Flexible and Kink-Resistant Braided Conduits for Peripheral Nerve Regeneration

Basak Acan Clements, Jared Bushman, Sanjeeva Murthy and Joachim Kohn*
NJ Center for Biomaterials, Rutgers – The State University of NJ, 145 Bevier Road, Piscataway, New Jersey, USA

Statement of Purpose: Peripheral nerves are intrinsically capable of regeneration, but they can only do so unaided across small gaps. Patients with untreatable nerve injuries face permanent loss of motor control and/or sensation. Grafting of autologous nerve remains the best option, but donor morbidity and supply limitations remain problematic. Synthetic conduits have entered the market but have been effective only for bridging small gaps (<3cm) due to their suboptimal mechanical and biological properties. Regeneration across long gaps may require a conduit that is porous to allow for nutrient diffusion and is capable of bending during patient movement without kinking or compression. Our previous work suggested that braiding could fulfill these criteria and impart conduit flexibility, kink resistance and porosity. In this study, braided nerve regeneration conduits were evaluated in a 16-week study in the 1 cm rat sciatic nerve injury model.

Methods: Braided conduits were fabricated by extruding tyrosine-derived polycarbonate (E0000) into thin polymer fibers, which were then spooled onto braiding spindles. A tubular braiding machine equipped with 24 carriers was used to braid conduits over a 1.5 mm thick Teflon mandrel. Kink tests were performed by bending the conduits 180° on a flexible wire. Conduit morphology was investigated by scanning electron microscopy (SEM). Braided conduits were coated with hyaluronic acid (HA) hydrogels to control porosity. *In vivo* nerve regeneration was evaluated in the 1 cm rat sciatic nerve defect by measuring the compound muscle action potentials (CMAP) at the dorsal and plantar foot muscles. At the 16-week endpoint, the nerves were harvested, cut into 1 µm sections and stained with Toluidine Blue for histomorphometric analysis. Muscles innervated by the sciatic nerve were also harvested and weighed.

Results: E0000 fibers of 100 µm average diameter were braided to produce conduits with polygonal pore dimensions varying between 15-100 µm. The braided conduits could be made in virtually unlimited diameter and length, and demonstrated elastic deformation under tension, compression and bending. Kink tests demonstrated that braided conduits resist kinking/cracking when bent at large angles; whereas extruded, electrospun, or dip-coated conduits cracked or kinked at the bending point (Fig. 1). Braided E0000 conduits were successfully implanted to bridge 1 cm rat sciatic nerve defects and significant recovery in the muscle mass and CMAP amplitute was measured, indicating reinnervation to distal muscle targets. Histological analysis showed a dense nerve cable with numerous axon bundles, but without an organized epineurium in braided conduits at 16 weeks. The lumen of these conduits and the nerve cable was highly

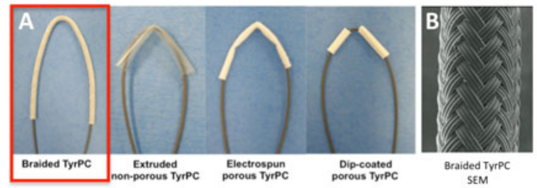

Fig.1 (A) Kink tests were performed on conduits fabricated by various techniques. Braided conduits demonstrated flexibility and non-kinking properties desired for bridging long gaps. (B) SEM image of a braided E0000 conduit.

vascularized and co-occupied by fibrous tissue. To control porosity, braided conduits were coated with HA hydrogels and tested in a 6-week *in vivo* study, as previously reported, where HA-coated conduits lead to increased axonal density and well-defined nerve cables in the conduits. Here we present the further evaluation of HA-coated conduits in a 16-week study where they were shown to enhance nerve regeneration by promoting the formation of a densely packed nerve cable surrounded by an epineurial layer with a higher density of myelinated axons (Fig. 2B) when compared to uncoated braided conduits (Fig. 2A). Animals treated with HA-coated braided conduits also had improved electrophysiological and muscle weight recovery compared to uncoated conduits. Further, this hydrogel coating did not alter the favorable mechanical and handling properties of the braided conduits and appears to be a promising strategy to improve the conduits' *in vivo* performance.

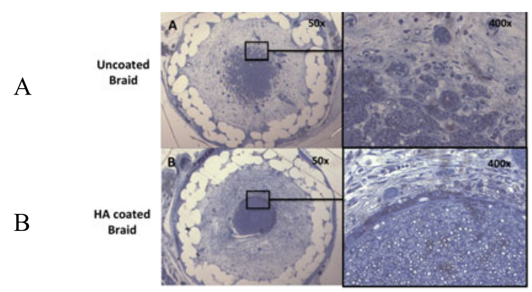

Fig.2. Cross sections of conduits explanted after 16 weeks *in vivo*. (A) The the nerve cable in the uncoated braided conduits appeared loosely packed without an epineurium. (B) Nerve cables in the HA-coated braided conduits were also densely packed with axons with a well-defined epineurium surrounding the fascicles.

Conclusions: E0000 braided conduits were porous, flexible, and kink resistant. *In vivo* nerve regeneration with braided E0000 conduits was encouraging and secondary HA coatings introduced further improvement. Braided conduits are exciting candidates that can be combined with biological components to more closely match or surpass the performance of autografts.