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Muscle reinnervation with nerve-muscle-endplate band grafting technique: correlation between force recovery and axonal regeneration

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ABSTRACT

Background: This study was designed to determine the correlation between functional recovery and the extent of axonal regeneration after muscle reinnervation with our recently developed nerve-muscle-endplate band grafting (NMEG) technique in a rat model.
Materials and methods: The right experimentally paralyzed sternomastoid (SM) muscle by nerve transection was immediately reinnervated with an NMEG pedicle harvested from a neighboring sternohyoid muscle. The NMEG pedicle contained a muscle block (6 × 6 × 3 mm), a donor nerve branch with nerve terminals, and a motor endplate band. Three months after surgery, the tetanic force of the SM muscle was measured and the regenerated axons in the muscle were detected using neurofilament immunohistochemistry.
Results: The results showed that the maximal tetanic force (a measure of muscle functional recovery) of the NMEG-reinnervated SM muscle reached up to 66.0% of the normal control. The wet weight of the reinnervated SM muscle (a measure of muscle mass recovery) was 87.2% of the control. The area fraction of the regenerating axons visualized with neurofilament staining within the NMEG-reinnervated SM muscle (a measure of muscle reinnervation) was 42.3%. A positive correlation was revealed between the extent of muscle reinnervation and maximal muscle force.
Conclusions: Our newly developed NMEG technique results in satisfactory functional outcomes and nerve regeneration. Further improvement in the functional recovery after NMEG reinnervation could be achieved by refining the surgical procedure and creating an ideal environment that favors axon-endplate connections and accelerates axonal growth and sprouting.

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1. Introduction

Peripheral nerve injuries and resultant muscle paralysis are caused mainly by trauma and surgical intervention, which represent a major medical problem [1–4]. Unfortunately, the presently existing nerve repair methods can result in poor functional outcomes.

Based on various situations, peripheral nerve injuries can be treated with nerve end-to-end anastomosis (EEA), nerve grafting, nerve transfer, neurotization, and conduit

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repair [5]. In general, EEA is commonly used when the two stumps of an injured nerve can be approximated without tension [6,7]. However, only about 50% of patients regain useful function [8,9]. Factors behind poor functional recovery include tension of the anastomosis, neuroma formation, scaring, and loss of the nerve fiber population [10]. Studies have shown that in EEA fewer nerve fibers could pass through the coaptation site and reach the target organ [11]. A significant nerve defect is a common clinical situation. In this case, autologous nerve grafts, nerve transfers, and tubulization may be used. Nerve grafting has been associated with poor functional outcomes when there is a long distance from the level of the injury to the target muscle. The recovery rate of motor function after autogenous nerve grafting is less than 40% [12]. Tubulization methods are feasible only in short nerve gaps [5]. If the gap exceeds 1.0–1.5 cm, regeneration is poor [13]. Longer defects (4.0–6.0 cm) result in useful reinnervation in only 13% of cases with reconstruction of peripheral nerve injuries with conduits [14,15]. For the nerve injuries in which the proximal nerve stump is unavailable, nerve transfer is an option. Nerve transfer is the surgical coaptation of a healthy nerve donor to an injured nerve. A nerve branch that innervates expendable muscle(s) can be repaired to a more functionally important distal stump of an injured nerve. Many nerve-to-nerve transfers have been used to repair the injured nerves in the hand and upper extremity with mixed results [16]. In many cases with trauma, the distal nerve stump might not be available for nerve repair. The only reconstructive option to reinnervate that muscle is direct nerve implantation (i.e., muscular neurotization) [17,18] or nerve-muscle pedicle (NMP) transfer. The NMP technique has been used for laryngeal [19–22] and facial reinnervation [23–25]. However, controversy exists concerning the success rate of the NMP method. Some authors reported satisfactory functional recovery [21,22], whereas others failed to document NMP-induced muscle reinnervation and functional recovery [26,27]. These results emphasize the great need to develop novel treatment strategies for the restoration of paralyzed muscles as the currently used reinnervation methods often result in poor functional recovery.

We recently developed a new reinnervation technique called “nerve-muscle-endplate band grafting (NMEG)” [28] and conducted a series of experiments in a rat model [29–33]. The development of this technique is based on the concept that a healthy motor endplate band with a nerve branch and terminals that innervates an expendable muscle can be transplanted to a more functionally important denervated muscle for restoring its motor function. The idea is that the implanted NMEG could provide an abundant source of nerve terminals and endplates for nerve regeneration and muscle reinnervation to restore motor function of the target muscle. Our studies showed that NMEG technique yielded satisfactory functional recovery.

The goal of this study was to document NMEG-induced muscle reinnervation and determine the correlation between functional recovery and axonal regeneration after NMEG procedure.

2. Materials and methods

2.1. Animals

The experiments were performed on 10 adult (3.5-mo-old) Sprague–Dawley female rats (Charles River Laboratories, Wilmington, MA), weighing 350–450 g. The rats were provided with *ad libitum* access to food and water and housed in standard cages in a 22°C environment with a 12:12-h light–dark cycle. Experimental procedures were reviewed and approved by the Institutional Animal Care and Use Committee before the onset of our experiments. All animals were handled in accordance with the Guide for Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication no. 85–23, revised 1996). All efforts were made to minimize the number of animals and their suffering during the experiments.

2.2. NMEG procedures

Animals used in this study underwent general anesthesia with a mixture of ketamine (80 mg/kg body wt) and xylazine (5 mg/kg body wt) administered intraperitoneally. Microsurgical procedures were performed under aseptic conditions. Under an Olympus SZX12 Stereo zoom surgical microscope (Olympus America Inc, Center Valley, PA), a midline cervical incision was made extending from the hyoid bone to the sternum to expose the right sternomastoid (SM) and sternohyoid (SH) muscles and their innervating nerves. The right SM muscle was denervated by removing a 5-mm segment of its innervating nerve. The nerve cut ends were coagulated using a bipolar cautery to prevent nerve regeneration. An NMEG pedicle was harvested from the right SH muscle. The SH nerve branch was identified on the lateral margin of the middle portion of the muscle and traced from the motor point to the motor zone where axon terminals and an endplates band are located. An NMEG harvested from the right SH muscle consisted of a block of muscle (~6 × 6 × 3 mm), an intact donor nerve branch with numerous nerve terminals, and an endplates band with numerous neuromuscular junctions. The presence of functioning NMEG was confirmed by observing its twitch contractions on nerve stimulation. A muscular defect of the same dimensions as the NMEG was made in an endplate-free region in the caudal portion of the right denervated SM muscle. The NMEG in continuity with its motor nerve branch and feeding vessels was embedded in the SM muscle defect and sutured with four to six 10–0 nylon microsutures (Fig. 1). After surgery, the wound was closed in layers with interrupted simple sutures of 4–0 Prolene.

2.3. Muscle force measurement

At the end of the 3-mo recovery period, the muscle force of the reinnervated SM was measured using a stimulation and recording system as described in our publications [28,30–33]. Briefly, the SM muscle was dissected free from surrounding tissue without damaging the SH nerve branch innervating the implanted NMEG. The rostral tendon of the muscle was sev-

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