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Early Outcomes in Targeted Muscle Reinnervation for Traumatic Amputations

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Abstract

Background Traumatic amputees commonly experience residual limb pain (RLP) and phantom limb pain (PLP) which present major barriers to rehabilitation. An evolving treatment, targeted muscle reinnervation (TMR), shows promise in reducing these symptoms. While initial data are encouraging, existing studies are low power, and more research is needed to assess the long-term outcomes of TMR. We present the results of self-reported outcome surveys distributed to major-limb amputees more than 1 year post-TMR which were compared with similar data from a landmark randomized control trial for context.

Methods Data was obtained from 17 adult traumatic amputees who were more than 1 year post-TMR using a numerical rating scale and the Patient-Reported Outcomes Measurement Information System survey tool. Results were compared with a 2019 randomized control trial by Dumanian et al which assessed TMR versus standard care (SC) after major limb amputation and demonstrated improvement in pain scores 1 year post-TMR.

Results There was a statistically significant reduction in this cohort of TMR amputees' RLP worst pain scores relative to the comparison study's SC amputees (without TMR). In general, there was no significant difference in outcomes between TMR cohorts. However, PLP worst pain was significantly higher in this cohort relative to the comparison study's TMR group.

Conclusion These findings support the use of TMR for reducing RLP in traumatic amputees. Relative to a similar group treated without TMR in the comparison study, this cohort's RLP was significantly improved. Future studies should aim to recruit more amputees to allow for analysis of functional outcomes, especially in upper limb amputees.

Keywords
- targeted muscle reinnervation
- phantom limb pain
- residual limb pain

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The leading causes of amputation, trauma and vascular disease, have resulted in over 2 million amputees residing in the United States alone, with that number expected to double by 2050.[1] The majority of these amputees suffer from a combination of residual limb pain (RLP) and phantom limb pain (PLP). These pain symptoms are associated with increased opiate use,[2] reduced prosthetic use, and difficulty with rehabilitation and ambulation.[3]

A significant cause of RLP after amputation is the development of painful terminal neuromas, which can form after major nerves are transected. Painful neuromas are frequently treated with surgical excision and burying of the nerve fascicle in nearby healthy tissue, such as muscle or fat.[4] However, over time the nerve will often regrow and form a new neuroma.

The mechanism for PLP is not well understood. Previous studies have described it as arising from a complex interaction between a painful neuroma and the central nervous system resulting in cortical reorganization.[5] PLP has historically been difficult to prevent and treat. Treatment with neuromodulators such as gabapentin is commonly attempted, but previous studies and meta-analyses have had conflicting results on its effectiveness.[6,7]

An evolving treatment, targeted muscle reinnervation (TMR), involves surgically excising neuromas at the severed end of major nerves and subsequently coapting the nerves to the divided motor nerves of nearby skeletal muscles.[8] This results in many of a coapted nerves' fascicles growing down the motor nerve and connecting with the muscle's motor endplates and sensory receptors. This has been described in previous studies as the result of giving the transected nerves' fibers "somewhere to go and something to do" by providing them a scaffold to grow upon that guides the growing nerve fascicles. TMR was initially developed for use in in myoelectric prosthetic; however, emerging data has shown TMR to be effective at preventing neuroma recurrence and subsequently reducing RLP and PLP.[9–12]

Rationale

TMR is gaining broader recognition as a mainstay in the prophylactic treatment of limb pain in amputees. Several studies have been performed over the past 3 years with the aim of validating the efficacy of TMR for treating limb pain in amputees.[9,10,12] While many of these showed marked reductions in PLP and RLP following TMR, existing studies involve small patient cohorts of fewer than 60 TMR amputees. This study aims to contribute to the existing literature by reporting outcomes from amputees treated with TMR at a single academic institution.

Methods

Study Design and Setting

This is a retrospective comparative study involving a single institution and a single surgeon. All amputees reviewed were treated by the senior author at Froedtert Hospital in Wauwatosa, WI, and followed up with providers associated with the Medical College of Wisconsin. All amputees recruited had their TMR performed on dates ranging from April 2018 to August 2020 and were over a year post-surgery from TMR. Amputee chart reviews, surveys, and data collection were performed from August 2021 to March 2022.

Participants/Study Subjects

Subjects were identified for inclusion in the study through a chart review of all amputees seen by the senior author with an associated TMR procedure code between 2018 and 2020. Inclusion criteria for the study included being over 18 years of age, having a traumatic amputation, and being over 1 year post-surgery from TMR.

Description of Surgery

TMR surgery has been well described.[13] While TMR can be performed concurrently with limb amputation, at our institution it is often performed as a staged procedure following amputation. For TMR after below-knee amputation, the tibial, common peroneal, medial, lateral sural, and saphenous nerves are identified. Any existing neuromas are excised from the ends of the severed major nerves. Next, the motor nerves of nearby skeletal muscles are identified using a nerve stimulator. Once identified, the motor nerves are divided, and the remaining healthy major mixed nerve fascicles are coapted to the motor nerve with 8–0 nylon sutures.

Chart Review

A retrospective chart review of all eligible amputees was performed. Amputee demographics were noted, including age, race, and gender. Procedure notes from each subject's amputation and TMR surgeries were reviewed to determine dates of procedures, location of amputation (e.g., left side, lower limb), type of amputation (e.g., below the knee), type of trauma sustained (e.g., motor vehicle collision), number of nerves transferred, and which nerves were transferred (e.g., medial sural nerve to lateral soleus motor nerve).

Pain outcomes were measured using several self-reported surveys. Note that 11-point numerical rating scale (NRS) (Survey 1) was used to determine pain outcomes to all eligible amputees who agreed to participate in the study. Amputees were asked to state their current RLP and PLP pain level, as well as the best and worst pain level during the previous 24 hours. The Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference Short-Form 8a (Survey 2) was also administered to further capture pain outcomes. Second, we assessed functional outcomes in lower extremity amputees by administering both the Neurology Quality-of-Life (Neuro-QOL) Item Bank v.10 - Lower Extremity Function (Mobility) 8-item Short-Form survey (Survey 3) as well as PROMIS Item Bank v.10 - Physical Function with Mobility Aid - Short-Form (Survey 4). Upper extremity amputees had their function assessed by administering the Orthotics Prosthetics Users Survey (OPUS) Upper Extremity Functional Status questionnaire (Survey 5).

Variables, Outcome Measures, Data Sources, and Bias

The primary pain outcome of this study was measured by Survey 1. The mean scores for worst pain reported in the last

24 hours for both RLP and PLP were compared with the mean TMR and standard care (SC) worst PLP and worst RLP pain scores at 1-year follow-up by the comparison study.[9] The stand-alone outcomes of measured current pain and best pain reported in the last 24 hours were reported but not contrasted as these measures were not provided in the comparison study.

The secondary pain outcome of this study was measured by Survey 2 and likewise had its mean scores compared with the mean TMR and SC PROMIS Pain Interference scores at 1-year follow-up by the comparison study.

Functional outcomes measured from Surveys 3 to 5 were reported as the mean *t*-scores associated with each survey. Survey 3 was compared and contrasted with the comparison study results; however, Survey 4 was not used by the comparison study and the results of Survey 5 were not reported in the comparison study due to too few upper extremity amputees measured.

To reduce potential respondent fatigue stemming from the administration of long phone call questionnaires this study did not include PROMIS Intensity or PROMIS Behavior surveys that were measured in the comparison study.

Demographics and Description of Study Population

The study subject population included 17 traumatic amputees: 14 lower limb and 3 upper limb. The population was of mixed race and gender consisting of adults over 18 years old. All prospective subjects were screened, and all eligible candidates were included in the study. ►**Tables 1** and **2** show additional information regarding patient demographics and treatment demographics, respectively.

The patient population we compared with was obtained from Dumanian et al's 2019 study and included 28 amputees with 14 having received TMR, of which 12 were lower limb and 3 were upper limb, and 14 having received standard treatment (SC), of which 14 were lower limb and 1 was upper limb. The population was of mixed race and gender consisting of adults over 18 years old.

Accounting for All Patients/Study Subjects

Thirty-four amputees with TMR codes since 2018 were deemed potentially eligible for inclusion in the study and were examined. Of these 34 prospective subjects, 10 were determined to be ineligible based on inclusion criteria with 4 amputees being deceased, 3 amputees having nontraumatic amputations, 2 amputees not having had an amputation performed, and 1 amputee being under the age of 18.

Twenty-four eligible amputees had their full chart review completed and were designated to be contacted for telephone survey. All 24 amputees were sent a standard email notifying them that they would be called via phone regarding our study 1 week prior to us calling them. During the telephone survey process, 7 amputees were unable to be contacted. All 17 prospective amputees contacted consented to enrolment in the study, were surveyed, and had their results included in this study.

Statistical Analysis and Study Size

Study size was determined based on the availability of amputees who met the study's inclusion criteria. The *n* value of TMR subjects in this study is also similar to the comparison study. Continuous variables from the NRS, PROMIS, and Neuro-QOL surveys were expressed as a mean with standard deviation while categorical variables were expressed as a number and percentage. Due to the low population of upper extremity amputee subjects, OPUS score statistics were not analyzed. NRS survey statistics were calculated from the raw scores whereas the PROMIS and Neuro-QOL survey raw scores were translated to their associated *t*-scores prior to analysis. Raw score and *t*-score averages were compared between subjects with and without RLP, as well as between amputees with and without PLP. These comparisons were performed using Student's *t*-tests.

Pearson's correlations were checked for RLP pain scores, PLP pain scores, and functional scores against age at time of amputation, time from amputation to TMR, and number of nerves transferred. The raw scores and *t*-scores from our

Table 1 Patient demographics

Variables	Treatment TMR ($n = 17$ patients; 17 limbs)		Comparison TMR ($n = 14$ patients; 15 limbs)		Comparison standard care ($n = 14$ patients; 15 limbs)	
Age (y), mean (SD)	52.1 (19.8)		39.6 (16.5)		45.3 (14.6)	
Sex						
Male	14	82.4%	12	80.0%	8	53.3%
Female	3	17.6%	2	13.3%	6	40.0%
Race/Ethnicity						
White/Caucasian	13	76.5%	10	66.7%	10	66.7%
Black/African American	3	17.6%	0	0.0%	3	20.0%
Multiracial	0	0.0%	3	20.0%	0	0.0%
Hispanic/Latino	1	5.9%	0	0.0%	0	0.0%
Other	0	0.0%	1	6.7%	1	6.7%

Abbreviations: SD, standard deviation; TMR, targeted muscle reinnervation.

Table 2 Treatment characteristics

Variables	Treatment TMR ($n = 17$)		Comparison TMR ($n = 15$)		Comparison standard care ($n = 15$)	
Nerves transferred, mean (SD)	4.2 (1.4)		2.9 (1.1)		2.3 (1.0)	
Reason for amputation						
Trauma	17	100%	13	86.7%	14	93.3%
Infection	0	0%	2	13.3%	1	6.7%
Amputated limb location						
Lower limb	14	82.4%	12	80.0%	14	93.3%
Upper limb	3	17.6%	3	20.0%	1	6.7%
Time since amputation						
Less than 1 y	0	0.0%	1	6.7%	1	6.7%
1–4 y	13	76.5%	3	20.0%	2	13.3%
5–9 y	2	11.8%	7	46.7%	8	53.3%
10+ y	2	11.8%	4	26.7%	4	26.7%
Most recent follow-up						
6 mo	0	0.0%	1	6.7%	0	0.0%
12 mo	0	0.0%	5	33.3%	5	33.3%
18 mo	3	17.6%	5	33.3%	5	33.3%
> 24 mo	14	82.4%	4	26.7%	5	33.3%
Mean (SD)	27.4 (7.6)		17.7 (7.5)		19.3 (5.8)	

Abbreviations: SD, standard deviation; TMR, targeted muscle reinnervation.

study were then measured against the comparison study. The mean scores for worst pain reported in the last 24 hours for RLP and PLP as well as the mean scores for RLP and PLP PROMIS Pain Interference were compared with the respective subgroups of both TMR and SC cohorts of the comparison study at 1-year follow-up. The difference of two means was compared between our study and the comparison study using pooled variance. A statistical significance threshold of *p*-value less than 0.05 was utilized for this study. All *p*-values were two-sided and *p*-value less than 0.05 was considered statistically significant. Statistical analysis was performed with SAS version 9.4 (SAS Institute).

The means and standard deviation of measured current pain and best pain reported in the last 24 hours were calculated but not compared with the comparison study. Scores from the Neuro-QOL Item Bank v1.0–Lower Extremity Function were compared with the comparison study mean *t*-score from the final follow-up in the TMR cohort. One subject's data was not included for the calculation of the Neuro-QOL – Lower Extremity and Physical Function Mobility – Lower Extremity scores due to an error in survey administration.

Results

A significant reduction in RLP, as measured by the NRS worst pain scale, was seen in patients who had received TMR relative to the cohort of amputees who underwent SC as reported by Dumanian et al. Mean RLP NRS worst pain scores were 3.1 ± 4.2 for treatment TMR amputees and 6.0 ± 2.8 for comparison SC amputees with a mean difference of –2.9 (–5.4 to 0.3) and a *p*-value of 0.0277. This result was deemed clinically relevant as it exceeds the 2-point mean difference outlined by the minimal clinically important difference for clinical relevance.[14] No significant difference was observed in PLP pain interference, RLP pain interference, or PLP NRS worst pain scores versus SC amputees. The results of these findings are also shown in ►**Tables 3** and **4**.

This study's TMR amputees showed no difference in pain interference scores or RLP NRS pain scores when compared with the comparison study's TMR amputees. However, they did show an increase in PLP NRS pain scores relative to the comparison study's TMR amputees. This study's lower extremity TMR amputees showed reduced lower extremity function scores on Neuro-QOL when compared with comparison TMR amputees. The results of these findings are shown in ►**Tables 3** and **4**.

This study's lower extremity TMR amputees showed reduced lower extremity function as indicated by lower extremity function scores on Neuro-QOL when compared with comparison TMR amputees. The 13 lower limb TMR amputees that were sampled had a mean *t*-score of 41.4 (21.1–58.6) compared with a mean *t*-score of 45.2 from the comparison TMR amputees at final follow-up. Although the PROMIS Lower Extremity Function survey was not used by the randomized control trial (RCT), the study's lower extremity TMR amputees' performance had a mean *t*-score of 42.4 (30.8–57.9). However, the PROMIS surveys are

Table 3 Numerical rating scale—worst pain comparison

Variables	Treatment TMR ($n = 17$)	Comparison TMR ($n = 15$)			Comparison standard care ($n = 15$)		
NRS – worst pain raw score	Mean (SD)	Mean (SD)	Mean difference (95% CI)	*p*-Value	Mean (SD)	Mean difference (95% CI)	*p*-Value
Phantom limb pain	5.1 (4.4)	2.6 (2.2)	2.5 (0.1–5.0)	0.0454	4.1 (3.0)	1.0 (–1.7 to 3.7)	0.4454
Residual limb pain	3.1 (4.2)	3.7 (2.0)	–0.6 (–2.9 to 1.7)	0.6126	6.0 (2.8)	–2.9 (–5.4 to 0.3)	0.0277

Abbreviations: CI, confidence interval; NRS, numerical rating scale; SD, standard deviation; TMR, targeted muscle reinnervation.

Table 4 PROMIS – Pain Interference comparison

Variables	Treatment TMR ($n = 17$)	Comparison TMR ($n = 15$)			Comparison standard care ($n = 15$)		
PROMIS Pain Interference – *t*-scores	Mean (SD)	Mean (SD)	Mean difference (95% CI)	*p*-Value	Mean (SD)	Mean difference (95% CI)	*p*-Value
Phantom limb pain	52.3 (11.2)	50.4 (9.8)	1.9 (–5.7 to 9.4)	0.6206	52.8 (8.9)	–0.5 (–7.8 to 6.7)	0.8803
Residual limb pain	50.4 (13.0)	56.8 (6.6)	–6.4 (–13.7 to 1.0)	0.0858	57.4 (8.6)	–7.0 (–14.9 to 0.9)	0.0808

Abbreviations: CI, confidence interval; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation; TMR, targeted muscle reinnervation.

standardized against the general United States population with a mean *t*-score of 50 and a standard deviation of 10 indicating that our amputees' results are lower but fall within 1 standard deviation.

Discussion

Background and Rationale

Chronic RLP and PLP are common and significant barriers to quality to life and functional rehabilitation in traumatic amputees. There is growing consensus that TMR provides improved pain control and functional recovery in amputees. Current research is limited by small patient cohorts and relatively short-term outcome data. This study reports pain and functional outcome data in a cohort of postsurgical TMR patients and corroborates the notion that TMR is beneficial for pain control in amputees.

Limitations

A major limitation of this study is the lack of longitudinal follow-up with amputees due to not having their baseline pain scores. Without having this reference point or a randomized matched cohort to compare with we are limited to reporting aggregate pain and functional outcomes in a small cohort of posttraumatic amputees. To provide context for the raw data, we structured the study in dialogue with the leading RCT on the subject and used similar outcome reporting surveys. In addition, we used the outcomes from the RCT's standard treatment group as a comparison point. However, this leads to multiple opportunities for bias as there was no control for differences between surgical techniques or postsurgical care.

Another significant limitation is self-report bias from patients stating their pain and function levels which could have led to an over- or underestimation of values. However, we attempted to control for this by administering similar surveys as prior studies that use neutrally worded questions and keep patient responses anonymous.

Outcomes

The most striking, and expected, result of our data are a significantly diminished residual limb "worst pain" score relative to the comparison study's standard treatment group. This can be intuitively interpreted as a corroboration that TMR is effective at treating and preventing the formation of painful neuromas. However, this improvement was not seen in PLP which corresponds with the notion that PLP is a complex phenomenon. Overall, our results align fairly well with the comparison study's results. The differences that do exist, including statistically significant differences, may not be meaningful in light of the limitations discussed.

Conclusion

Chronic pain is a significant challenge for amputees that has a large impact on their quality life. Our study demonstrates that TMR can offer durable improvements to RLP years after treatment. However, PLP may show variable results in the long term due to its complex nature. Future research should aim to further increase statistical power by including more patients. Pre- and postop surveys should also be added to allow for longitudinal assessment of outcomes. In light of growing consensus that TMR is the gold standard treatment

in traumatic amputation, randomization to "standard treatment" without TMR is likely now unethical.

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Conflict of Interest
None declared.

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