In Vivo Evaluation Of Novel Biphasic Conducting Tubes For Peripheral Nerve Repair

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Statement of Purpose: Each year 400,000 Americans sustain nerve transection injuries which require surgical intervention for repair. Due to rapid scar formation which blocks nerve outgrowth, there are no treatment options for the approximately 90% of patients who have gaps greater than 3 cm. Electrical stimulation across nerve gaps have accelerated axon outgrowth up to three times the normal rate for up to 48 hours. Further, electric fields up to 600 um have directed and accelerated axon outgrowth across nerve gaps in corneal nerve repair. These data led to the **hypothesis** that repeated electric field gradients up to 600 um would maximize axonal outgrowth. Previously, we have shown that biphasic conducting materials promoted enhanced neurite outgrowth along an electric field in vitro in under three days.

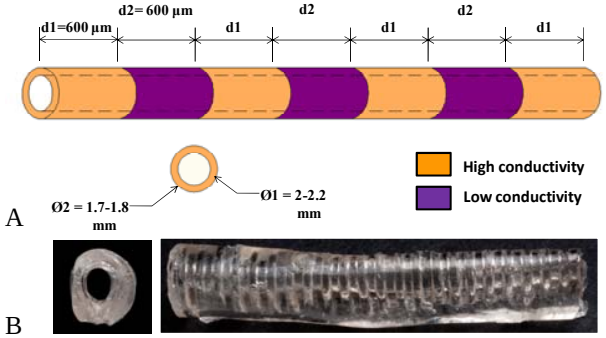
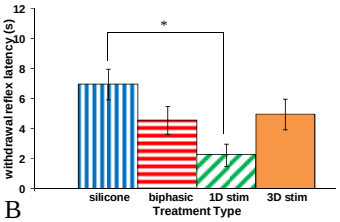


Figure 1. The purpose of this project was to evaluate the in vivo effects of biphasic conducting conduits (with and without external electrical stimulation) in a 1 cm rat sciatic nerve model. [A] Biphasic tube schematic [B] Sample of implanted biphasic tubes.

Methods: Target materials properties were determined based on mechanical properties of excised nerve (elastic moduli: 0.4-0.7 N/mm^2, tensile strength: 0.21 – 1.49 N), human nerve healing time frame (3-12 months), and ohms law applied to known electric field properties surrounding nerve tissue for conductivity range (1E-4 S/cm (low), 1E-6 S/cm (high)). Biphasic conducting tubes were prepared using poly (glycerol sebacate) acrylate synthesized with 40% acrylation with high conductivity regions doped with 0.05% poly(pyrrole). Per Institutional Animal Care and Use Committee approval, either a silicone (control) or biphasic tube was implanted into a 1 cm rat sciatic nerve gap. Biphasic tubes were either implanted alone or with an implantable circuit which induced electrical stimulation of 3 V, 20 Hz for either one or three days (n = 6 per group). Functional, sensory, electrophysiological, and histological results were collected via walking track with sciatic function index (SFI) analysis, hot plate withdrawal reflex latency, compound motor action potential (CMAP), and nerve densities, respectively, prior and up to two weeks post injury.

Results: Sciatic function indices (0 = uninjured, -90 = max injury) showed 50% recovery for rats with biphasic tubes with three days stimulation at two weeks. There was no significant functional recovery observed for any other treatment. [Figure 2A] Electrophysiological recovery was observed for greater than 50% of the rats treated with biphasic conducting tubes in only two weeks with no significant differences in either conduction velocity or signal amplitude in all cases, at two weeks. No CMAP recovery was observed for any control rats at two weeks. Sensory recovery data suggested a trend of improvement in sensation of heat for all biphasic tube treatments with statistically significant recovery for rats with biphasic tubes with one day of stimulation ($p<0.01$). (Figure 2B) Histological samples taken at midpoints of proximal, medial, and distal segments of the tubes indicated no apparent scar tissue formation within the biphasic tubes. Further, there were no significant differences between biphasic tubes alone and undamaged control nerves for axon numbers and maturation in the proximal sections as indicated by axon densities and myelination ratios.

		CMAP/ Rats	SFI
silicone	0 weeks		-13.75 ± 1.92
	2 weeks		-78.91 ± 2.84*
	No CMAP	6/6	-78.91 ± 2.84*
	CMAP	0/6	N/A
biphasic	0 weeks		-12.02 ± 1.25
	2 weeks		-77.25 ± 1.93*
	No CMAP	2/6	-71.72 ± 1.96*
	CMAP	4/6	-80.58 ± 2.50*
biphasic + 1 day stim	0 weeks		-6.09 ± 3.02
	2 weeks		-77.65 ± 6.69*
	No CMAP	1/5	-73.34 ± 10.34*
	CMAP	4/5	-78.52 ± 7.93*
biphasic + 3 day stim	0 weeks		-9.47 ± 2.35
	2 weeks		-65.61 ± 9.02*
	No CMAP	3/6	-79.93 ± 5.10*
	CMAP	3/6	-46.51 ± 17.81*



A B

Figure 2. A. Rats treated with biphasic tubes with three days stimulation and CMAP recovery demonstrated 50% recovery in function in two weeks. B. Sensory stimuli response for rats treated with biphasic tubes and one day of stimulation occurred in 1/3 the time of rats treated with control silicone tubes.

Conclusions: Comparisons of the biphasic tube treatment results to published results of presently offered treatments of autografts, collagen tubes, poly (glycolic acid) tubes and poly (caprolactone) tubes implied that the biphasic tube treatment results may be more rapid and extensive in repair in two weeks than that observed in six to eight times the time frame for existing treatment options, including autografts. The data imply that biphasic tubes may enable faster axonal recovery than existing treatments. Future work will include a longer study with a larger n, inclusion of an autograft control group, and additional histological analysis to confirm and elucidate underlying cellular and molecular mechanisms. These results indicate that biphasic conducting tubes may be promising devices to extend options for peripheral nerve repair to previously untreatable patients and may improve surgical success for treatable patients.

References:

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