Effectiveness of Targeted Muscle Reinnervation or Targeted Nerve Innervation on neuroma pain and development in people with upper and lower extremity amputation

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Clinical Question: Does primary and secondary targeted muscle reinnervation or targeted nerve innervation prevent neuroma formation and neuroma related pain in upper extremity and lower extremity amputees?

Background: The loss of an arm or leg is a major injury that often affects a person's occupation, personal relationships, and overall quality of life. An average of 25% of amputees,[1] upwards of 71% in traumatic cases,[2] will develop chronic residual limb pain that can interfere with the patient's ability to comfortably wear and use a prosthesis. This can inhibit a patient's ability to participate in recreational or occupational activities, reduce their level of independence, and negatively affect their overall quality of life. This chronic pain is often caused by a neuroma, a group of disorganized axons, encased in scar and fibrous tissue, that develops at the end of a severed nerve.[3] Current prosthetic, nonsurgical, and surgical treatments are often temporary or ineffective.[3]

Targeted muscle reinnervation (TMR) was first performed in 2002 to permit intuitive control of prostheses. While pain was not the primary concern, neuromas were excised as part of the procedure.[4] Targeted nerve innervation (TNI) was first performed in 2006 with the main goal being neuroma prevention.[4] Like TMR, it transfers a transected proximal nerve to a denervated muscle allowing regenerating axons to grow in an organized matter.[5] Both can be performed in the acute/primary setting for neuroma prevention and the non-acute/secondary setting for neuroma revision. The goal of this CAT is to determine if TMR or TNI is a superior method for neuroma prevention.

Search Strategy:
Databases Searched: 1) Google Scholar, 2) PubMed, and 3) www.oandp.org
Search Terms: Combinations of the following terms were used: "targeted muscle reinnervation," "targeted nerve innervation," neuroma, pain, amputation, amputees, "targeted reinnervation," prevention, and standard neuroma excision and burial
Inclusion/Exclusion Criteria: Inclusion: articles in English using TMR or TNI to address neuromas, 2002-2016; Exclusion: articles assessing myoelectric control, secondary sources/reviews

Synthesis of Results: Four articles, one pre-clinical, one case study, and two retrospective cohort studies, were included in this CAT. Anecdotal patient reports and clinical experience indicated that TMR could have an unforeseen effect on neuroma development and pain and in 2012, neuroma development was evaluated in animal models where post-TMR histological results showed progression toward pre-injury values.[6] This study provided the foundational evidence needed to transition the research focus to clinical trials in humans. In the retrospective studies conducted in 2014, TMR was found to be 100% successful in the primary setting and 80% in the secondary,[4] and TNI was found to be 92% successful in the primary setting and 87% in the secondary.[5] In unsuccessful cases, pain was either improved but not resolved,[4,5] localized at the sites of nerves not included in the procedure,[4] or had an unknown cause for which neuroma could not be ruled out.[4] Further, a case study found that TMR resulted in less pain interference and pain behaviour than normative scores based on the US general population.[7]

The results and conclusions of these studies were consistent with each other, but it is important to note that a majority of the studies were conducted at the same institution and had researchers in common.[4-7] Also, most of the studies did not use a validated pain scale or radiographic imaging,[4,5] were affected by transfer bias, lacked long term results, and had a small sample size.[4-7] Despite their limitations, these studies created a stable platform for a large, multi-institutional randomized control trial (RCT) that is now underway.[8]

Clinical Message: The results of the included studies are consistent, but the qualitative and quantitative evidence needed to support TMR or TNI as the best treatment option for amputees who suffer from neuroma related pain and associated activity restrictions is limited. Further research is warranted to provide conclusive evidence that these procedures are superior to the other options available.

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Evidence Table

	Kim et al., 2012[6]	Cheesborough et al., 2014[7]	Souza et al., 2014[4]	Pet et al., 2014[5]
Purpose	Create a TMR model to assess the effects TMR has on neuroma histomorphology	Document clinical evidence that TMR can be a viable treatment for neuroma pain in an acute setting	Evaluate the effects of TMR on residual limb neuroma pain in upper extremity amputees	Determine if TNI prevents primary neuroma formation and/or reduces secondary neuroma pain in upper and lower extremity amputees
Study Design	Before-and-after trial	Case Study	Retrospective cohort	Retrospective cohort
Setting	Northwestern University Center for Comparative Medicine and the Bioimaging Facility	Northwestern University Feinburg School of Medicine	Northwestern University Feinburg School of Medicine	University of Washington and Harborview Medical Center
Population	5 New Zealand White rabbits Forelimb amputation and a rectus abdominis (RA) flap transfer 3 nerve coaptations: (The median nerve, radial nerve, and ulnar nerve innervated to 3 motor nerves of the transferred rectus abdominis)	One 54 year old female (first documented case using TMR) Traumatic (MVA) left transhumeral amputee 4 nerve coaptations (medial, posterior, and two lateral cords) 8-month follow-up	26 patients from 2002-2012 (11 primary; 15 secondary) Amputation levels: 10 shoulder disarticulation, 16 transhumeral Total number of nerve transfers: 82 (average of 2-5 per patient) Inclusion criteria: history of amputation treated with TMR, follow-up of $\geq$6 months	24 patients from 2006-2012 (12 primary; 12 secondary) Amputation levels: 19 upper extremity and 16 lower extremity Total number of nerve transfers: 76 nerves (average of 1-4 per patient) Inclusion criteria: history of major U/LE amputation treated with TNI, follow-up of $\geq$8 months for the primary group and $\geq$4 months for the

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				secondary group, established painful neuroma in the secondary group Exclusion criteria: Non-traumatic mechanisms of amputation in the primary group
Intervention	Secondary TMR surgery	Primary TMR surgery	TMR for the primary purpose of myoelectric prosthesis control	Primary and secondary TNI surgery
Outcomes	Myelinated fiber count and cross-sectional areas Nerve specimens harvested before and after TMR and (analysis completed by a single observer)	Patient Reported Outcomes Measurement Information System (PROMIS) - Pain behavior and pain interference (average score among the US population is 50)	Pre- and post-operative assessment of localized neuroma pain and prosthetic fitting Included hospital and out patient records of the surgeon, physiatrist, OT, PT, and prosthetist	Presence or absence of palpation-induced neuroma pain during the last recorded follow-up Neuroma related pain was defined as localizable tenderness and a reproducible Tinel's
Key Findings	Decrease the myelinated fiber counts and increased fascicle diameters (progress back towards the preinjury values and away from neuroma values)	The patient showed no evidence of neuroma pain during the clinical exam and demonstrated minimal pain interference (score of 39) and pain behavior (score of 37)	14/15 pts with neuroma pain before TMR experienced complete resolution of pain in the transferred nerves 0/11 pts without neuroma pain before TMR developed neuromas after the procedure	11/12 primary TNI pts and 20/23 secondary TNI pts were free of palpation-induced neuroma pain at their last follow-up

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			23/26 were successfully fitted with a myoelectric prosthesis (26/26 pts were fitted with a prosthesis)	
Conclusions	TMR gives a transected nerve a distal target allowing the nerve to grow in an organized fashion that is closely related to the preinjury histologic	TMR may be used in the acute trauma setting to prevent neuroma pain	TMR may be effective for management of neuroma pain following upper limb amputation	Primary and secondary TNI provide a distal target for regenerating nerve axons, making it a viable treatment strategy for neuroma pain prevention in upper/lower extremity amputees
Strengths	Collecting/analysing data with blinding to reduce bias Provided objective data with animals that supports subjective data with humans	Reliable and valid outcome measure	Unanticipated benefit – the documented effects are free of assessor and selection bias.	Main goal was the treatment of neuromas – more thorough documentation
Limitations	Small sample size No behavioral variables Only worked with mixed major nerves and not sensory nerves Took place at the same location as the other included	Case study of a single patient Brevity and omission of important details (i.e. what was performed during the clinical exam to assess neuroma related pain and by whom/where). Took place at the same location as the other included	Small sample size Unanticipated benefit – lack of radiographic imaging and standardized validated pain assessment Does not include lower extremity patients Took place at the same location as the other included	Small sample size Lack of radiographic imaging and standardized validated pain assessment Limited number of lower extremity patients Took place at the same location as the other included

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	studies with similar researchers	studies with similar researchers	studies with similar researchers Diagnoses based on findings by independent evaluations of multiple providers in different locations	studies with similar researchers Did not account for late recurrence of symptomatic neuroma Transfer, selection, and assessor bias

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