Targeted Muscle Reinnervation (TMR): Current Research and Clinical Applications

ABSTRACTS | BIBLIOGRAPHY

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The Checkpoint® Nerve Stimulator can be used to identify motor nerves and muscle during TMR and other procedures.
Targeted Muscle Reinnervation Combined with a Vascularized Pedicled Regenerative Peripheral Nerve Interface

Valerio I, Schulz SA, West J, Westenberg RF, Eberlin KR

Abstract

Symptomatic neuromas and pain caused by nerve transection injuries can adversely impact a patient's recovery, while also contributing to increased dependence on opioid and other pharmacotherapy. These sources of pain are magnified following amputation surgeries, inhibiting optimal prosthetic wear and function. Targeted muscle reinnervation (TMR) and regenerative peripheral nerve interfaces (RPNI) represent modern advances in addressing amputated peripheral nerves. These techniques offer solutions by essentially providing neuromuscular targets for transected peripheral nerves "to grow into and reinnervate." Recent described benefits of these techniques include reports on pain reduction or ablation (eg, phantom limb pain, residual limb pain, and/or neuroma pain).1-6 We describe a technical adaptation combining TMR with a "pedicled vascularized RPNI (vRPNI)." The TMR with the vRPNI surgical technique described offers the advantage of having a distal target nerve and a target muscle possessing deinnervated motor end plates which may potentially enhance nerve regeneration and muscle reinnervation, while also decreasing amputated nerve-related pain.
A Single Incision Anterior Approach for Transhumeral Amputation Targeted Muscle Reinnervation

Daly MC, He JJ, Ponton RP, Ko JH, Valerio IL, Eberlin KR

Abstract

Targeted muscle reinnervation (TMR) is an evolving technique with promising results for prevention and treatment of neuropathic pain, as well as modulation of control for myoelectric prostheses. The previously described and most commonly used technique for transhumeral TMR combines both an anterior and posterior approach to access the major peripheral nerves of the upper extremity. In this article, we review the literature for transhumeral TMR and describe a more expeditious and efficient anterior-only approach that offers safe access through a single incision.
Targeted Muscle Reinnervation Improves Residual Limb Pain, Phantom Limb Pain, and Limb Function: A Prospective Study of 33 Major Limb Amputees

Mioton LM, Dumanian GA, Shah N, Qiu CS, Ertl WJ, Potter BK, Souza JM, Valerio IL, Ko JH, Jordan SW

Abstract

Background: Targeted muscle reinnervation is an emerging surgical technique to treat neuroma pain whereby sensory and mixed motor nerves are transferred to nearby redundant motor nerve branches. In a recent randomized controlled trial, targeted muscle reinnervation was recently shown to reduce postamputation pain relative to conventional neuroma excision and muscle burying.

Questions/Purposes: (1) Does targeted muscle reinnervation improve residual limb pain and phantom limb pain in the period before surgery to 1 year after surgery? (2) Does targeted muscle reinnervation improve Patient-reported Outcome Measurement System (PROMIS) pain intensity and pain interference scores at 1 year after surgery? (3) After 1 year, does targeted muscle reinnervation improve functional outcome scores (Orthotics Prosthetics User Survey [OPUS] with Rasch conversion and Neuro-Quality of Life [Neuro-QOL])?

Methods: Data on patients who were ineligible for randomization or declined to be randomized and underwent targeted muscle reinnervation for pain were gathered for the present analysis. Data were collected prospectively from 2013 to 2017. Forty-three patients were enrolled in the study, 10 of whom lacked 1-year follow-up, leaving 33 patients for analysis. The primary outcomes measured were the difference in residual limb and phantom limb pain before and 1 year after surgery, assessed by an 11-point numerical rating scale (NRS). Secondary outcomes were change in PROMIS pain measures and change in limb function, assessed by the OPUS Rasch for upper limbs and Neuro-QOL for lower limbs before and 1 year after surgery.

Results: By 1 year after targeted muscle reinnervation, NRS scores for residual limb pain from 6.4 ± 2.6 to 3.6 ± 2.2 (mean difference -2.7 [95% CI -4.2 to -1.3]; p < 0.001) and phantom limb pain decreased from 6.0 ± 3.1 to 3.6 ± 2.9 (mean difference -2.4 [95% CI -3.8 to -0.9]; p < 0.001). PROMIS pain intensity and pain interference scores improved with respect to residual limb and phantom limb pain (residual limb pain intensity: 53.4 ± 9.7 to 44.4 ± 7.9, mean difference -9.0 [95% CI -14.0 to -4.0]; residual limb pain interference: 60.4
± 9.3 to 51.7 ± 8.2, mean difference -8.7 [95% CI -13.1 to -4.4]; phantom limb pain intensity: 49.3 ± 10.4 to 43.2 ± 9.3, mean difference -6.1 [95% CI -11.3 to -0.9]; phantom limb pain interference: 57.7 ± 10.4 to 50.8 ± 9.8, mean difference -6.9 [95% CI -12.1 to -1.7]; p ≤ 0.012 for all comparisons). On functional assessment, OPUS Rasch scores improved from 53.7 ± 3.4 to 56.4 ± 3.7 (mean difference +2.7 [95% CI 2.3 to 3.2]; p < 0.001) and Neuro-QOL scores improved from 32.9 ± 1.5 to 35.2 ± 1.6 (mean difference +2.3 [95% CI 1.8 to 2.9]; p < 0.001).

**Conclusions:** Targeted muscle reinnervation demonstrates improvement in residual limb and phantom limb pain parameters in major limb amputees. It should be considered as a first-line surgical treatment option for chronic amputation-related pain in patients with major limb amputations. Additional investigation into the effect on function and quality of life should be performed.
Targeted Muscle Reinnervation in Oncologic Amputees: Early Experience of a Novel Institutional Protocol


Abstract

Background: We describe a multidisciplinary approach for comprehensive care of amputees with concurrent targeted muscle reinnervation (TMR) at the time of amputation.

Methods: Our TMR cohort was compared to a cross-sectional sample of unselected oncologic amputees not treated at our institution (N = 58). Patient-Reported Outcomes Measurement Information System (NRS, PROMIS) were used to assess postamputation pain.

Results: Thirty-one patients underwent amputation with concurrent TMR during the study; 27 patients completed pain surveys; 15 had greater than 1-year follow-up (mean follow-up 14.7 months). Neuroma symptoms occurred significantly less frequently and with less intensity among the TMR cohort. Mean differences for PROMIS pain intensity, behavior, and interference for phantom limb pain (PLP) were 5.855 (95%CI 1.159-10.55; P = .015), 5.896 (95%CI 0.492-11.30; P = .033), and 7.435 (95%CI 1.797-13.07; P = .011) respectively, with lower scores for TMR cohort. For residual limb pain, PROMIS pain intensity, behavior, and interference mean differences were 5.477 (95%CI 0.528-10.42; P = .031), 6.195 (95%CI 0.705-11.69; P = .028), and 6.816 (95%CI 1.438-12.2; P = .014), respectively. Fifty-six percent took opioids before amputation compared to 22% at 1 year postoperatively.

Conclusions: Multidisciplinary care of amputees including concurrent amputation and TMR, multimodal postoperative pain management, amputee-centered rehabilitation, and peer support demonstrates reduced incidence and severity of neuroma and PLP.
Preemptive Treatment of Phantom and Residual Limb Pain with Targeted Muscle Reinnervation at the Time of Major Limb Amputation

Valerio IL, Dumanian GA, Jordan SW, Mioton LM, Bowen JB, West JM, Porter K, Ko JH, Souza JM, Potter BK

Abstract

Background: A majority of the nearly 2 million Americans living with limb loss suffer from chronic pain in the form of neuroma-related residual limb and phantom limb pain (PLP). Targeted muscle reinnervation (TMR) surgically transfers amputated nerves to nearby motor nerves for prevention of neuroma. The objective of this study was to determine whether TMR at the time of major limb amputation decreases the incidence and severity of PLP and residual limb pain.

Study Design: A multi-institutional cohort study was conducted between 2012 and 2018. Fifty-one patients undergoing major limb amputation with immediate TMR were compared with 438 unselected major limb amputees. Primary outcomes included an 11-point Numerical Rating Scale (NRS) and Patient-Reported Outcomes Measurement Information System (PROMIS) pain intensity, behavior, and interference.

Results: Patients who underwent TMR had less PLP and residual limb pain compared with untreated amputee controls, across all subgroups and by all measures. Median “worst pain in the past 24 hours” for the TMR cohort was 1 out of 10 compared to 5 (PLP) and 4 (residual) out of 10 in the control population (p = 0.003 and p < 0.001, respectively). Median PROMIS t-scores were lower in TMR patients for both PLP (pain intensity [36.3 vs 48.3], pain behavior [50.1 vs 56.6], and pain interference [40.7 vs 55.8]) and residual limb pain (pain intensity [30.7 vs 46.8], pain behavior [36.7 vs 57.3], and pain interference [40.7 vs 57.3]). Targeted muscle reinnervation was associated with 3.03 (PLP) and 3.92 (residual) times higher odds of decreasing pain severity compared with general amputee participants.

Conclusions: Preemptive surgical intervention of amputated nerves with TMR at the time of limb loss should be strongly considered to reduce pathologic phantom limb pain and symptomatic neuroma-related residual limb pain.
Targeted Muscle Reinnervation for Prosthesis Optimization and Neuroma Management in the Setting of Transradial Amputation

Pierrie SN, Gaston RG, Loeffler BJ

Abstract

Targeted muscle reinnervation (TMR) is a surgical technique that improves modern myoelectric prosthesis functionality and plays an important role in the prevention and treatment of painful postamputation neuromas. Originally described for transhumeral amputations and shoulder disarticulations, the technique is being adapted for treatment of transtibial, transfemoral, transradial, and partial hand amputees. We describe a new technique for forearm TMR following transradial amputation with an emphasis on selecting nerve transfer patterns, managing sensory nerves, improving terminal soft tissue coverage, and employing pattern recognition technology.
Targeted Muscle Reinnervation Technique in Below-Knee Amputation

Bowen JB, Ruter D, Wee C, West J, Valerio IL

Abstract

Approximately 25 percent of major limb amputees will develop chronic localized symptomatic neuromas and phantom limb pain in the residual limb. A method to treat and possibly prevent these pain symptoms is targeted reinnervation. Previous studies prove that targeted reinnervation successfully treats and, in some cases, resolves peripheral neuropathy and phantom limb pain in patients who have undergone previous amputation (i.e., secondary targeted reinnervation). This article seeks to share the authors' clinical indications and surgical technique for targeted muscle reinnervation in below-knee amputation, a surgical description currently absent from our literature. Targeted reinnervation for the below-knee amputee has been performed on 22 patients at the authors' institution. Each patient has been followed on an outpatient basis for 1 year to evaluate symptoms of neuroma or phantom limb pain, patient satisfaction, and functionality. All subjects have denied neuroma pain following amputation. The majority of subjects reported phantom pain at 1 month. However, at 3 months, all patients reported resolution of this pain. Dumanian et al. first noted the improvement of symptomatic neuroma and phantom limb pain in patients undergoing targeted reinnervation to provide intuitive control of upper limb prostheses. These findings have been substantiated by multiple previous studies at various amputation levels. This study extends the success of targeted muscle reinnervation to below-knee amputations and provides a description for this technique.
Targeted Muscle Reinnervation in the Lower Leg: An Anatomical Study

Fracol ME, Janes LE, Ko JH, Dumanian GA

**Background:** Targeted muscle reinnervation reroutes the ends of cut nerves to reinnervate small motor nerves of nearby muscles, with the goal of reducing neuroma pain and/or improving prosthesis function. Anatomical roadmaps for targeted muscle reinnervation have been established in the upper extremity and thigh, but not for the lower leg.

**Methods:** The major branch points of motor nerves and the motor entry points to muscles of the leg were dissected in five cadaver specimens. Leg length was defined as distance from the lateral femoral condyle to the lateral malleolus. The distances from the lateral femoral condyle to major branch points and motor entry points were recorded as percentages of leg length to identify targets for targeted muscle reinnervation.

**Results:** The tibialis anterior and extensor digitorum longus were both acceptable targets in the anterior compartment, with an average 4.4 motor entry points within 10 to 80 percent and 3.0 motor entry points within 20 to 80 percent leg length, respectively. The peroneus longus was the best target in the lateral compartment, with an average 5.8 motor entry points within 20 to 70 percent leg length. The gastrocnemius and soleus were both acceptable targets in the superficial posterior compartment, with an average 4.4 motor entry points within 0 to 40 percent and 6.2 motor entry points within 20 to 80 percent leg length, respectively for each muscle. The flexor digitorum longus was the best target in the deep posterior compartment, with an average 6.0 motor entry points within 30 to 90 percent leg length.

**Conclusions:** Targeted muscle reinnervation is technically feasible in the lower leg. This cadaveric study provides a roadmap for incision placement and identification of motor nerve targets.

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Targeted Muscle Reinnervation Treats Neuroma and Phantom Pain in Major Limb Amputees: A Randomized Clinical Trial


Abstract

Objective: To compare targeted muscle reinnervation (TMR) to “standard treatment” of neuroma excision and burying into muscle for postamputation pain.

Summary Background Data: To date, no intervention is consistently effective for neuroma-related residual limb or phantom limb pain (PLP). TMR is a nerve transfer procedure developed for prosthesis control, incidentally found to improve postamputation pain.

Methods: A prospective, randomized clinical trial was conducted. 28 amputees with chronic pain were assigned to standard treatment or TMR. Primary outcome was change between pre- and postoperative numerical rating scale (NRS, 0–10) pain scores for residual limb pain and PLP at 1 year. Secondary outcomes included NRS for all patients at final follow-up, PROMIS pain scales, neuroma size, and patient function.

Results: In intention-to-treat analysis, changes in PLP scores at 1 year were 3.2 versus -0.2 (difference 3.4, adjusted confidence interval (aCI) -0.1 to 6.9, adjusted P = 0.06) for TMR and standard treatment, respectively. Changes in residual limb pain scores were 2.9 versus 0.9 (difference 1.9, aCI -0.5 to 4.4, P = 0.15). In longitudinal mixed model analysis, difference in change scores for PLP was significantly greater in the TMR group compared with standard treatment [mean (aCI) = 3.5 (0.6, 6.3), P = 0.03]. Reduction in residual limb pain was favorable for TMR (P = 0.10). At longest follow-up, including 3 crossover patients, results favored TMR over standard treatment.

Conclusions: In this first surgical RCT for the treatment of postamputation pain in major limb amputees, TMR improved PLP and trended toward improved residual limb pain compared with conventional neurectomy.

Trial Registration: NCT 02205385 at ClinicalTrials.gov
Targeted Muscle Reinnervation to Improve Pain, Prosthetic Tolerance, and Bioprosthetic Outcomes in the Amputee

Bowen JB, Wee CE, Kalik J, Valerio IL

Abstract

Scope and Significance: There are ~185,000 amputations each year and nearly 2 million amputees currently living in the United States. Approximately 25% of these amputees will experience chronic pain issues secondary to localized neuroma pain and/or phantom limb pain.

Problem: The significant discomfort caused by neuroma and phantom limb pain interferes with prosthesis wear, subjecting amputees to the additional physical and psychological morbidity associated with chronic immobility. Although numerous neuroma treatments are described, none of these methods are consistently effective in eliminating symptoms.

Translational Relevance: Targeted muscle reinnervation (TMR) is a surgical technique involving the transfer of residual peripheral nerves to redundant target muscle motor nerves, restoring physiological continuity and encouraging organized nerve regeneration to decrease and potentially prevent the chaotic and misdirected nerve growth, which can contribute to pain experienced within the residual limb.

Clinical Relevance: TMR represents one of the more promising treatments for neuroma pain. Prior research into "secondary" TMR performed in a delayed manner after amputation has shown great improvement in treating amputee pain issues because of peripheral nerve dysfunction. "Primary" TMR performed at the time of amputation suggests that it may prevent neuroma formation while avoiding the risks associated with a delayed procedure. In addition, TMR permits the target muscles to act as bioamplifiers to direct bioprosthetic control and function.

Summary: TMR has the potential to treat pain from neuromas while enabling amputee patients to return to their activities of daily living and improve prosthetic use and tolerance. Recent research in the areas of secondary (i.e., delayed) and primary TMR aims to optimize efficacy and efficiency and demonstrates great potential for establishing a new standard of care for amputees.
Targeted Muscle Reinnervation in the Upper Extremity Amputee: A Technical Roadmap

Gart MS, Souza JM, Dumanian GA

Abstract

Targeted muscle reinnervation (TMR) offers the potential for improved prosthetic function by reclaiming the neural control information that is lost as a result of upper extremity amputation. In addition to the prosthetic control benefits, TMR is a potential treatment for postamputation neuroma pain. Here, we present our surgical technique for TMR nerve transfers in transhumeral and shoulder disarticulation patients.

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Targeted Muscle Reinnervation: A Novel Approach to Postamputation Neuroma Pain

Souza JM, Cheesborough JE, Ko JH, Cho MS, Kuiken TA, Dumanian GA

Abstract

Background: Postamputation neuroma pain can prevent comfortable prosthesis wear in patients with limb amputations, and currently available treatments are not consistently effective. Targeted muscle reinnervation (TMR) is a decade-old technique that employs a series of novel nerve transfers to permit intuitive control of upper-limb prostheses. Clinical experience suggests that it may also serve as an effective therapy for postamputation neuroma pain; however, this has not been explicitly studied.

Questions/Purposes: We evaluated the effect of TMR on residual limb neuroma pain in upper-extremity amputees.

Methods: We conducted a retrospective medical record review of all 28 patients treated with TMR from 2002 to 2012 at Northwestern Memorial Hospital/Rehabilitation Institute of Chicago (Chicago, IL, USA) and San Antonio Military Medical Center (San Antonio, TX, USA). Twenty-six of 28 patients had sufficient (> 6 months) follow-up for study inclusion. The amputation levels were shoulder disarticulation (10 patients) and transhumeral (16 patients). All patients underwent TMR for the primary purpose of improved myoelectric control. Of the 26 patients included in the study, 15 patients had evidence of postamputation neuroma pain before undergoing TMR.

Results: Of the 15 patients presenting with neuroma pain before TMR, 14 experienced complete resolution of pain in the transferred nerves, and the remaining patient's pain improved (though did not resolve). None of the patients who presented without evidence of postamputation neuroma pain developed neuroma pain after the TMR procedure. All 26 patients were fitted with a prosthesis, and 23 of the 26 patients were able to operate a TMR-controlled prosthesis.

Conclusions: None of the 26 patients who underwent TMR demonstrated evidence of new neuroma pain after the procedure, and all but one of the 15 patients who presented with preoperative neuroma pain experienced complete relief of pain in the distribution of the transferred nerves. TMR offers a novel and potentially more effective therapy for the management of neuroma pain after limb amputation.
The Effects of Targeted Muscle Reinnervation on Neuromas in a Rabbit Rectus Abdominis Flap Model

Peter S. Kim, MD, Jason H. Ko, MD, Kristina K. O’Shaughnessy, MD, Todd A. Kuiken, MD, PhD, Eric A. Pohlmeyer, PhD, Gregory A. Dumanian, MD

Abstract

Purpose: A targeted muscle reinnervation (TMR) model was created using a pedicled rabbit rectus abdominis (RA) flap to receive the input from previously amputated forelimb neuromas. We hypothesize that a segmental muscle flap can undergo TMR and that it is possible to differentiate the signal from 3 independent nerves. In addition, by virtue of the nerve coaptation, the morphology of the previous amputation neuroma would become more like that of an in-continuity neuroma.

Methods: Five New Zealand white rabbits had a forelimb amputation. In a second-stage surgery, an RA flap was transposed onto the chest wall. After neuroma excision, 3 neurorrhaphies were made between the median nerve, radial nerve, and ulnar nerves, and 3 motor nerves of the RA. After 10 weeks, the electrophysiologic properties of the reinnervated flap were tested. Nerve specimens from the median, radial, and ulnar nerves were harvested before and after TMR to quantify the histomorphometric changes effected by TMR on the mixed nerve neuromas.

Results: Of the 12 nerve coaptations performed in the 4 viable flaps, all 12 were grossly successful. Muscle surface EMG data demonstrated that the RA retained its segmental innervation pattern after TMR. Similarly, prolonged stimulation of 1 nerve reinnervating the RA resulted in the depletion of glycogen specific to the territory of the muscle stimulated by that nerve. TMR was found to favorably alter the histomorphometric characteristics of the neuroma by decreasing myelinated fiber counts and increasing fascicle diameter in the transferred nerves.

Conclusions: This study demonstrates that 1 segmented muscle having TMR by multiple nerve ingrowth and in turn generate discrete EMG signals. During this process, the previous amputation neuroma undergoes favorable morphologic alteration. Clinical relevance: Based on these preclinical results, this technique might be useful in upper extremity amputees to recruit target muscles to have reinnervation to drive myoelectric prostheses and to treat symptomatic neuromas.
Targeted Reinnervation in the Transfemoral Amputee: a Preliminary Study of Surgical Technique

Agnew SP, Schultz AE, Dumanian GA, Kuiken TA

Abstract

Background: Lower limb amputation is a common and growing problem in the United States. Current prosthetic technology is insufficient for transfemoral amputees to safely control their prostheses for demanding exercise such as stair climbing. Using a technique called targeted reinnervation, intuitive control of prosthetic devices has been achieved for upper limb amputees. To bring this technique to transfemoral amputees, a comprehensive understanding of the location of motor and sensory nerves is required.

Methods: Five lower limbs were dissected and the locations of motor points for 13 muscles of the thigh were documented, as was the location of the posterior femoral cutaneous nerve of the thigh. A transfemoral amputation was performed on one limb to demonstrate the targeted reinnervation procedure. The tibial and common peroneal divisions of the sciatic nerve were coapted to the motor points of the semimembranosus and biceps femoris, respectively. The posterior femoral cutaneous nerve was coapted in end-to-side fashion to the tibial nerve.

Results: The average number of motor points per muscle were as follows: sartorius, 4.75; rectus femoris, 3.25; vastus lateralis, 4.5; vastus intermedius, 4.5; vastus medialis, 4; adductor brevis, 2.3; adductor longus, 3; adductor magnus, 2.7; gracilis, 3; semitendinosus, 1.5; semimembranosus, 2.5; biceps femoris long head, 2.75; and biceps femoris short head, 1.

Conclusion: The results of this study indicate that targeted reinnervation is technically feasible in a transfemoral amputee.

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Resistance Training Enhances Skeletal Muscle Innervation Without Modifying the Number of Satellite Cells or their Myofiber Association in Obese Older Adults
María Laura Messi, Tao Li, Zhong-Min Wang, Anthony P. Marsh, Barbara Nicklas, Osvaldo Delbono
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Targeted Muscle Reinnervation and Advanced Prosthetic Arms
Jennifer E. Cheesborough, Lauren H. Smith, Todd A. Kuiken, Gregory A. Dumanian
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TARGETED MUSCLE REINNERVATION (TMR): CURRENT RESEARCH AND CLINICAL APPLICATIONS

Sensory cortical re-mapping following upper-limb amputation and subsequent targeted reinnervation: A case report
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