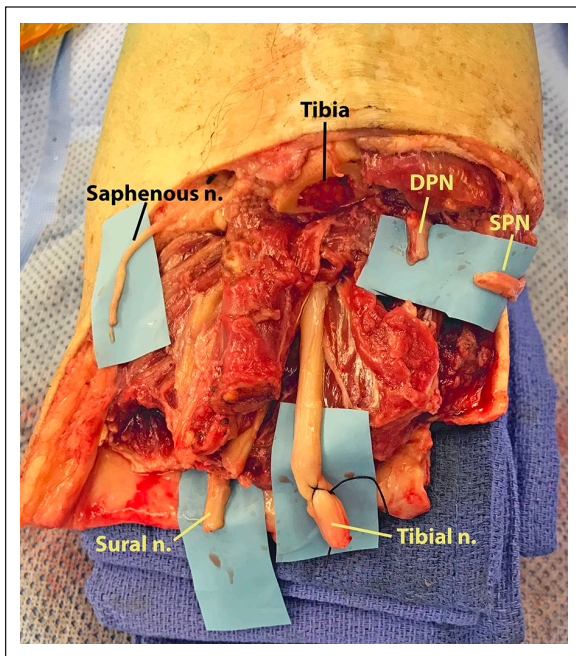


Figure 1. Intra-operative photo demonstrating the saphenous, sural, tibial, deep peroneal (DPN), and superficial peroneal (SPN) nerves in a below knee amputation prior to targeted muscle reinnervation.

the transhumeral level, TMR is usually performed for the musculocutaneous, median, ulnar and radial nerves (Table 1). For shoulder disarticulations, or very proximal transhumeral amputations, the infraclavicular brachial plexus is exposed.²¹ The cords of the brachial plexus can also be identified at this level. The specific nerve coaptations performed may vary at this level; see Table 1.

In below knee amputations, TMR is typically performed for the saphenous, sural, superficial and deep peroneal and the tibial nerves (Figure 1).²⁹ The common nerve transfers

performed for TMR in below knee amputations are summarized in Table 2.²⁹ In transfemoral amputations, TMR is usually performed for the tibial and common peroneal nerves. The posterior femoral cutaneous nerve may be coapted end-to-side to the tibial nerve for sensory reinnervation, if desired.⁴ The common nerve transfers performed for TMR in transfemoral amputations (Figure 2) are also summarized in Table 2.

Outcomes

Since its inception, the literature continues to demonstrate reliable improvement in outcomes with TMR related to both pain and function for patients requiring amputation. Souza et al.¹⁹ retrospectively evaluated the effect of TMR on residual neuroma pain in upper-extremity amputees. The primary purpose for TMR in this case series was improved myoelectric control for shoulder disarticulations and transhumeral amputations. Of the 26 patients in this study, 15 had evidence of postamputation neuroma pain before undergoing TMR. Of these 15 patients with neuroma pain, 14 had complete resolution, and one patient had improvement, but not complete resolution, of pain. The other 11 patients did not have any evidence of postamputation neuroma pain and remained free of neuroma pain after the procedure.¹⁹ A recent randomized control trial assessed the effect of TMR on 28 amputees with established neuroma pain who were assigned randomly to standard treatment with traction neurectomy or TMR.¹⁴ This study demonstrated a trend toward reduced RLP in the TMR group. Phantom limb pain scores were significantly better in the TMR group compared to traction neurectomy group. Results from this study also suggested that earlier (i.e. primary) TMR may be more effective in the prevention and treatment of neuropathic pain.¹⁴

Valerio et al.³⁰ performed a multi-institutional cohort study to assess the preemptive treatment of PLP and RLP

Table 2. Recipient motor branches frequently utilized for targeted muscle reinnervation for each major nerve of the lower extremity by amputation level.

| Donor nerve | Recipient motor nerve branches |
|--|---|
| Below knee amputations | |
| Posterior tibial nerve | Medial or lateral gastrocnemius, tibialis posterior, medial or lateral soleus |
| Deep peroneal nerve | Tibialis anterior, peroneus longus or peroneus brevis, medial soleus |
| Superficial peroneal nerve | Peroneus longus or peroneus brevis |
| Saphenous nerve | Medial gastrocnemius, medial soleus or vastus medialis |
| Sural nerve | Tibialis posterior or soleus |
| Transfemoral amputations | |
| Common peroneal nerve | Biceps femoris |
| Tibial nerve | Semimembranosus |
| Posterior femoral cutaneous nerve | Tibial nerve (end to side) |

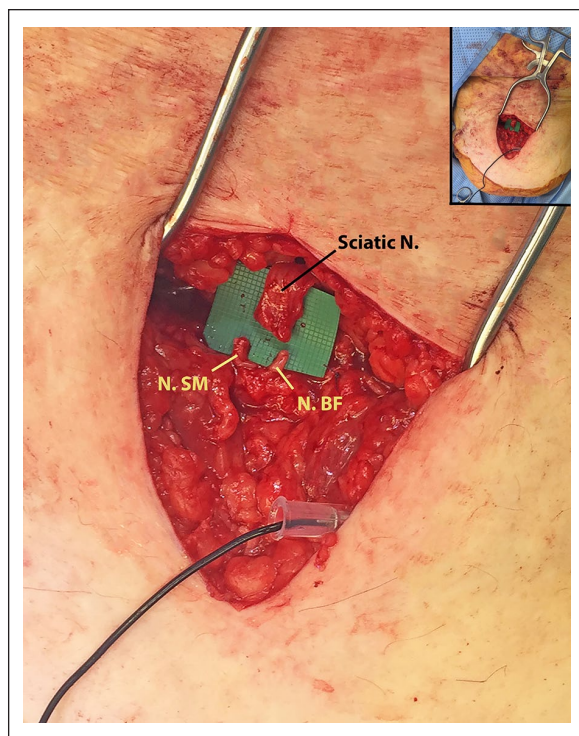


Figure 2. This patient with an above knee amputation is positioned prone for secondary targeted muscle reinnervation. The sciatic nerve will be divided into the tibial and common peroneal divisions and coapted to the nerves to the semimembranosus (SM) and biceps femoris (BF), respectively.

with TMR at the time of major limb amputation. Fifty-one patients undergoing immediate TMR were compared with 438 unselected major limb amputees. This cohort study demonstrated lower rates of PLP in the TMR group compared to the control group. Patient-Reported Outcomes Measurement Information System (PROMIS) scores were lower in the TMR group for PLP, pain behavior, pain interference and RLP. There were significant improvements in numerical rating scale pain scores as well. The TMR group also demonstrated a reduction in the use of opioid medications. The

authors of this study recommended strong consideration of primary TMR to reduce pathologic PLP and symptomatic neuroma-related RLP.³⁰

Bowen and colleagues performed TMR on 22 below knee amputations: 18 primary and 4 secondary amputations.²⁹ No patients developed symptomatic neuromas during the average follow up period of 18 months. In regard to PLP, 72% of patients in the primary amputation group experienced PLP in the first month, with an abrupt decline to 19% 3 months post-operatively and 13% at 6 months. These rates of neuroma pain and PLP represented substantial improvement over the control rates at their institution with traditional amputation.²⁹

Discussion

TMR is still a relatively new area of peripheral nerve surgery, and many questions remain. The ideal time interval as well as the differences in outcomes of primary versus secondary TMR still need to be further elucidated. As the procedure requires microsurgical nerve coaptation, it is often performed by a peripheral nerve surgeon. This may limit the applicability as a primary technique in many centers, due to the overall paucity of peripheral nerve surgeons. The exact groups of patients that will benefit most from the procedure also needs to be better defined. Although, it is highly possible that all patients would benefit from TMR, factors such as patient age and amputation level may come into play. Recently, a hind limb amputation model in rats has been developed for further study of neuroma prevention with TMR; in addition to an earlier study looking at the effects of TMR on neuromas in a rabbit rectus abdominis flap model.^{31,32} These models may serve as the basis for future clinical studies.

Alternative techniques for the management of neuroma pain in amputees have also been described, including regenerative peripheral nerve interface (RPNI).³³ RPNI uses free muscle grafts as physiologic targets. A series of patients treated with RPNI for post-amputation neuroma pain included 46 RPNIs in 16 patients. At 7.5-month follow-up, there was a 71% reduction in neuroma pain and 53% reduction in PLP.³³

There are similarities between TMR and RPNI, such as allowing for nerve regeneration into a functional target and creating a good environment for the nerve ending with coverage of the nerve end with muscle and stable soft tissue. However, further studies are needed to compare outcomes of TMR and how they relate to outcomes of RPNI. The use of acellular nerve allografts (ANA) as a cap to limit axon regeneration has also been investigated for the management of neuroma pain.³⁴ Proof of concept was established in a rat model demonstrating that ANAs attached to the proximal end of an injured nerve limited axon growth in a controlled manner, resulting in a lack of neuroma formation. In addition, the extent of axon growth from the injured nerve into the ANA was dependent on the ANA length.³⁴ Clinically, this would allow the surgeon to reliably terminate the axonal regeneration from an injured nerve by selecting an appropriate length ANA. This provides a less technically challenging, but more costly option for neuroma management. However, this technique differs markedly from TMR and RPNI as it does not provide functional nerve receptors or motor targets.

There are several limitations to this review. Overall, TMR is still a very new technique—in its infancy stage. Therefore, there is only a small number of studies to draw conclusions from, mostly out of 1-2 centers that have the bulk of the experience with this technique. There is a need for further high level research and randomized controlled trials in this field. Currently, there is only one randomized clinical trial (RCT) comparing TMR to the standard treatment of neuroma excision and burying into muscle.¹⁴ In addition, many specialties at virtually every major surgical center perform major limb amputation. Due to the scale of practice change that would occur with recommending TMR at the time of each primary limb amputation, there is a need for consistent high level evidence to support this practice. Further elucidating any differences in pain outcomes between the upper and lower extremities may also help answer the question of the role of primary TMR, as significantly more lower extremity amputations are performed compared to amputations in the upper extremity. Early studies seem to report higher percentages of pain free patients undergoing upper extremity TMR when compared to studies reporting on lower extremity TMR. However, early results in both upper and lower extremities appear very promising.

Conclusion

These novel surgical techniques are revolutionizing the thought processes and outcomes for prevention and management of amputation-related pain. TMR is an effective technique and represents a significant advance in the field of amputation surgery. It should be considered by all surgeons performing amputation surgery as it has the potential to prevent the development of both PLP and RLP. This technique is gaining acceptance across a variety of amputation sites, residual limb levels and indications. The benefits of TMR are expected to impact many medical specialties.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval was not sought for the present study because this was a review article and did not involve any patients.

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Informed consent

Informed consent was not sought for the present study because this was a review article and did not involve any subjects.

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