Preemptive Treatment of Phantom and Residual Limb Pain with Targeted Muscle Reinnervation at the Time of Major Limb Amputation

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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. (J Am Coll Surg 2019;228:217–226. © 2019 Published by Elsevier Inc. on behalf of the American College of Surgeons.)

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Abbreviations and Acronyms

IPTW = inverse probability of treatment weighting
IQR = interquartile range
PLP = phantom limb pain
PROMIS = Patient-Reported Outcomes Measurement Information System
NRS = Numerical Rating Scale
TMR = targeted muscle reinnervation

Phantom limb pain (PLP) is the perception of discomfort in the limb no longer present, with prevalence as high as 85%.[1-4] Although the mechanisms of PLP are not well understood, PLP is associated with aberrancies at multiple levels of the peripheral and central nervous systems, often leading to a multitude of proposed pharmacologic, interventional, and behavioral treatments.[5-10] Unfortunately, the majority of strategies, such as neuromodulators, regional analgesia, transcutaneous electrical nerve stimulation (TENS), and mirror box therapy, have been ineffective or inconsistent.[11-16]

Other studies reporting effective treatments have been limited by short-term follow-up or involve interventions requiring repetitive treatments for indefinite periods.[13,17] Meanwhile, rates of residual limb (ie residuum or "stump") pain have been reported between 10% and 76%.[1-4] Residual limb pain is localized, radiating pain often caused by symptomatic neuromas, which may be irritated by pressure, light touch, and hot or cold extremes.[18] Symptomatic neuromas are a frequent cause of chronic pain and revision surgery, as well as measurable decreases in prosthetic function and quality of life.[19,20] Current management options include burying the end of the nerve in muscle, bone, or vein, and end-to-end nerve coaptation (centro-central anastomosis).[21-25] These strategies aim to convert symptomatic neuromas to non-symptomatic neuromas, but do not address the underlying pathology of disorganized axon regeneration without a terminal nerve receptor. With no consistently effective treatments, amputee-related pain management continues to rely on pharmacologic therapy, largely in the form of opioids. However, in the face of the current opioid crisis and the known limited efficacy of opioids in managing amputee-related pain, we are further motivated to seek new strategies to prevent symptomatic neuromas and phantom limb phenomena.[26,27]

Targeted muscle reinnervation (TMR) is a peripheral nerve transfer procedure, first performed by Dumanian in 2002, which reroutes the amputated axons to motor endplates and sensory organelles in nearby muscles via a novel nerve transfer.[28,29] In contrast to other published handling of end-neuromas, where the goal of surgery has been to hide or protect the neuroma, TMR gives the amputated nerves "somewhere to go and something to do." After reinnervation, target muscles demonstrate synaptic input similar to physiologic innervation and may provide new myoelectric sites for intuitive control of advanced robotic prostheses.[30] This functional aspect may, in turn, play a role in preventing pathologic central reorganization and phantom limb pain.[31,32] A previous retrospective study noted that patients undergoing TMR for improved prosthesis control noticed improvement in pre-existing pain.[33] We hypothesized that the alternative mechanism of amputated nerve healing provided by TMR could favorably alter both local stump pain and the upstream effects of nerve injury that occur in the brain, collectively termed PLP.

To test our hypothesis, we benchmarked pain among a large, unselected population of amputees using a standard 0 to 10 Numerical Rating Scale (NRS) and the Patient-Reported Outcomes Measurement Information System (PROMIS).[34] We used this baseline for comparison with patients undergoing major limb amputation and immediate TMR as a preemptive pain management strategy.

METHODS

This work was approved by The Ohio State University Institutional Review Board (Protocol Number 2017C0150). This work was also approved by the Northwestern University Institutional Review Board (Protocol Number STU00205866).

Patient populations

General amputee population

To define normative data for the general amputee population, patient-reported outcomes measures were obtained from unselected amputees recruited through local prosthetic and orthotic clinics as well as pain clinics, amputee clinics, amputee support groups, amputee activity clubs, amputee-targeted trade shows, and professional conferences throughout North America. Surveys were further advertised through www.amputee-coalition.org and www.amputeeresearch.com. The large outreach resulted in 1,203 survey respondents in total; 434 were excluded due to incomplete and/or duplicate survey responses; 53 were removed based on amputation of digits rather than major limbs; 278 were excluded due to presence of characteristics not found in the immediate TMR cohort (>9 years since amputation [n = 223], diabetes as reason for amputation [n = 42], and

hemipelvectomy [n = 13]). The final general amputee sample size was 438 respondents.

Patients undergoing primary amputation with concurrent targeted muscle reinnervation for preemptive management of pain

Patients with various traumatic, neoplastic, and vascular indications (eg unresectable tumors, trauma, ischemia, unsalvageable total joint replacement), scheduled for amputation between 2012 and 2018, were offered a consultation to undergo concurrent TMR. Referrals were at the discretion of the surgical team performing the amputation. Patients who underwent TMR within 14 days of primary amputation were eligible. Patients were excluded if they were less than 18 years of age, had cognitive impairment, were enrolled in other studies relating to neuropathic pain, had open wounds, or were actively undergoing radiation therapy. Minimum follow-up time was 3 months. Survey response rate was 51 of 60 surviving eligible patients (85%).

Targeted muscle reinnervation surgical technique

Major peripheral nerves were tagged as encountered by the resecting surgeons, often at the time of major vessel ligation (eg tibial nerve with posterior tibial vessels, deep peroneal nerve with anterior tibial vessels). Either through the open surgical incision or through a separate proximal longitudinal incision, the remaining major mixed and larger sensory nerves (eg superficial peroneal, sural nerves) were identified based on anatomy and mobilized proximally. Small motor nerves innervating nearby muscles rendered functionless by the amputation were identified using a handheld nerve stimulator, marked, and divided. The major mixed nerve or sensory nerve sectioned by the amputation (eg tibial nerve) was then coapted to the distal segment of the motor nerve (eg motor nerve to the soleus muscle) with a tension-free end-to-end neurorrhaphy (Fig. 1). The proximal end of pure motor nerves do not form symptomatic neuromas, a lesson learned from muscle flap surgery, and were therefore left otherwise untreated. All major mixed nerves and larger sensory nerves were transferred to a motor nerve branch "target." Typical TMR donor-target nerve transfer combinations and recommended incisions for transhumeral, transradial, transfemoral, and transtibial amputations have been published previously elsewhere.[35-38] Performance of the amputation and postoperative care were otherwise unchanged.

Patient-reported outcomes measures

Survey participants and TMR patients were asked to rate their worst, best, and current pain levels over the past 24 hours on a 0 to 10 Numerical Rating Scale (NRS). To supplement the traditional NRS, 3 additional Patient-Reported Outcomes Measurement Information System instruments (PROMIS Pain Behavior—Short Form 7a, Pain Intensity—Short Form 3a, and Pain Interference—Short Form 8a) asked participants to rate their pain over longer recall periods and further quantified pain-related behavior and the degree to which pain affects or interferes with daily functioning.[39-41] The PROMIS is a well-validated toolbox developed with NIH funding using modern psychometric techniques, common data elements, and universal metrics for comparison across conditions.[34,42] Higher PROMIS t-scores indicate more severe symptoms. Participants in all cohorts were asked to complete the NRS scales and PROMIS with respect to both phantom and residual limb pain.

Statistical analyses

Inverse probability of treatment weighting (IPTW) was used to estimate the average treatment effect of immediate TMR in comparison with the general amputee group.[43] The weights serve to adjust for imbalance in patient characteristics in the raw data and allow estimation of the average treatment effect. Patients in the general amputee population with characteristics not present in the TMR cohort were excluded (time since amputation $>$ 9 years, amputation due to diabetes, hemipelvectomy). Among remaining patients, a logistic regression model was used to estimate the probability of receiving immediate TMR. The outcome was immediate TMR and the model included the following covariates: reason for amputation, time since amputation, level of amputation, age range, sex, race, education, and ability to work. For each patient, the inverse treatment probability was calculated (ie the inverse probability of actual treatment received), and the weights were stabilized by multiplying by the probability of receiving the treatment.[43] The stabilized IPTW weights were used for all further analyses.

Balance diagnostics were assessed by comparing standardized differences in patient characteristics for the original data and after IPTW adjustment. Statistical comparison by chi-square test was also performed before and after IPTW adjustment. The Surveyfreq SAS/STAT procedure was used to properly implement IPTW variance estimation.

The 12 primary outcomes (3 NRS and 3 PROMIS outcomes each for phantom and residual limb pain) were

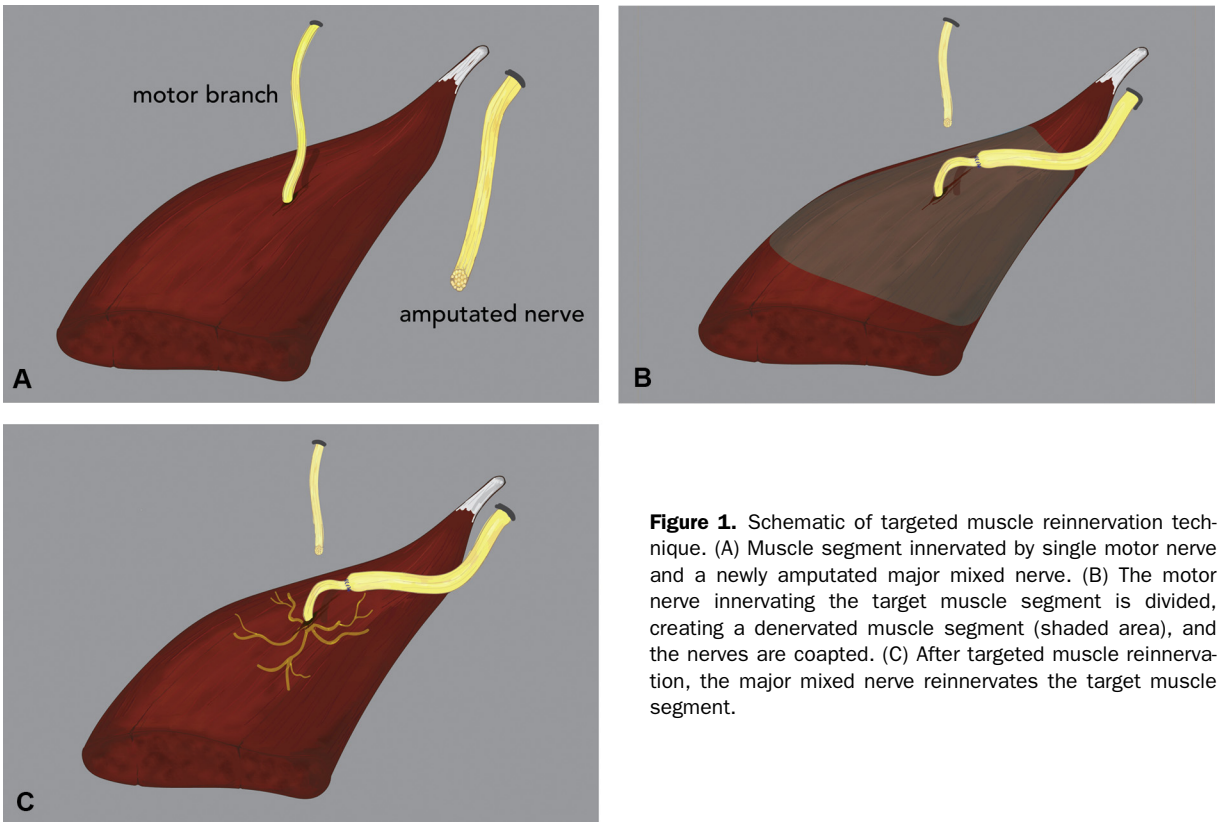

Figure 1. Schematic of targeted muscle reinnervation technique. (A) Muscle segment innervated by single motor nerve and a newly amputated major mixed nerve. (B) The motor nerve innervating the target muscle segment is divided, creating a denervated muscle segment (shaded area), and the nerves are coapted. (C) After targeted muscle reinnervation, the major mixed nerve reinnervates the target muscle segment.

summarized as median and interquartile range (IQR) because the measures were not normally distributed. Nonparametric Wilcoxon rank-sum tests using the stabilized IPTW weights were used to compare each outcome between groups using the "svyranktest" procedure in the R package "survey."[44,45] Holm's procedure for multiple testing was used to control the overall type I error rate at $\alpha = 0.05$ (eg the lowest p value was evaluated at the 0.004 threshold).[46] Patients with missing outcome data were excluded from analysis for that outcome. In sensitivity analyses, multiple imputation was used for patients with missing outcome values.

As a secondary analysis the NRS "worst pain" scores were categorized as follows: no pain (NRS 0), mild pain (NRS 1 to 3), moderate pain (NRS 4 to 6), severe pain (NRS 7 to 10). Ordinal logistic regression with IPTW adjustment was performed to estimate the odds of having higher pain in the immediate TMR group compared with the general amputee group for both phantom and residual limb pain. Summary statistics regarding opioid use among TMR patients are presented without IPTW adjustment. Statistical analyses were conducted using SAS/STAT software (SAS Institute) and R.[47]

RESULTS

Details of the 51 patients in the TMR cohort are shown in Table 1. Median (IQR) follow-up time for the TMR cohort was 330 days (199 to 438 days) (range 3 months to 5.3 years) from the time of TMR. More than 1 year of follow-up was obtained for 64.7% of TMR respondents. The most common indications for amputation were cancer (39.2%) and trauma (31.4%). Seventy-one percent involved the lower extremity. Most patients (88.2%) underwent TMR on the day of the amputation; the remaining patients underwent TMR within 14 days (Table 1, unadjusted). Patient characteristics before and after application of IPTW adjustment are

Table 1. Patient Characteristics by Treatment, With and Without Inverse Probability of Treatment Weighting Adjustment

	Unadjusted data			Data adjusted by inverse probability of treatment weighting		
Variable	**TMR, n = 51, n (%)**	**General, n = 438, n (%)**	**Standardized difference, p value**	**TMR, n = 43, n (%)**	**General, n = 440, n (%)**	**Standardized difference, p value**
Age range, y			0.18, 0.70			0.22, 0.59
18–34	11 (21.6)	83 (18.9)		11 (26.1)	84 (19.1)	
35–49	14 (27.5)	103 (23.5)		12 (26.8)	110 (24.9)	
50–59	14 (27.5)	114 (26.0)		11 (25.2)	114 (26.0)	
60+ y	12 (23.5)	138 (31.5)		9 (21.9)	132 (30.0)	
Sex			−0.14, 0.33			−0.19, 0.23
Male	30 (58.8)	288 (65.8)		24 (55.9)	286 (65.0)	
Female	21 (41.2)	150 (34.2)		19 (44.1)	154 (35.0)	
Race			0.07, 0.89			0.17, 0.61
Black/African American	3 (5.9)	29 (6.6)		2 (3.7)	28 (6.3)	
White	43 (84.3)	374 (85.4)		39 (91.3)	378 (85.8)	
Other	5 (9.8)	35 (8.0)		2 (5.1)	35 (7.9)	
Hispanic ethnicity	5 (9.8)	26 (5.9)	0.14, 0.28	2 (5.1)	26 (5.9)	−0.04, 0.82
Married	29 (56.9)	250 (57.1)	0.00, 0.98	24 (55.5)	250 (56.7)	−0.03, 0.87
Bachelor's degree or higher	18 (35.3)	153 (34.9)	0.01, 0.96	12 (26.9)	151 (34.3)	−0.16, 0.16
Unable to work	14 (27.5)	94 (21.5)	0.14, 0.33	13 (29.4)	98 (22.3)	0.16, 0.29
Reason for amputation			0.94, <0.001*			0.23, 0.79
Cancer	20 (39.2)	22 (5.0)		5 (11.0)	40 (9.1)	
Infection	5 (9.8)	90 (20.5)		7 (16.4)	85 (19.4)	
Ischemia	2 (3.9)	43 (9.8)		2 (4.2)	40 (9.1)	
Trauma	16 (31.4)	171 (39.0)		17 (40.2)	167 (37.9)	
Other	8 (15.7)	112 (25.6)		12 (28.2)	108 (24.4)	
Time since amputation			0.34, 0.02*			0.22, 0.16
<1 y	18 (35.3)	88 (20.1)		13 (31.2)	96 (21.7)	
1–9 y	33 (64.7)	350 (79.9)		30 (68.8)	345 (78.3)	
Level of amputation			0.64, <0.001*			0.12, 0.96
Above elbow	4 (7.8)	14 (3.2)		1 (3.4)	15 (3.5)	
Above/through knee	18 (35.3)	159 (36.3)		14 (33.0)	161 (36.5)	
Below elbow	4 (7.8)	13 (3.0)		3 (5.9)	17 (3.8)	
Below knee	18 (35.3)	245 (55.9)		23 (54.4)	236 (53.5)	
Shoulder disarticulation	7 (13.7)	7 (1.6)		1 (3.2)	12 (2.7)	

*Significant.
TMR, targeted muscle reinnervation.

presented in Table 1. Balance between the TMR and general groups was much improved after IPTW adjustment, particularly for reason for amputation, time since amputation, and level of amputation. Patient-reported pain outcomes for the Numerical Rating Scale (NRS) and PROMIS are reported in Table 2. Median worst phantom and residual limb pain were lower in the TMR cohort compared with the general amputee population (median worst pain 1 vs 5 out of 10 for phantom, $p = 0.003$; 1 vs 4 for residual, $p < 0.001$; Fig. 2). The NRS best pain and current pain scores were also lower in the TMR cohort than in the general amputee population ($p < 0.001$ for each). Each PROMIS t-score for phantom pain was lower in the TMR cohort than in the general amputee population (36.3 vs 48.4 for intensity, 50.1 vs 56.6 for behavioral, 40.7 vs 55.8 for interference, $p < 0.001$ for each; Fig. 3). Residual limb pain PROMIS t-scores were also lower in the TMR cohort (30.7 vs 46.8 for intensity, 36.7 vs 57.3 for behavioral, 40.7 vs 57.3 for

Table 2. Patient Outcomes with Inverse Probability of Treatment Weighting Adjustment

	TMR		General		
Outcome	**Median (IQR)**	**Missing, n**	**Median (IQR)**	**Missing, n**	**p Value**
Phantom limb pain: numerical rating scale					
Worst pain	1 (0–5)	0	5 (1–7)	1	0.003
Best pain	0 (0–0)	0	0 (0–3)	7	<0.001
Current pain	0 (0–1)	0	1 (0–4)	8	<0.001
Phantom limb pain: PROMIS t-scores					
Intensity	36.3 (31–40)	0	48.4 (41–54)	3	<0.001
Behavioral	50.1 (37–52)	0	56.6 (51–61)	8	<0.001
Interference	40.7 (41–41)	0	55.8 (41–63)	4	<0.001
Residual limb pain: numerical rating scale					
Worst pain	1 (0–3)	1	4 (1–7)	2	<0.001
Best pain	0 (0–0)	1	1 (0–3)	6	<0.001
Current pain	0 (0–0)	0	2 (0–4)	12	<0.001
Residual limb pain: PROMIS t-scores					
Intensity	30.7 (31–36)	0	46.8 (41–52)	4	<0.001
Behavioral	36.7 (37–50)	0	57.3 (52–61)	6	<0.001
Interference	40.7 (41–41)	0	57.3 (41–64)	5	<0.001

IQR, interquartile range; PROMIS, Patient-Reported Outcomes Measurement Information System; TMR, targeted muscle reinnervation.

interference, $p < 0.001$ for each). Results were consistent in sensitivity analysis using multiple imputation.

The worst NRS pain scores for phantom and residual limb pain are presented in Table 3. In the general population, 21.5% of participants were free of phantom limb pain (NRS 0) and 19.5% were free of residual limb pain. In the TMR cohort, 45.3% of patients were free of phantom limb pain and 49.2% were free of residual limb pain. More than 30% of general amputee participants had severe (NRS 7 to 10) phantom limb pain (33.4%) and severe residual pain (31.9%), compared with 18.7% and 16.9% of TMR patients, respectively. In ordinal logistic regression modeling, TMR patients had 3.03 times higher odds of having lower phantom limb pain than participants in the general amputee population and 3.92 times higher odds of having lower residual limb pain.

Prescription history was available for 41 of 51 immediate TMR patients (Fig. 4). Nearly half of patients (46%) were taking opioids preoperatively. All patients were prescribed opioid pain medications immediately postoperatively. Prevalence of opioid prescriptions decreased to 61% by 6 weeks, 37% by 3 months, and 21% by 12 months. By indication, opioid prescriptions decreased from 63% preoperatively to 25% at 12 months for cancer patients; rates for trauma patients remained relatively unchanged from the premorbid state (9.1% preoperatively to 10% at 12 months). The objective prescription data from the Ohio Automated Rx Registry System (OARRS) was consistent with self-reported opioid use (percent agreement 91%, Cohen's kappa 0.713).

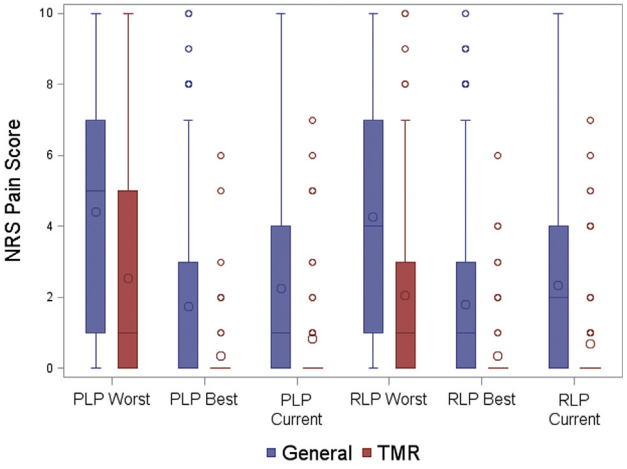

Figure 2. Weighted box plots for phantom limb pain (PLP) and residual limb pain (RLP) Numerical Rating Scale (NRS, 0 indicating no pain and 10 indicating most severe pain) for worst and best over the past 24 hours and current. TMR, targeted muscle reinnervation.

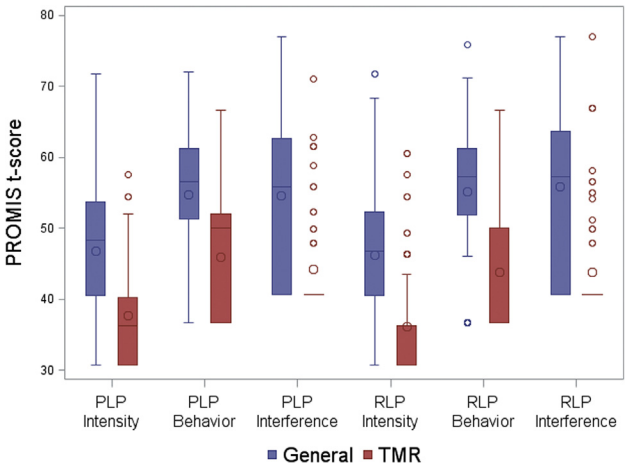

Figure 3. Weighted box plots for phantom limb pain (PLP) and residual limb pain (RLP) PROMIS pain intensity, behavior, and interference. PROMIS, Patient-Reported Outcomes Measurement Information System; TMR, targeted muscle reinnervation.

DISCUSSION

Our study demonstrates that targeted muscle reinnervation markedly decreases phantom limb pain and residual limb pain compared with pain in otherwise untreated amputees when performed immediately at the time of major limb amputation. Patients who underwent TMR achieved a pain-free rate of more than 45%, twice that of our general amputee cohort (21.5% phantom/19.5% residual), and in stark contrast to literature pain-free rates as low as 9%.[3] Targeted muscle reinnervation decreased 11-point pain NRS by 4 points for phantom pain and 3 points for residual pain. Phantom limb pain may be more successfully prevented than residual limb pain because although the former is thought to be purely a nerve issue, the latter can be due to numerous conditions including residual limb ischemia, bone spurs, and unstable skin coverage, among other causes. In studies of both chronic and acute pain, a change in NRS of 2 points has been shown to be clinically important and correlated to a patient's need to take additional pain medication.[48,49] Significant differences in PROMIS pain measures further support the efficacy of immediate TMR for both phantom and residual limb pain. These outcomes are similar to that described for the first patient to undergo concurrent TMR at the time of traumatic shoulder disarticulation, who is without any local pain and has occasional light intensity phantom limb sensations 5 years after surgery.[50]

Phantom limb sensations and pain have been associated with dysfunction at multiple neural levels, from the periphery to sensorimotor cortex.[5-10] Harris[51] hypothesized that efferent-afferent incongruence, or incongruence between motor intention and movement and sensory feedback, was the driver of pathologic phantom pain. Histologic studies in animal models of TMR revealed physiologic nerve-to-nerve healing, and high-density electromyography in transhumeral TMR patients demonstrated that synaptic input to reinnervated targets after TMR was similar to that in physiologically innervated muscles.[30,52] Additionally, functional magnetic resonance imaging (fMRI) of post-TMR amputees, non-TMR amputees, and healthy controls showed more similarities between post-TMR amputees and healthy controls than between post-TMR amputees and non-TMR amputees.[53] Therefore,

Table 3. Numerical Rating Scale Worst Pain, Categorized, with Inverse Probability of Treatment Weighting Adjustment

NRS worst pain category	TMR, n (%)	General, n (%)	Ordinal logistic regression odds ratio for lower pain (95% CI), p value
Phantom limb pain			3.03 (1.46, 6.31), 0.003
No pain (0)	19.5 (45.3)	94.4 (21.5)	
Mild pain (1–3)	11.8 (27.3)	90.4 (20.6)	
Moderate pain (4–6)	3.8 (8.8)	107.9 (24.6)	
Severe pain (7–10)	8.1 (18.7)	146.6 (33.4)	
Residual limb pain			3.92 (1.89, 8.15), <0.001
No pain (0)	21.1 (49.2)	85.4 (19.5)	
Mild pain (1–3)	12.6 (29.3)	105.9 (24.2)	
Moderate pain (4–6)	2.0 (4.7)	107.5 (24.5)	
Severe pain (7–10)	7.3 (16.9)	139.6 (31.9)	

NRS, Numerical Rating Scale; TMR, targeted muscle reinnervation.

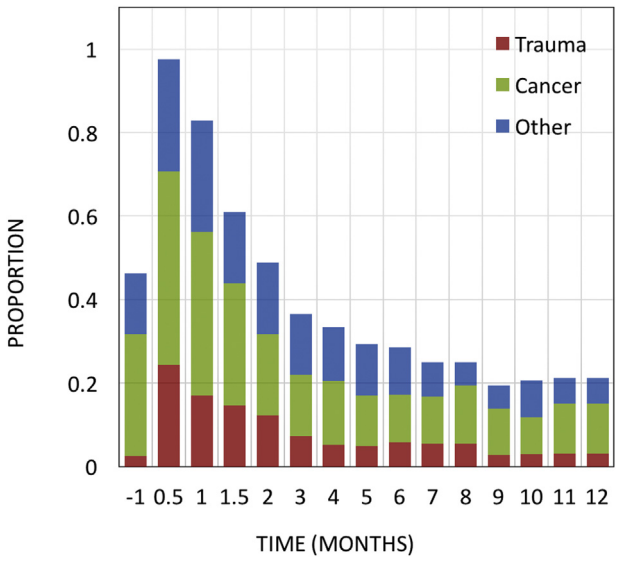

Figure 4. Opioid prescription patterns pre- and postoperatively for targeted muscle reinnervation cohort (n = 41).

we postulate that TMR establishes new efferent and afferent signals to and from the reinnervated muscle, obviating cortical incongruence and maladaptive phantom pain. These clinical data provide additional evidence for the importance of afferent feedback in phantom limb phenomena.

Although the majority of TMR patients reported a worst pain score of 3 or less, 5 patients reported severe pain. On retrospective review of these outliers, 4 had multiple failed limb salvage attempts, 1 of these patients had a peripheral nerve sheath tumor as the primary pathology, and 1 had a history of an ischemic injury to the distal upper limb. All patients had a history of severe chronic pain for years to decades preceding amputation and TMR. There is some evidence to suggest a central effect of prolonged noxious stimuli, but the literature remains mixed on the impact of preamputation pain on PLP.[54] Despite severe pain scores, however, 2 are able to use a prosthetic on a regular basis. One patient has stopped taking opioids, while another has reduced their dose of pain medication. Future studies will allow us to identify high risk patients and refine relative indications and contraindications for TMR.

Our study is not without limitations. As with many studies of pain, 1 weakness of this study is the requirement of patients to distinguish, recall, and self-report outcomes. We have chosen the 11-point NRS as a commonly used measure for patient-reported pain outcomes, in addition to PROMIS measures, which have been validated across multiple specialties.[42] Further, our survey data represent a single snapshot in time. The NRS and PROMIS pain measures attempt to assess pain over both 24-hour and 7-day recall periods. We chose to recruit non-TMR amputees through a large outreach of amputee-related clinics and conferences rather than to withhold TMR from our eligible patients, which represents a selection bias. This was an ethical decision. However, using this approach allowed us to obtain a larger sample of the general non-TMR amputee population with longer follow-up. Other limitations are the differences between the TMR cohort and the general amputee population with respect to reason for amputation, level of amputation, and time since amputation, which we adjusted for by performing inverse propensity of treatment weighted analysis. The significance of TMR as a novel surgical technique includes its origins as a means for intuitive prosthetic control[28,29]; however, it should be noted that pain outcomes were independent of myoelectric prosthetic use because the majority of our patients were lower extremity amputees. The effect of myoelectric prosthetic use on phantom limb pain cannot be assessed from this study. Finally, the use of opioid prescription data as a proxy of pain medication usage assumes that the patient is taking the medication as prescribed and has no other source of opioids. Opioid use within the general amputee population was not collected and should be a subject of future works.

Targeted muscle reinnervation at the time of amputation adds minimal risk and recovery beyond the index amputation, as the surgical insult to remove the limb is far greater than the dissection to perform the required nerve transfers. Immediate TMR often requires an additional incision, approximately 1 extra hour of surgical time, and a team knowledgeable in the performance of nerve transfers. Any surgeon with peripheral nerve experience and familiarity with major peripheral nerve anatomy may be trained in TMR. Of note, an operating microscope is not required for the nerve transfers. Performing TMR at the time of amputation avoids a separate operation to address the nerves and may speed time to rehabilitation and prosthesis use. Furthermore, TMR facilitates, rather than hinders, future advanced prostheses. With an urgency to decrease opioid use and dependence, preemptive management of chronic amputee-related pain with TMR should become routine at the time of amputation.

CONCLUSIONS

We present evidence from more than 50 surgical patients from 2 institutions that early intervention with targeted muscle reinnervation significantly improves neuropathic pain outcomes in major limb amputees. Patients receiving TMR had 3.03 times higher odds of having lower phantom limb pain and 3.92 times higher odds of having lower residual limb pain compared with general amputee participants. Given the high prevalence of phantom limb pain, TMR has the potential to have an impact on a large number of future amputees. Our findings represent a new surgical paradigm for the prevention of amputee-related phantom and residual limb pain and should be considered a mainstay of multidisciplinary, comprehensive amputee care.

Author Contributions

Study conception and design: Valerio, Dumanian, Jordan, Mioton, Souza, Potter

Acquisition of data: Valerio, Dumanian, Jordan, Mioton, Bowen, West, Ko, Souza, Potter

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Drafting of manuscript: Jordan, Mioton, Porter

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Invited Commentary

Targeted Muscle Reinnervation: A Significant Advance in the Prevention and Treatment of Post-Amputation Neuropathic Pain

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"Preemptive treatment of phantom and residual limb pain with targeted muscle reinnervation at the time of major limb amputation"