The Development of NeuraGen

Joseph Nichols filed a patent for the first type I collagen nerve guide in October 1986. After further development to make the conduit more permeable to infiltration by neurotrophic proteins, this conduit became the product now known as the NeuraGen Nerve Guide.

First Primate Study:

Primate studies were performed to confirm the ability of NeuraGen to bridge nerve gaps safely, prior to clinical studies in humans. The first primate study of NeuraGen, published in 1990, showed excellent regeneration and functional recovery results (as determined by histology and electrophysiology) 14 months after the conduit was used to repair 2 cm ulnar nerve gaps.

Second Primate Study:

In the second primate study, in which the efficacy of NeuraGen was compared to direct suture and nerve graft repair for 5 mm median/ulnar nerve gaps, all treatments provided equivalent functional reinnervation by the final follow-up assessment. This and other nonclinical histological studies demonstrated that the NeuraGen device is completely resorbed with no evidence of untoward inflammatory reaction.

Pilot Clinical Study:

The first clinical implantation of NeuraGen was performed in Denmark as part of a pilot clinical study sponsored by Integra LifeSciences, which showed that the device was biocompatible and safe for human use. No adverse events were reported, and no neuroma formation was observed during follow-up.

Randomized Controlled Trial:

The preliminary pilot data were followed up with an Integra-sponsored randomized, prospective multicentered trial that compared the clinical efficacy of the NeuraGen nerve conduit to that of the gold standard, direct suture, for the repair of defects of the median/ulnar nerves. Boekstyns et al. compared the clinical outcomes of 23 nerves treated with NeuraGen to 21 nerves treated through neurorrhaphy; electrophysiological and hand function outcomes were assessed as well as product safety. At the 24 month follow up, there was no difference in outcomes between the NeuraGen-treated patients and those who underwent direct suture repair. Furthermore, the study patients showed no adverse reactions to NeuraGen-treatment.

The NeuraGen Difference: An Investment in Data

Patient outcomes are important to you and your patients—NeuraGen has more published clinical data than any other collagen-based nerve conduit.*

* Including all publications that report the outcomes of more than 5 patients, as of April 1, 2019.

The NeuraGen Studies

Approximately 400 Nerves Repaired in 18 Clinical Studies

- 10+ years of clinical evidence
- 16 centers
- Gap lengths up to 2.7 cm
- Mostly traumatic nerve injuries

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Title</th>
<th>NeuraGen Conduits Studied</th>
<th>Nerves Repaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huber et al. 2017</td>
<td>Recovery of mechanical detection thresholds after direct digital nerve repair versus conduit implantation</td>
<td>11</td>
<td>Digital</td>
</tr>
<tr>
<td>Krarup et al. 2017</td>
<td>Sensation, mechanoreceptor, and nerve fiber function after nerve regeneration</td>
<td>11*</td>
<td>Median and Ulnar</td>
</tr>
<tr>
<td>Wilson et al. 2017</td>
<td>Lingual Nerve Microneurosurgery Outcomes Using 2 Different Conduits: A Retrospective Cohort Study</td>
<td>28</td>
<td>Lingual and Inferior Alveolar</td>
</tr>
<tr>
<td>Klein et al. 2016</td>
<td>Collagen type I conduits for the regeneration of nerve defects</td>
<td>10</td>
<td>Radial and Ulnar</td>
</tr>
<tr>
<td>Krarup et al. 2017</td>
<td>Remodeling of motor units after nerve regeneration studied by quantitative electromyography</td>
<td>11*</td>
<td>Median and Ulnar</td>
</tr>
<tr>
<td>Lohmeyer et al. 2014</td>
<td>Prospective clinical study on digital nerve repair with collagen nerve conduits and review of literature</td>
<td>49</td>
<td>Digital</td>
</tr>
<tr>
<td>Schmauss et al. 2014</td>
<td>In nerve regeneration after reconstruction with collagen nerve conduits terminated after 12 months? the long-term follow-up of two prospective clinical studies.</td>
<td>20*</td>
<td>Digital</td>
</tr>
<tr>
<td>Boekstyns et al. 2019</td>
<td>Collagen conduit versus microsurgical neurotomy: 2-year follow-up of a prospective, blinded clinical and electrophysiological multicenter randomized, controlled trial</td>
<td>23</td>
<td>Median and Ulnar</td>
</tr>
<tr>
<td>Diestelkoch et al. 2013</td>
<td>Type I collagen nerve conduits for median nerve repairs in the forearm</td>
<td>9</td>
<td>Median</td>
</tr>
<tr>
<td>Erakat et al. 2015</td>
<td>Interval Between Injury and Lingual Nerve Repair as a Prognostic Factor for Success Using Type I Collagen Conduit</td>
<td>23</td>
<td>Lingual</td>
</tr>
<tr>
<td>Haug et al. 2013</td>
<td>Sensory Recovery 1 Year After Bridging Digital Nerve.</td>
<td>45</td>
<td>Digital</td>
</tr>
<tr>
<td>Wolfe et al. 2017</td>
<td>Use of bioabsorbable nerve conduits as an adjunct to brachial plexus neurotomy</td>
<td>10</td>
<td>Brachial Plexus</td>
</tr>
<tr>
<td>Taras et al. 2018</td>
<td>Reconstruction of digital nerves with collagen conduits</td>
<td>23</td>
<td>Digital</td>
</tr>
<tr>
<td>Wengenroth &amp; Kallialainen. 2016</td>
<td>Collagen tube conduits in peripheral nerve repair: A retrospective analysis.</td>
<td>126</td>
<td>Digital, Radial, Median, Ulnar, Median, etc.</td>
</tr>
<tr>
<td>Lohmeyer et al. 2009</td>
<td>The clinical use of artificial nerve conduits for digital nerve repair: a prospective cohort study and literature review</td>
<td>15</td>
<td>Digital</td>
</tr>
<tr>
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<td>Early clinical experience with collagen nerve tubes in digital nerve repair</td>
<td>12</td>
<td>Digital</td>
</tr>
<tr>
<td>Farsle and Jansen, 2008</td>
<td>A bioabsorbable collagen nerve cuff (NeuraGen) for repair of lingual and inferior alveolar nerve injuries: a case series</td>
<td>9</td>
<td>Lingual and Inferior Alveolar</td>
</tr>
<tr>
<td>Ashley et al. 2007</td>
<td>Collagen nerve guides for surgical repair of brachial plexus birth injury</td>
<td>5</td>
<td>Brachial Plexus</td>
</tr>
</tbody>
</table>

* Follow-up of repairs previously studied

TOTAL: 418
The Next Generation of Nerve Repair

“...The surgical techniques and technologic advances currently used in [nerve repair] have made it possible to consistently expect vast improvement in the lives of patients, but there remains room for continued advancement... the focus of nerve repair has shifted toward manipulation of the biological environment within the conduit on a molecular level, with the result that many new materials are being added as substrates within the conduit.”

— Wilson et al.

Integra is investing in the development of a next generation collagen nerve conduit filled with a matrix of collagen and chondroitin-6-sulfate.

Results of a study, conducted in a rat model of peripheral nerve repair, showed that the collagen conduit filled with a matrix of collagen and chondroitin-6-sulfate (c6s) was more effective in achieving functional motor recovery than a hollow conduit. Axon counts in the collagen/c6s matrix filled conduit were comparable with those in a reversed autograft at 12 weeks after repair.29

Development of Integra’s next generation collagen nerve conduit includes the collection of clinical evidence to demonstrate the device’s safety and efficacy. Thus, an Integra-sponsored pilot study of the collagen and chondroitin-6-sulfate filled conduit is currently ongoing.

References: