Nerve traction as a graft-free strategy to repair peripheral nerve gaps

Authors: Elisabeth Orozco[1], MS; Koichi Masuda, MD[2]; Justin Brown, MD[3]; Sameer B. Shah, PhD[1,2]

Introduction: Current strategies for repairing severe peripheral nerve injuries are often unsuccessful, leaving patients with motor dysfunction, sensory loss, and chronic pain. Primary nerve transections require the reconnection of the proximal stump to its original distal stump. More rapid and more distal reconnection of proximal and distal stumps improves the prognosis for functional recovery; large gaps hinder efficacious reconnectivity. A variety of non-autologous and autologous grafts have yielded positive results for bridging gaps <3 cm (in humans), however, outcomes remain poor for larger gaps. Thus, though autografts remain the standard of care for larger gaps, there is need for new solutions. Autografts are additionally limited by insufficient source tissue, the requirement for additional surgery, and donor site morbidity, including the possibility of painful neuroma formation. Though surgical dogma encourages tension-free nerve repairs (largely to avoid the catastrophic consequences of failure at the fragile repair site), there is strong evidence in animal models and patients that when safely possible, end-to-end repair is favorable to graft-based repair. Enhanced outcomes with end-to-end repair are likely due to improved stump-to-stump alignment, matched axonal and stump geometry, and only a single interface across which axons must regenerate. Therefore, to facilitate end-to-end repair, we developed graft-free, implantable device-based strategies to reconnect proximal nerve stumps to distal stumps.

Materials and Methods: To test our strategy, under institutional IACUC approval, we created gaps in sciatic nerves of 5 month-old male and female rabbits. In the first set of experiments, moderate 10-15mm nerve gaps were reconnected end-to-end following redistribution of tension away from the repair site. To this end, proximal and distal stumps were safely secured in custom-designed nerve cuffs and guided together along a rigid backbone prior to performing an end-to-end repair. In the second set of experiments, a large 25-30mm nerve gap was repaired. Nerve stumps were secured to nerve cuffs as above. The proximal stump was progressively drawn towards the distal stump gradually by means of an externalized guidewire, which moved the proximal cuff along a rigid backbone. After daily lengthening for 2 weeks, nerves stumps were trimmed and sutured together end-to-end, tension-free. Reversed autografts, used to bridge 10-15mm nerve gaps, served as standard of care controls. Structural regeneration was evaluated through neuromuscular immunohistochemistry. Proximal nerve stumps were labeled with nodal markers, beta3-tubulin, and laminin to evaluate the morphology of lengthened neurons. Distal stump cross sections were labeled with beta3-tubulin and laminin to obtain axonal count/density. Endplate density and morphology were assessed using alpha-bungarotoxin labeling and muscle fiber size was calculated based on laminin labeling. Tibialis anterior twitch and tetanic forces and rabbit paw spread were evaluated as functional outcomes. Mean outcomes were expressed as a ratio of injured to contralateral. A minimum of N=7 rabbits per group were compared using an unpaired t-test.

Results: Feasibility of a protected end-to-end repair of moderate gaps up to 15mm was confirmed based on an intact end-to-end repair site upon device removal, even with additional tension imposed by ankle dorsiflexion and knee extension. Feasibility of end-to-end repairs of large gaps after gradual nerve lengthening was confirmed based on elimination of the nerve gap and successful end-to-end repair after device removal; end-to-end repairs remained protected during ankle and knee movement. At 24 weeks after injury, regenerative structural and functional outcomes were equal or better in tension redistributed end-to-end repairs (first set of experiments) as well as gradually lengthened and end-to-end repaired nerves (second set of experiments), including higher axon counts in the distal stump and 50-200% higher tibialis anterior (ankle dorsiflexor) twitch and tetanic tension compared to autografts (Figure 1). Preliminary results also indicate improved neuromuscular structural regeneration compared to corresponding autograft repairs (Figure 2).

Discussion: For moderate gaps, redistributing tension away from the repair site into healthy nerve regions allows for superior functional outcomes compared to autografts. Progressive nerve lengthening followed by end-to-end repair also enhances regenerative outcomes for large nerve gaps compared to autografts.

Significance/Clinical Relevance: Tension-based strategies offer a promising alternative to graft-based approaches. Through both tension-based approaches to nerve repairs, we demonstrated: i) improved functional outcomes following end-to-end nerve repair compared to standard-of-care autograft-based repairs; ii) spared donor site morbidity versus autograft-based repairs; iii) a potential solution for repairing large nerve gaps, a clinical challenge with no effective regenerative solution. Each of these value additions will have a significant positive impact on patient sensorimotor function, and as a consequence, quality of daily living.