Targeted Muscle Reinnervation for neuropathic pain in amputees

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INTRODUCTION

- Amputations are unfortunately necessitated annually in over a million people worldwide for various indications ranging from trauma, tumors, ischemia to diabetic complications[1], with numbers expected to double by 2050[2].
- Following amputation, 75% of patients[134567] suffer from post-amputation pain, with a major source being neuropathic or neuroma-associated pain[13];fig.1.

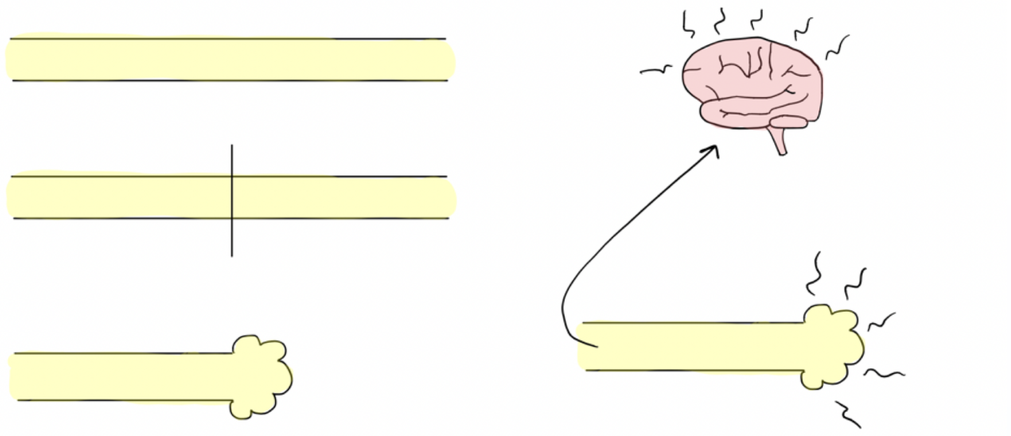

Figure 1. Neuroma formation following nerve transection and pain signaling to the brain.

- The chronic pain restricts prosthesis wear[89], limits physically mobility[10] and quality of life[11], ultimately affecting both mental and physical health[1]. Thus, it is vital that effective, long-term analgesia to neuropathic pain is developed.
- Several nonsurgical therapies, including first-line pain medications[121314] and psychological therapies[15] have shown limited benefit in providing analgesia to neuropathic pain.
- The traditional surgical treatments available such as traction neurectomy[4] or neuroma excision followed by deep implantation into local muscle[1617] are not consistently or universally effective[18192021].
- One surgical procedure that has shown promising results is targeted muscle reinnervation (TMR)[184]. This aims to prevent neuroma reformation by promoting physiological nerve regeneration instead, and therefore, provide long-term analgesia.

OBJECTIVES

- To present the current TMR technique and review the evidence for contemplating TMR as the new surgical first-line for neuropathic pain management in amputees.
- To consider the notion of pre-emptive TMR done at the time of amputation and the concept of combining TMR with adjuncts such as regenerative peripheral nerve interface (RPNI) and vascularized RPNI (vRPNI) to further improve achieved pain-relief.
- To propose that optimal analgesia can be best achieved by combining surgical techniques with pharmacological and psychological therapies in a multi-disciplinary, combinatorial approach.

TECHNIQUE

- Following amputation, the transected sensory nerves undergo aberrant, disorganized growth, as they attempt to reach a distal target, forming neuroma[1232425] (fig.1), causing severe debilitating pain[26].
- Targeted muscle reinnervation (TMR) for neuropathic pain treatment, involves:

1. Surgical excision of the neuroma; fig.2.
2. Transection of motor branches innervating redundant local muscles; fig.2.
3. Coaptation of sensory branches, proximal to the excised neuroma, to the cut distal motor branches; fig.3.

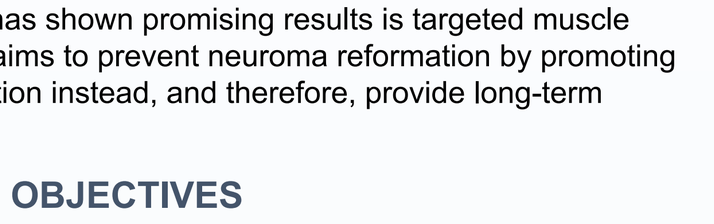

Figure 2. TMR can be conceptualized as a three-step procedure. The first step is to excise the pain-causing neuroma at the end of the sensory branches. The second step is to identify and cut the motor branches innervating the redundant local muscles.

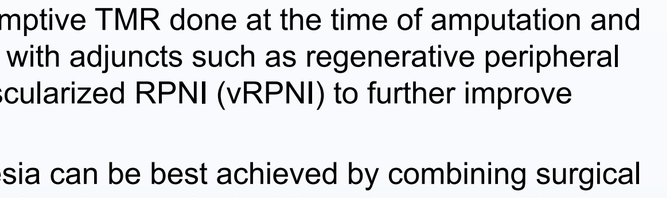

Figure 3. The third step is to coapt the cut sensory branches to the distal cut motor branches.

EFFICACY

- Several studies[27] ranging from case-reports[2829] to randomized prospective clinical trials[16] have consistently shown improvement in post-amputation neuropathic pain following TMR; see table.1.

Table 1. All TMR studies reviewed.

Author and Year	Study Type	Data Collection Method	Control	Outcomes Measured	Outcome Instrument	TMR Type	Study Size	No. with pre-operative NS	% with reduced NS
Pet et al (2014)[30]	CTS	Retrospective	No	Pain	Ad hoc survey	Secondary	35	23	87
Pet et al (2014)[30]	CTS	Retrospective	No	Pain	Ad hoc survey	Primary	12	N/A	92
Souza et al (2014)[18]	CTS	Retrospective	No	Pain	Ad hoc survey	Secondary	26	15	93
Cheesborough et al (2014)[31]	CS	Prospective	N/A	Pain	Clinical exam and PROMIS	Primary	1	1	100
Cheesborough et al (2015)[29]	CS	Prospective	N/A	Not specified	Anecdotal	Secondary	1	1	100
Dumanian et al (2019)[16]	RCT	Prospective	Yes	Pain	NRS	Secondary	28	28	67
Bowen et al (2019)[32]	CTS	Prospective	Yes	Pain	Unknown	Secondary	4	N/A	100
Bowen et al (2019)[32]	CTS	Prospective	Yes	Pain	Unknown	Primary	18	N/A	100
Valerio et al (2019)[33]	CTS	Un-defined	Yes	Pain	NRS and PROMIS	Primary	51	N/A	100

NS = Neuroma Symptoms; CTS = Clinical Therapeutic Study; CS = Case Study; RCT = Randomised Clinical Trial; PROMIS = Patient Reported Outcomes Measurement Information System; NRS = Numerical Rating Scale.

- However, ongoing research utilizing larger sample sizes, appropriate control groups, validated outcome measures and adequately long follow up times are needed to draw firm conclusions[27].

FUTURE DIRECTIONS

- The future holds several exciting avenues to be explored, including pre-emptive TMR done at the time of amputation, combining TMR with other compatible surgical treatments and adopting a multi-disciplinary approach to post-amputation pain treatment.
- Recent evidence suggests that performing TMR at the time of amputation reduces the incidence of both phantom and neuropathic pain[33], which has been consistently supported by several studies[223031].
- Another developing idea is the combination of TMR with other compatible surgical treatments, such as RPNI[34], which alone can reduce neuroma pain by 71%[34] and can be readily combined with TMR to enhance the results achieved[4].
- Modern medical care is rightfully shifting towards multi-disciplinary, patient-centered care and so it is vital to consider pharmacological, radiological and psychological therapies that can be used in conjunction with TMR to provide the best outcome for the patient.
- In order to expound the recommended ideas, several objective, comparative studies are required that employ the same methodology and outcome measures to allow valid comparisons to be made.

CONCLUSIONS

- Care of amputees suffering from severe, debilitating neuropathic pain should utilize TMR and offer a multi-disciplinary, combined therapy.
- Strong emerging evidence shows that TMR is very effective at reducing post-amputation neuropathic pain in the long-term and is also superior to current commonly used surgical therapy.
- Recent evidence suggests a possible role for adjunctive TMR at the time of amputation, as well as a role for combining TMR with other novel techniques to achieve the most effective analgesia.
- These techniques offer a long-term solution to neuroma-associated pain, improving the amputees' prosthesis use and quality of life, and should be combined with pharmacological and psychological therapies to achieve the most optimal results.

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