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Targeted Muscle Reinnervation Treats Neuroma and Phantom Pain in Major Limb Amputees

A Randomized Clinical Trial

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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

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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.

Keywords: neuroma, phantom limb pain, postamputation pain, randomized clinical trial, targeted muscle reinnervation

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Many of the 2 million amputees in the United States suffer from chronic pain, either isolated to the residual limb itself or as phantom limb pain (PLP) perceived in the limb no longer present. Prevalence rates of residual limb pain vary widely, from 10% to 76%, while rates of PLP have been reported as high as 85%.[1–4] Residual limb pain and PLP cause measurable decreases in prosthetic function and poor quality of life.[5,6]

Simplistically, *residual limb* pain is predominantly driven by cut nerve endings that form *terminal-neuromas*—disorganized axons encased in scar. Numerous treatments for neuromas have been described in the literature, though no single neuroma treatment has been shown to be consistently effective or superior. Previously reported pain management strategies have emphasized nerve ablation techniques with focused radiofrequency waves or injected neurotoxins. Alternative surgical approaches excise the neuroma and transpose the remaining nerve fascicles into a more favorable microenvironment such as bone, fat, vein, or even back onto itself.[7,8] Of the surgical strategies for neuroma management, the most commonly considered for symptomatic neuromas is excision and burying the freshened nerve ending into a nearby healthy muscle.[9] Common to all of these neuroma treatment procedures is the physiologic certitude that the freshly treated nerve will attempt to regenerate and subsequently will reform a new neuroma. Treatment success for these procedures requires that the newly created neuroma be less symptomatic than the neuroma that was removed.

Related to, but distinct from, residual limb pain is phantom limb pain. PLP is thought to be a complex interplay between the painful neuroma and multiple levels of the central nervous system resulting in cortical reorganization that has proven even more difficult than neuroma pain to prevent or reverse.[10–14] While neuromodulators such as gabapentin may have some effect on phantom pain,[15] 2 recent meta-analyses failed to demonstrate a meaningful benefit to these or any other medical treatments.[16–18]

A conceptually different strategy for handling the terminal end of a divided nerve originated in a procedure first performed by Dumanian in 2002 called Targeted Muscle Reinnervation (TMR) for the brain control of advanced myoelectric prostheses for amputees.[19] The terminal neuroma is removed and the newly freshened nerve is coapted to a newly divided nearby motor nerve. The fascicles, primed to regenerate, grow down the motor nerve to enter and re-innervate the newly denervated muscle.[20,21] Some fascicles connect with motor end-plates, while others connect to the numerous sensory end organs such as proprioceptors that exist within the muscle. What distinguishes TMR from all other treatments of neuromas is that the fascicles of the mixed major and sensory nerves are channeled toward nerve receptor targets. Also important is the experience from surgeons performing muscle flap transfer surgery that the proximal aspect of a divided *motor* nerve never forms a symptomatic neuroma.

Contrary to early concerns that TMR could create or worsen pain, it was observed that TMR patients had less pain postprocedure. These observations were published in a multicenter retrospective study.[22] A preclinical animal model confirmed histologic restoration of myelinated nerve morphology with TMR.[23] TMR gives the regenerating fascicles ''somewhere to go and something to do,'' thus serving to heal rather than hide the amputated nerve ending. Functional motor units produced by TMR may reverse the pathologic central reorganization associated with PLP.[24,25] In contrast, standard neuroma treatments do not provide a distal nerve receptor for potential reinnervation and do not attempt to heal the end of the nerve.

In this study, we performed a prospective, single-blinded, randomized controlled trial (RCT) of amputees with neuroma-related pain to compare the effectiveness of TMR to standard treatment of neuroma excision and burying the nerve ending in muscle.[26] Outcomes included patient-reported residual limb pain and PLP measures, functional outcomes, and neuroma size by magnetic resonance imaging (MRI).

METHODS

Patient Population

Twenty-eight major limb amputees over the age of 18 years with chronic pain were prospectively enrolled in an IRB-approved surgical trial at Northwestern and Walter Reed National Military Medical Center. Major limb amputees above the wrist or ankle, older than 18 years old, and who had not undergone prior neuroma treatments for pain after their initial amputation were randomized in the operating room to either undergo standard neuroma surgery or TMR with the opening of an envelope created using a random number generator dictating their method of treatment. The protocol for patients with multiple limb loss was to randomize the patient to a single procedure, but to obtain outcome data from each limb individually. Patients were blinded to their intervention for 1-year postsurgery. Patients in the standard treatment arm still suffering from significant neuroma-related pain at 1 year were offered TMR, if requested. Patient-reported outcome (PRO) data were obtained pre- and postoperatively at 3-month intervals for 1 year and at the conclusion of the study. There were 3 above elbow and 1 below elbow amputations, as well as 10 above knee and 16 below knee amputations for the 30 limbs treated.

Over the 3 years of patient recruitment, approximately 85 patients were screened to find the 28 patients who participated in this randomized clinical trial. As per protocol, a third cohort of 33 amputees was created who underwent TMR for residual limb pain or PLP but who were not randomized for reasons of prior surgical treatment for painful nerves, refusal to participate in the clinical trial, or the concomitant need for improved prosthetic control.

Standard Neuroma Treatment of Neuroma Excision and Muscle Burying

Standard neuroma treatment involves excising the neuroma back to visibly healthy appearing nerve fascicles (Fig. 1, left). The nerve is mobilized proximally and tunneled into the deep aspect of nearby muscle without tension. The muscle itself is chosen if it has limited excursion and is away from joint motion to avoid tugging on the nerve. The end of the nerve is held in place with fine sutures between the nerve and the entry point of the muscle.[27] Selection of nerves to be treated *for both groups* was determined preoperatively by the location and distribution of pain found on physical examination including the presence or absence of Tinel's signs.

TMR Surgical Technique

Detailed descriptions of TMR have been previously published (Fig. 1, right).[28–31] Neuromas are dissected and excised to healthy fascicles prior to transfer. Motor nerves innervating nearby muscles rendered functionless by the amputation are identified using a

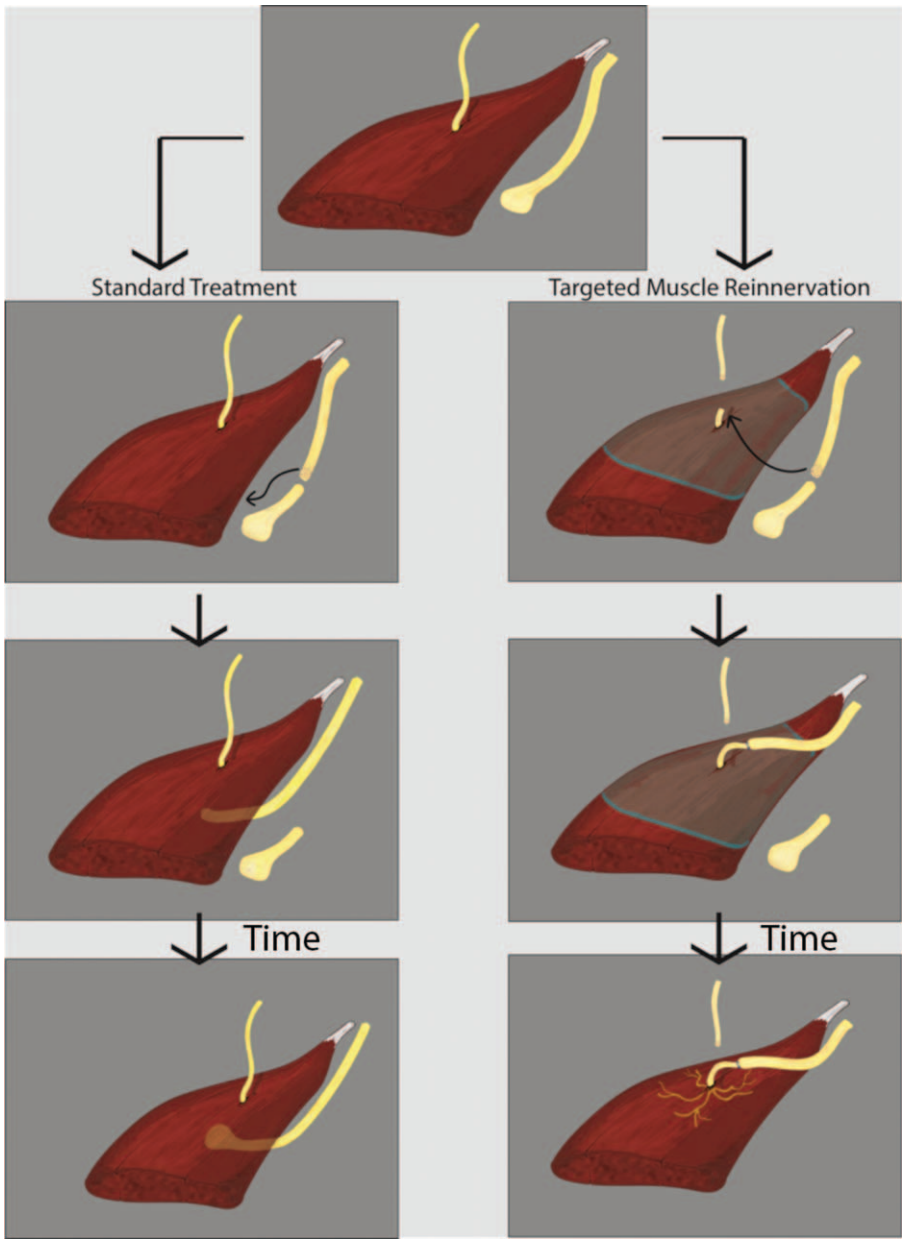

FIGURE 1. *Center top:* Schematic of muscle segment innervated by single motor nerve, and major mixed nerve ending in terminal neuroma. Left: Step 1, neuroma is excised. Step 2, freshened nerve is buried under a nearby muscle. Step 3, Over time, a new neuroma forms but is padded or protected by the overlying muscle. Right: Step 1, neuroma is excised and motor nerve innervating the muscle segment is divided creating a denervated muscle segment (blue shading). Step 2, freshened nerves are coapted. Step 3, major mixed nerve reinnervates muscle segment.

handheld nerve stimulator to serve as potential recipients of TMR nerve transfers. The major mixed nerve sectioned by the amputation (eg, tibial nerve) is then coapted to the surgically divided distal segment of the motor nerve (eg, motor nerve to the soleus muscle) using loupe magnification and 6-0 or 7-0 sutures. Pure sensory nerves including the sural or saphenous nerves were similarly treated when located. There were no differences in the postoperative recovery protocols between patient groups.

Pain Measures

Pain data were captured via 2 different PRO scales. The 11-point (0–10) Numerical Rating Scale (NRS) was incorporated as the gold standard direct assessment and primary outcome for pain. Patients were asked to report their worst and best pain levels in the past 24 hours and their current pain levels. To supplement this NRS scale, secondary outcomes included 3 Patient-Reported Outcomes Measurement Information System (PROMIS) assessments: Pain Behavior – Short Form 7a, Pain Intensity—Short Form 3a, and Pain Interference—Short Form 8a.[32–34] PROMIS is a validated toolbox for generalized pain, though the use of this tool to assess the localized pain and discomfort of an amputee had not previously been attempted. Participants in all cohorts were asked to complete the NRS scales and PROMIS measures distinguishing residual limb pain and PLP with the visual aid of an avatar (Fig. 2).

Radiologic Measures

Enrolled patients underwent MRI neurogram of the affected limb preoperatively and 1-year postoperatively. Imaging studies were performed using 3 Tesla machines at both sites. Radiologists were asked to identify and measure neuromas in a blinded fashion. A

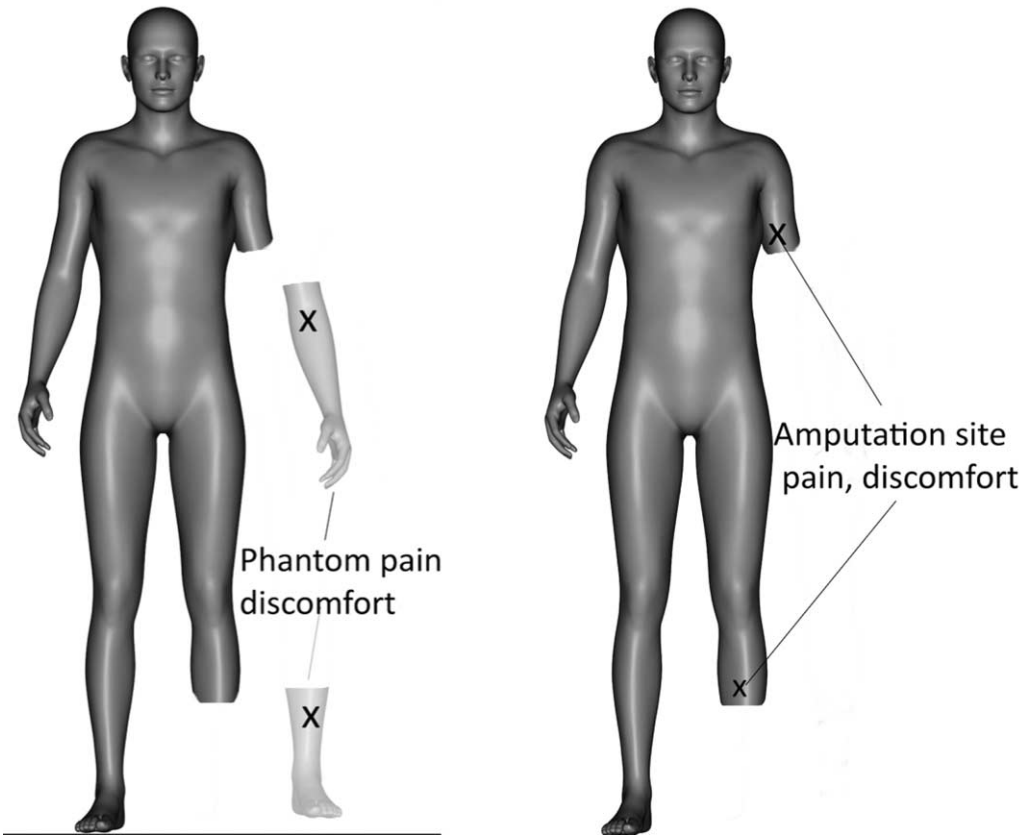

FIGURE 2. Avatar pictorally distinguishing neuroma pain from phantom limb pain.

neuroma was defined as a swelling on the end of a cylindrically shaped nerve. The boundaries of these swollen areas were measured and recorded in cubic millimeters.

Functional Assessment

Neuro-Quality of Life (Neuro-QOL) was used to assess functional outcomes in lower extremity amputees. The Orthotics Prosthetics Users Survey Upper Extremity form was used to assess functional outcomes in upper extremity amputees.

Statistical Analyses

The 2 primary outcomes, change in NRS worst pain score from baseline to 1 year postsurgery for phantom and residual limb pain, were compared between treatments groups in an intention to treat analysis using 2-sample *t* tests with the Satterthwaite method for unequal variances. A Bonferroni adjustment was applied to the *P* values and confidence intervals of the effect estimate to account for the 2 comparisons and control the type I error for the primary outcomes at $\alpha=0.05$ overall. The adjustment consisted of multiplying each *P* value by 2 and calculating 97.5% confidence intervals to achieve 95% simultaneous confidence intervals. The normality of the difference scores was evaluated before performing the *t* tests.

Four patients had missing data at the 1-year follow-up time and data were taken from the nearest available follow-up time. One patient in the standard care arm was in severe pain and converted to TMR after 6 months; NRS scores from the 6-month follow-up time were used for the primary analyses for this patient. One TMR patient (2 limbs) and 1 standard care patient were missing 1-year data but did have data at 18 months, which were used for the primary outcomes. Two patients (1 TMR and 1 standard care) had 2 amputations treated; pain scores for each limb were evaluated as independent observations.

As a sensitivity analysis for the primary outcomes, comparisons at the 1-year follow-up time were analyzed utilizing longitudinal linear mixed models incorporating all available data. The model outcomes were the NRS change from baseline scores for all follow-up times, calculated by subtracting the NRS worst pain value at each time point from the NRS worst pain value at baseline for each patient. A random subject effect was included, along with a spatial power correlated error structure modeling correlation in outcomes from the same patient over time, allowing stronger correlation in outcomes occurring closer together in time. Patients with missing data at the 1-year time point were accounted for through the restricted maximum likelihood estimation procedure utilizing all data available at other follow-up times. In each model, 1 for phantom pain and 1 for residual limb pain, a 1-degree of freedom parameter contrast comparing the group treatment effects at the 1-year follow-up outcomes was constructed to obtain the comparison of interest. Results for secondary outcomes are reported as point estimates for effect sizes and unadjusted confidence intervals. All statistical analyses were conducted using SAS/STAT software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Enrollment and Study Termination

The trial intended to recruit 200 patients but was stopped early with recruitment of 28 patients, without a formal stopping rule. Study enrollment was slow in this surgical trial of an orphan patient

TABLE 1. Baseline Characteristics

Variable	TMR (n = 14 Patients; 15 Limbs)		Standard Care (n = 14 Patients; 15 Limbs)	
	Patient Level			
Age (yrs), mean (SD)	39.6 (16.5)		45.3 (14.6)	
Male	12	85.7%	8	57.1%
Race/ethnicity				
Caucasian	10	71.4%	10	71.4%
African American	0	0.0%	3	21.4%
Multiracial	3	21.4%	0	0.0%
Hispanic/latino	0	0.0%	0	0.0%
Other	1	7.1%	1	7.1%
Occupation status				
Employed for wages	4	28.6%	3	21.4%
Self-employed	0	0.0%	2	14.3%
Military	2	14.3%	1	7.1%
Student	1	7.1%	0	0.0%
Unable to work	2	14.3%	5	35.7%
Retired	5	35.7%	3	21.4%
Number of nerves Treated, mean (SD)	2.9 (1.1)		2.3 (1.0)	
	Limb Level			
Location of limb				
Lower limb	12	80.0%	14	93.3%
Upper limb	3	20.0%	1	6.7%
Mechanism of amputation				
Trauma	13	86.7%	14	93.3%
Infection	2	13.3%	1	6.7%
Time since amputation				
Less than 1 year	1	6.7%	1	6.7%
1–4 yrs	3	20.0%	2	13.3%
5–9 yrs	7	46.7%	8	53.3%
10+ yrs	4	26.7%	4	26.7%
Latest follow-up timepoint				
6 mo	1	6.7%	0	0.0%
12 mo	5	33.3%	5	33.3%
18 mo	5	33.3%	5	33.3%
24+ mo	4	26.7%	5	33.3%
Mean (SD)	17.7 (7.5)		19.3 (5.8)	

population with limited access to a study site. The study was terminated after 3 years of study enrollment (2014–2017). The 28 patients (30 limbs) were allocated equally between the 2 intervention groups (Table 1).

Primary Outcomes

At 1-year postsurgery there was evidence of greater reduction in NRS worst PLP for patients receiving TMR compared with those receiving standard of care, although the difference was not strictly significant after applying the Bonferroni adjustment [mean (adjusted CI) for difference in change scores = 3.4 (−0.1, 6.9), adjusted P = 0.06] (Table 2). The average decrease in PLP was 3.2 in the TMR arm compared with an average increase of 0.2 in the standard care arm. In longitudinal mixed model analysis, the difference in change scores at 1-year postsurgery was significantly greater in the TMR arm compared with standard care [mean (adjusted CI) = 3.5 (0.2, 6.7), adjusted P = 0.03].

Change in NRS worst residual limb pain did not differ significantly between randomized groups, although the effect was in direction of greater decrease for the TMR group [mean (adjusted CI) for difference in change scores = 1.9 (−0.5, 4.4), adjusted P = 0.15]. The average decrease in pain was 2.9 in the TMR arm and 0.9 in the standard care arm. The mixed model results for the group comparison at 1 year yielded similar results [mean (adjusted CI) = 2.1 (−0.3, 4.6), adjusted P = 0.10].

Secondary Outcomes

Group means and standard deviations are presented for NRS worst pain scores at baseline, last follow-up, and change from baseline to last follow-up. The point estimates for mean differences in change scores between groups are presented with unadjusted 95% confidence intervals. These results are presented both for the intention to treat randomized groups and additionally incorporating crossover results for patients randomized to and receiving standard care and then crossing over to TMR during the study (Table 3).

PROMIS scale outcomes are similarly reported as mean and standard deviation at baseline, 1-year, last follow-up, and change from baseline. The mean differences in change scores between groups are presented with unadjusted 95% confidence intervals (Tables 4 and 5).

Fully 72% of TMR patients had either no PLP or mild PLP at longest follow-up. This contrasts with the standard treatment arm, which had 40% of patients having no PLP to mild PLP after surgery. For residual limb pain, the percentage of the TMR patient cohort being pain free or suffering from mild pain increased from 0% preoperatively to 67% postoperatively. This compares to the standard arm with 27% having no residual limb pain to mild residual limb pain at longest follow-up.

Functional Outcomes

As most upper extremity candidates desired improved terminal device control that precluded randomization, there were too few

TABLE 2. Primary Outcomes: NRS Scores for Worst Pain at Baseline and 1 Year*, Mean (SD)

	TMR (n = 15)			Standard Care (n = 15)			
Outcome	Baseline	1 Yr	Change	Baseline	1 Yr	Change	Mean (Adjusted 95% CI)† Difference of Change Scores
Worst phantom limb pain	5.8 (3.2)	2.6 (2.2)	3.2 (2.9)	3.9 (2.7)	4.1 (3.0)	−0.2 (4.9)	3.4 (−0.1, 6.9)
Worst residual limb pain	6.6 (2.0)	3.7 (2.0)	2.9 (2.2)	6.9 (2.5)	6.0 (2.8)	0.9 (3.3)	1.9 (−0.5, 4.4)

*Values for 3 patients (4 limbs) taken from other time points (1 at 6 mo; 3 at 18 mo).
†Bonferroni adjusted 95% simultaneous confidence intervals.

TABLE 3. NRS Worst Pain Scores at Last Follow-up, Mean (SD)

Intention to Treat, no Crossover Results

	TMR (n = 15)			Standard Care (n = 15)			
Outcome	Baseline	Last FU	Change	Baseline	Last FU	Change	Mean (95% CI)* Difference of Change Scores
Worst phantom limb pain	5.8 (3.2)	2.3 (2.3)	3.5 (3.1)	3.9 (2.7)	4.4 (3.3)	−0.5 (5.3)	4.0 (0.8, 7.2)
Worst residual limb pain	6.6 (2.0)	3.6 (2.1)	3.0 (2.1)	6.9 (2.5)	5.7 (3.0)	1.2 (3.5)	1.8 (−0.3, 4.0)

Crossovers to TMR Included in Results for Both Arms

	TMR (n = 18)†			Standard Care (n = 15)			
Outcome	Baseline‡	Last FU	Change	Baseline	Last FU	Change	Mean (95% CI)* Difference of Change Scores
Worst phantom limb pain	5.5 (3.2)	1.9 (2.2)	3.6 (3.1)	3.9 (2.7)	4.4 (3.3)	−0.5 (5.3)	4.1 (1.1, 7.1)
Worst residual limb pain	6.9 (2.0)	3.3 (2.0)	3.7 (2.5)	6.9 (2.5)	5.7 (3.0)	1.2 (3.5)	2.5 (0.4, 4.6)

*Unadjusted confidence intervals; inferences drawn from the intervals may not be reproducible.
†Includes 3 crossovers from standard care arm.
‡Included preop scores for 3 crossover patients.

TABLE 4. PROMIS Pain Scales at 1 Year*, Mean (SD)

	TMR (n = 15)			Standard Care (n = 15)			
Outcome	Baseline	1 Yr	Change	Baseline	1 Yr	Change	Mean (95% CI)† Difference of Change Scores
Phantom limb pain							
Intensity	52.4 (11.2)	38.0 (7.2)	13.7 (10.7)	48.3 (9.5)	45.8 (10.9)	2.0 (17.9)	11.7 (−0.3, 23.7)
Behavior	58.3 (11.8)	50.7 (9.9)	7.6 (9.7)	58.5 (9.7)	52.0 (8.4)	6.5 (14.9)	1.1 (−8.3, 10.5)
Interference	60.2 (12.5)	50.4 (9.8)	9.8 (8.9)	57.9 (11.0)	52.8 (8.9)	5.1 (16.0)	4.7 (−5.0, 14.3)
Residual limb pain							
Intensity	55.7 (7.6)	44.5 (8.2)	11.5 (8.3)	55.0 (5.5)	49.5 (8.3)	5.7 (8.1)	5.8 (−0.9, 12.4)
Behavior	61.5 (3.7)	56.8 (7.0)	4.7 (7.1)	61.9 (4.3)	56.6 (6.5)	5.3 (10.4)	−0.5 (−7.2, 6.1)
Interference	64.4 (7.0)	56.8 (6.6)	7.6 (9.2)	65.8 (5.1)	57.4 (8.6)	8.5 (11.0)	−0.9 (−8.5, 6.7)

*Values for 3 patients (4 limbs) taken from other time points (1 at 6 mo; 3 at 18 mo).
†Unadjusted confidence intervals; inferences drawn from the intervals may not be reproducible.

TABLE 5. PROMIS Pain Scales at Last Follow-up, Mean (SD)

	TMR (n = 15)			Standard Care (n = 15)			
Outcome	Baseline	Last FU	Change	Baseline	Last FU	Change	Mean (95% CI)* Difference of Change Scores
Phantom limb pain							
Intensity	52.4 (11.2)	41.1 (9.5)	11.3 (9.3)	48.3 (9.5)	46.3 (10.4)	2.0 (17.9)	9.3 (−1.4, 20.0)
Behavior	58.3 (11.8)	50.9 (11.3)	7.4 (10.2)	58.5 (9.7)	55.4 (6.9)	3.1 (13.4)	4.3 (−4.7, 13.2)
Interference	60.2 (12.5)	51.5 (9.7)	8.8 (8.6)	57.9 (11.0)	53.8 (10.5)	4.1 (17.6)	4.7 (−5.6, 15.3)
Residual limb pain							
Intensity	55.7 (7.6)	44.8 (8.8)	10.8 (7.1)	55.0 (5.5)	50.0 (8.8)	5.1 (7.4)	5.8 (−0.3, 11.2)
Behavior	61.5 (3.7)	57.6 (7.4)	3.9 (6.9)	61.9 (4.3)	57.3 (6.9)	4.6 (10.7)	−0.7 (−7.5, 6.1)
Interference	64.4 (7.0)	56.1 (6.5)	8.3 (8.6)	65.8 (5.1)	58.0 (8.7)	7.8 (11.4)	0.5 (−7.0, 8.1)

*Unadjusted confidence intervals; inferences drawn from the intervals may not be reproducible.

upper extremity patients (n = 4) for analysis of OPUS-UE data. Analysis of the lower extremity NEURO-QOL results, representing 24 patient responses, revealed little difference between groups at 1 year. When crossover data were included and at final follow-up, the mean NEURO-QOL *t* score increased from 39.9 to 45.2 in the TMR cohort showing functional improvement.

Radiologic Outcomes

Twenty-five of the 28 enrolled patients underwent both preoperative and postoperative imaging of their affected limb(s). Postoperative nerve volumes were 378 mm^3 for TMR and 552 mm^3 for standard surgery. While 64 nerves were treated, only 25 nerves transferred were visualized by MRI by radiology for measurement.

There were no surgical complications to report.

DISCUSSION

This prospective, multicenter, randomized clinical trial provides evidence that TMR decreases phantom pain in major limb amputees, with an average decrease of 3.2 in the TMR arm compared with an average increase of 0.2 in the standard treatment arm at the defined 1-year end point. Changes in NRS of 2 points has been shown to be clinically important and correlated to a patient's need to take additional pain medication in studies of both chronic and acute pain.[35,36] Residual limb pain showed a trend towards improvement in the TMR group over standard treatment, with average decreases in pain of 2.9 versus 0.9, though this did not reach statistical significance. A failure to reach statistical significance may be due to residual limb pain being caused not only by neuromas, but also due to bone spurs, ischemia, or other conditions[37] that were not addressed by this surgical procedure. At final follow-up of just under 1 $^1/_2$ years, including crossovers, TMR had a decrease of PLP of 3.6 versus an increase of 0.5 for standard treatment, and a decrease of residual limb pain of 3.7 versus 1.2 for muscle burying. To our knowledge, this is the first surgical RCT for the treatment of neuromas.

We postulate that TMR treats pathologic pain through a physiologic nerve healing mechanism that establishes a new afferent signal from muscular sensory receptors and thus, closes the efferent-afferent feedback loop. The process of TMR inherently creates a denervated muscle segment that in turn provides a neurotrophic signal for regeneration of fascicles down the distal motor nerve stump to empty motor endplates and proprioceptors. Studies regarding direct muscle neurotization have long hypothesized that the sensitivity of innervated muscles to acetylcholine is limited and denervated muscle fibers are more readily accepting of neurotization, and we postulate that it is the connection to the terminal receptor that is the cause for the lasting decrease in pain. A point to be repeated is that the newly cut motor nerves do not become symptomatic neuromas. No function is lost from the division of the recipient motor nerve, as the muscle does not maintain any motor function after limb amputation. A surgical concern that the size mismatch between donor and recipient nerves with TMR could create symptomatic neuromas-in-continuity did not materialize. In comparison, standard treatment of neuromas of excision and muscle burying simply places the nerve ending in a healthy, innervated, vascular bed without neurotrophic signals or a reinnervation target and was ineffective for the treatment of either phantoms or residual limb pain in these patients.

We believe that this data is the first to demonstrate in a randomized, blinded trial the persistent long-term improvement of phantom limb pain by any modality. Major limb amputation, and resulting peripheral nerve deafferentation, has been shown to affect multiple neural levels from the periphery to the sensorimotor cortex that contribute to phantom limb phenomena.[9–13] Ectopic discharges from disorganized axonal sprouting at the cut nerve ending cause local residual limb pain, and there is evidence to suggest that neuroma pain is a driver of PLP. Harris hypothesized that incongruence between motor efferents and sensory feedback leads to pathologic pain,[38] thus providing the basis for behavioral therapies such as mirror therapy and augmented reality training.[39] These strategies, as well as those standard procedures that attempt to find the neuroma a more protected microenvironment, have been met with limited success likely because they do not address aberrant electric activity from the nerve ending.[40] TMR in the established amputee may reverse maladaptive cortical reorganization, with functional MRI demonstrating motor and sensory cortical maps more similar to healthy controls than to non-TMR amputees.[41] TMR for amputees demonstrates improvement but not complete elimination in PLP for most patients, implying that central changes may be only partly reversible.[42] This also raises the question whether the performance of TMR concurrently at the time of amputation will be effective in the prevention of residual limb pain and PLP.[43]

Strengths of the study include the adherence to protocol, reasonable follow-up for all patients, and the crossover patients demonstrating that patients can be successfully treated for pain even after initial management failures. The concept that the ''healing'' of an injured nerve results in a long-term improvement in pain has already been established for the treatment of neuromas in patients with intact limbs.[44,45] It is the special situation of the amputee that there is no distal nerve present for potential repair—hence the need to utilize a nearby expendable muscle filled with receptors for a TMR nerve transfer.

Functional outcomes did not show clear improvement with TMR, though the trend was toward improvement when crossover patients were included. Functional outcomes depend not only on the presence or absence of neuroma pain, but other issues including limb strength, prosthetic function, and patient motivation. MRI neurograms proved to inadequate and insensitive to locate the affected nerves found by physical examination in both treatment arms.

While the trial planned for 200 participants, many fewer procedures were performed than anticipated. At the beginning of the trial, it was hoped that multiple centers scattered geographically around the United States would be involved to perform these surgeries. Despite intensive work, only 2 of 7 planned centers both maintained the required surgeon complement and were able to obtain institutional review board clearance in a timely enough manner to participate. In addition, many more amputees than expected had undergone prior neuroma excision and burying, therefore disqualifying them from being randomized for this trial, as the participating surgeons felt it unethical to repeat an operation that had failed before. Third, the patients were communicating with each other through the internet, with several patients changing their minds and refusing to be randomized at the last minute after hearing more about standard surgery. We treated 33 patients outside of the trial and without randomization. Review of these patients showed outcomes remarkably similar to the TMR patients treated inside the trial. Looking at the overall conduct of this RCT, the lead authors feel that the overall minimum number of patients underwent an unsuccessful procedure (burying) while still being able to demonstrate the efficacy of TMR.

A weakness of this study is the requirement of patients to self-report pain and to distinguish residual limb pain from PLP. Patient-reported outcome instruments, while subject to patient bias, are the gold standard for evaluating pain. We acknowledge that the NRS data in this study represents a 1-time evaluation of pain that can often change over the course of hours, weeks, and months. We administered 3 supplemental PROMIS item banks, which have not yet been validated in people living with chronic postamputation pain. We observed some correlation between the 11-point NRS and PROMIS

Pain Intensity, but poor correlation with PROMIS Pain Behavior and Pain Interference (data not shown). We postulate that longstanding behavioral adaptations from living with chronic pain may make these measures slow to change. Another weakness of the study is that only 1 standard neuroma surgery was used for the comparison to TMR. Neuroma excision and muscle burying is the most widely performed and accepted surgical treatment for neuromas. Muscle burying also has in common with all of the other treatments of neuromas the physiologic consequence that a new neuroma will form after treatment. Also not tested was the recently devised regenerative peripheral nerve interface or RPNI, that like TMR was created to achieve improved prosthetic control. Like TMR, RPNI's attempt to achieve a connection between nerve endings and nerve receptors that appear on newly revascularized free muscle grafts that are surgically wrapped around these newly divided nerve endings. Early reports show a decrease in both pain and phantoms.[45] Considering the difficulty with patient recruitment in this randomized study, further comparisons of these various techniques may only be achieved using a unified patient outcome tool that will be shared between institutions.

CONCLUSIONS

TMR resulted in improved phantom limb pain and trended toward improved residual limb pain in major limb amputees compared with conventional surgical therapy. Future studies will focus on the surgical refinements of the procedure, as well as the application of TMR to specific indications for amputation such as vascular disease.

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