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Peripheral Nerve

Targeted Muscle Reinnervation for Limb Amputation to Avoid Neuroma and Phantom Limb Pain in Patients Treated at a Pediatric Hospital

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Background: Amputees frequently experience chronic neuroma-related residual limb and phantom limb pain (PLP). Targeted muscle reinnervation (TMR) transfers transected nerves to nearby motor nerves to promote healing and prevent neuroma formation and PLP. The purpose of this study was to report outcomes of TMR in a series of children and young adults treated at a pediatric hospital.

Methods: Patients undergoing major limb amputation with TMR were included with minimum one year follow-up and completed questionnaires. Primary clinical outcomes included incidence of symptomatic neuromas, PLP, residual limb pain, narcotic use, and neuromodulator use. A follow-up phone survey was conducted assessing five pediatric Patient Reported Outcomes Measurement Information System (PROMIS) metrics adapted to assess residual limb and PLP.

Results: Nine patients (seven male and two female patients, avg. age = 16.83 ± 7.16 years) were eligible. Average time between surgery and phone follow-up was 21.3 ± 9.8 months. Average PROMIS Pediatric t-scores for measures of pain behavior, interference, quality—affective, and quality—sensory for both PLP and residual limb pain were nearly 1 standard deviation lower than the United States general pediatric population. One patient developed a symptomatic neuroma 1 year after surgery.

Conclusions: Compared with an adult patient sample reported by Valerio et al, our TMR patients at Nationwide Children's Hospital (NCH) showed similar PLP PROMIS t-scores in pain behavior (50.1 versus 43.9) and pain interference (40.7 versus 45.6). Both pediatric and adult populations had similar residual limb pain including PROMIS pain behavior (36.7 adult versus 38.6 pediatric) and pain interference (40.7 adult versus 42.7 pediatric). TMR at the time of amputation is feasible, safe, and should be considered in the pediatric population. *(Plast Reconstr Surg Glob Open 2023; 11:e4944; doi: 10.1097/GOX.0000000000004944; Published online 13 April 2023.)*

INTRODUCTION

For adult patients who have undergone limb amputation, innovative surgical methods have been shown to decrease phantom limb pain (PLP) and improve function. However, the outcomes of these techniques have not been well documented in the pediatric population.[1] Although there is controversy surrounding whether limb-salvage or amputation is associated with superior functional outcomes, it is clear that regardless of the procedure performed, physical aptitude is associated with improved outcomes.[2] With this in mind, it is intuitive that when amputation is chosen to optimize physical function,

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it should yield improved outcomes and minimize phantom and residual limb pain.

Transient neuropathic pain occurs in 12%–83% of pediatric patients undergoing limb-salvage or amputation, with wide variability reported between studies.[3] However, persistent postamputation pain related to residual limb or "stump" pain and PLP can be debilitating and lead to prosthetic abandonment in amputees. Residual limb pain is most commonly secondary to symptomatic neuromas, which develop in approximately 30% of major limb amputees.[4] Although PLP typically improves with respect to frequency and intensity with time, it may persist months to years after amputation.[5] Unfortunately, there is a paucity of literature, specifically large prospective studies, conducted to determine the true incidence and impact of PLP in the pediatric population.

Strategies for the prevention and treatment of post-amputation pain vary from local and regional anesthetics, pharmacologic modalities including narcotics, neuromodulators, and NMDA receptor antagonists, surgical techniques, and finally, cognitive behavioral therapy. Specifically, there are more than 150 surgical treatments described in the literature for the prevention and treatment of neuromas; this myriad of treatments highlights that no intervention has been shown to be consistently superior. The gold standard for the last few decades has been traction neurectomy, a procedure associated with at minimum a 24% failure rate for the treatment of neuromas.[6] With respect to PLP, multiple preventative and treatment approaches have been attempted with concrete evidence supporting the use of mirror therapy,[7] early evidence that use of narcotics may prevent the development of cortical re-organization associated with PLP[8] and only mixed results with neuromodulators such as gabapentin.[9–12]

Recently, targeted muscle reinnervation (TMR), a procedure initially developed to improve myoelectric prosthetic control,[13] has gained popularity for the treatment of symptomatic neuromas[14] and as a preventative measure at the time of amputation to minimize the risk of developing subsequent neuromas and PLP.[15,16] TMR is a microsurgical technique involving the transfer of amputated peripheral nerves to small motor nerves in a nearby muscle target. The severed nerve from the amputation is subsequently able to regenerate to a new muscle target in an organized fashion, eliminating the disorganized regeneration resulting in neuroma formation and PLP. TMR is typically applied to pure sensory, as well as mixed motor and sensory nerves at the site of amputation.

This technique has demonstrated benefit in the adult population, with improved neuroma pain, and patient-reported outcomes improved by 13.7%.[17] Based on the effect of TMR on the development of postamputation neuroma-related pain and PLP and the potential for use of myoelectric prostheses, we sought to determine the effect of TMR on residual limb pain and PLP in pediatric patients undergoing amputation. Given that the surgical technique and concept of TMR is similar for the adult and pediatric population, we hypothesized benefits in pain and outcomes would be demonstrated in our pediatric patients. We assessed secondary outcomes, including rates of prosthetic utilization and complications, and postoperative narcotic and neuromodulator dependence. Although a pediatric case has been reported in the literature,[18] this study represents the first case series of successful TMR reported in the pediatric population.

Takeaways

Question: Does targeted muscle reinnervation improve neuroma and phantom limb pain in children after amputation?

Findings: This retrospective review demonstrated decreased phantom limb and residual limb pain, as well as early prosthetic adoption.

Meaning: Targeted muscle reinnervation in the pediatric population provides similar pain benefits as adults and should be considered for all children undergoing major limb amputation.

METHODS

All patients undergoing amputation with TMR as treatment for oncologic, traumatic, and infectious diseases at a large pediatric hospital in the Midwestern United States between 2016 and 2020 were included in the study. All patients were younger than 18 years of age, with the exception of a single patient who was 23 years old. All patients were treated at the same pediatric institution. Patients had a minimum of 1 year of clinical follow-up from the time of their initial surgery. One patient was lost to follow-up after 5 months and was excluded from the study. After obtaining approval from the local institutional review board, patient medical records were reviewed and patient demographics (including age, sex, diagnosis, and utilization of adjuvant therapies) were identified. Outcomes including local and systemic disease control, incidence of postoperative neuroma and PLP, and time to prosthetic use were assessed. More specifically, the presence of symptomatic postoperative neuromas and PLP, as well as prosthetic use, were assessed and noted in the chart at postoperative visits with the plastic and reconstructive surgery and orthopedic oncology clinical providers at 1 month, 1–3 months, 3–6 months, and 12 months.

A follow-up telephone call was conducted to assess five Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric Self-Report measures adapted for both residual limb pain and PLP. (**See table, Supplemental Digital Content 1,** which displays the questionnaire. (A) Patients were asked the included questions twice, once in regard to pain in the residual limb and once for pain in the phantom limb. Questions comprising the PROMIS Numerical Pain Scale, Pain Behavior, Pain Interference, Pain Quality—Affective, and Pain Quality—Sensory were included. (B) Patient demographics and clinical course. **http://links.lww.com/PRSGO/C507**). These PROMIS Pediatric measures included Pain Intensity, Pain Behavior, Pain Interference, Pain Quality—Affective, and Pain Quality—Sensory. The PROMIS Numeric Rating

Scale (NRS)—Pediatric Pain Intensity 1a was a single-item assessment tool rating pain on average over the past 7 days from 0 (no pain) to 10 (worst pain you can think of). Pain Behavior Short Form 8a assessed all behaviors typically indicative of an individual experiencing pain. Pain Interference Short Form 8a assessed the consequences of pain, including the extent to which pain hindered engagement with social, cognitive, emotional, physical, and recreational activities. As the description and feeling of pain tends to be variable, Pain Quality measured both the physical sensations (eg, burning, throbbing, tingly) and affective components associated with pain (eg, felt unpleasant, annoying, unending).

All measures, except Pain Intensity (where the raw NRS score was used), were calibrated to produce standardized t-scores. A higher t-score indicated worse pain, with 50 representing the standardized average for the general pediatric population of the United States.

RESULTS

Nine patients (seven male and two female patients, avg. age = 16.83±7.16 years) underwent amputation with TMR between 2016 and 2020 and met all inclusion criteria. Patient demographics and clinical course for each of the nine patients are summarized in Supplemental Digital Content 1. (**See table, Supplemental Digital Content 1**, which displays the questionnaire. (A) Patients were asked the included questions twice, once in regard to pain in the residual limb and once for pain in the phantom limb. Questions comprising the PROMIS Numerical Pain Scale, Pain Behavior, Pain Interference, Pain Quality-Affective, and Pain Quality-Sensory were included. (B) Patient demographics and clinical course. **http://links.lww.com/PRSGO/C507**). The diagnoses for these patients included Ewing sarcoma, two; osteosarcoma, four; septic shock, one; trauma, one; and giant cell tumor of the bone, one, as well as various amputations levels (transfemoral, four; transtibial, three; trans-radial, one; middle ray resection, one). The six sarcoma patients were treated with neoadjuvant and adjuvant chemotherapy. Four of the five lower extremity amputees received prosthetics at a mean of 4 months (range 2–6 months) postoperatively. One patient developed a symptomatic neuroma in a nerve that was not included in initial TMR procedure (lateral femoral cutaneous nerve) after 12 months and underwent revision TMR with subsequent resolution of pain. For the patient with severe septic shock, acute amputations of all four extremities were performed as life-saving measures. TMR was subsequently performed for all four extremities once the patient was medically stable and able to take part in rehabilitation. In all other patients, TMR was performed concurrently at the time of acute amputation and wound closure.

The majority of patients (80%) were able to discontinue narcotic use by 3 months, with less than 33% of patients reporting occasional use on an as needed basis. (**See figure, Supplemental Digital Content 2**, which displays the narcotic use following targeted muscle reinnervation surgery. **http://links.lww.com/PRSGO/C508**). Regarding neuromodulators, one patient discontinued use by 6 weeks after surgery, four patients discontinued neuromodulators by 12–15 months, three patients required ongoing use at last follow-up, and one patient did not require any neuromodulators.

The average time between surgery and telephone follow-up was 21.3±9.8 months. For the patient with septic shock, telephone follow-up took place 16 months after his amputations and 9 months after TMR. Of note, Pain Intensity scores (0–10 scale) were 3.7±2.1 (range 0–7) for PLP and 2.0±1.8 (range 0–5) for residual pain. PROMIS scores for each patient are reported as t-scores and are summarized in Table 1.

DISCUSSION

Our findings demonstrate that pediatric patients undergoing amputation with TMR have t-scores that are on average nearly a standard deviation below the average general pediatric US population. Only one patient had an NRS or t-score greater than 5 or 50, respectively, and of

Table 1. Numerical Pain and PROMIS (T-score) Outcomes

		Residual Limb					Phantom Limb				
ID	Amputation Level	Numerical Pain Scale	Pain Behavior	Pain Interference	Pain Quality Affective	Pain Quality Sensory	Numerical Pain Scale	Pain Behavior	Pain Interference	Pain Quality Affective	Pain Quality Sensory
1	AKA	0	20	34	34.6	32.2	2	41.9	47.1	34.6	38.9
2	AKA	2	47.3	50.6	49	34.7	5	45.7	48.4	49	49.4
3	BKA	3	41.9	38.7	43.5	40.7	0	20	34	34.6	32.2
4	Middle ray resection	0	20	34	34.6	32.2	2	41.9	34	43.5	45
5	Trans-radial	5	41.9	34	43.5	38.9	5	44.8	34	43.5	40.7
6	BKA	4	52.5	66.5	49	64	7	48.1	62.4	51.4	60.9
7	BKA	2	50.7	49.8	43	49.9	3	46.2	46.6	43	47.8
8	Bilateral BKA Bilateral AEA	0	26	34	34.6	41.3	5	59.9	58.4	47.5	53.7
9	AKA	2	47.3		46.5	43.7	4	47.3		43.5	43.7
	Mean	2.0	38.6	42.7	42.0	42.0	3.7	44.0	45.6	43.4	45.8
	SD	1.8	13.1	11.9	6.0	10.0	2.1	10.5	11.1	5.8	8.4

AKA: Above knee amputation; BKA: Below knee amputation; AEA: Above elbow amputation.

note, this patient had the longest follow-up of the cohort (40.5 months) and only recently developed symptoms.

In comparison with an adult oncology cohort (N = 51) undergoing amputation with TMR,[19] our pediatric population has similar PLP PROMIS t-scores in pain behavior (50.1 versus 43.9), pain interference (40.7 versus 45.6), and pain intensity NRS raw scores. Both pediatric and adult populations also had similar residual limb pain including PROMIS pain behavior (36.7 adult versus 38.6 pediatric) and pain interference (40.7 adult versus 42.7 pediatric). In the prior study, the adult TMR cohort had statistically and clinically meaningful better residual and PLP PROMIS scores in comparison with a general adult population.[19] Although it is impossible to infer an expected difference between TMR and non-TMR pediatric patients based on these findings, it is promising that similar results are seen between the pediatric and adult patients. In addition, we found that patients undergoing amputation with TMR had early prosthetic adoption. Finally, chronic narcotic and neuromodulator use was minimal in this patient population.

There are several limitations to our study. The most significant limitation is the lack of a direct comparison with a non-TMR pediatric population; however, given the small cohort, it is unlikely that a statistically significant difference would be appreciated. Due to the retrospective nature of our study, it was difficult to objectively determine prosthetic wear rates beyond the time to when the patient received their prosthetic. There are also several limitations that are inherent to the limited role that amputation plays in the management of pediatric bone tumors, including small sample size, effects of chemotherapy, heterogeneous patient population, and short-term follow-up. With respect to follow-up, we did note that the patient with the longest follow-up (40.5 months) had the highest pain scores and had more recently developed worsening pain. Longer follow-up may be beneficial to determine stability of pain scores over time. Finally, we acknowledge that the TMR population used in this study has mixed etiologies (trauma, infectious, oncologic), as well as one patient who underwent delayed TMR, and this may play a role in outcomes. However, we felt it was more important to assess the overall outcomes of TMR in the pediatric population with a larger cohort rather than limit the series by preoperative diagnosis.

Despite these limitations, our results suggest that TMR may be effective in the pediatric population as a method to prevent residual limb pain and PLP, which are symptoms that often hinder an amputee's recovery. These early data support further efforts to determine the effect of TMR on patient-reported outcomes and objective functional outcomes in the pediatric population, specifically designing a multicenter study comparing traditional amputation techniques with targeted muscle reinnervation. As this study focused specifically on noncongenital amputation, an additional area of exploration may include studying the adaptation of TMR in congenital limb amputations and the adaptation of myoelectric prosthetics in this population.

TMR has the potential to positively impact outcomes through improved prosthetic use, decreased chronic pain with a subsequent decrease in narcotic and neuromodulator dependence, and improved physical function. Our results suggest that among the pediatric population, TMR provides similar benefits in reducing residual limb and PLP, as has been observed in adults. TMR at the time of amputation is feasible, safe, and should be considered in the pediatric population.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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