Corporate Report

a report by
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Traditional nerve repair techniques of suturing severed nerve ends together to repair small deficits (4mm or less), or harvesting nerve grafts to bridge larger deficits (5mm or greater), are fraught with difficulty. Important tenants such as trimming back damaged nerve tissue, avoiding tension at the repair site and the careful symmetric placement of suture must be observed for a successful repair. Still, scar formation often results in traditional repairs blocking regenerating axons, and poor alignment of nerve ends misdirects axons. In addition, a nerve graft must be utilised for deficits greater than 5mm, requiring additional time to harvest the nerve tissue and place it properly. Grafting causes morbidity of donor site, loss of sensation, painful neuroma formation and scarring. Even with technical advances over the years with operating microscopes, microsurgical instruments and improved surgical technique, physical limitations prevent the satisfactory repair of individual nerve fibres.

The traditional nerve repair technique relates to research carried out in the 1940s, in which the mistaken conclusion was made that nerve fibres regenerate only in the direction in which they are physically aligned.[1] However, prior work in the 1920s theorised that some factor directs the growth of regenerating axons,[2] and much effort was conducted in the 1980s to identify a mechanism of nerve regeneration and isolate those growth factors.[3] Mechanical alignment, contact recognition, neurotropism and neurotrophism were all postulated as possible mechanisms. Numerous researchers starting in the 1980s used conduits of different materials to identify the physiologic processes occurring within a chamber across a gap and to improve regeneration.[4] The chamber research identified growth factors, i.e. neurotropic factors, that guided the sprouting axon towards nerve tissue, and even allowed for the preferential reinervation of motor fibres over sensory fibres when the gap between nerve ends was at least 5mm.[5] Further theorised were neurotrophic factors that support nerve fibre growth when fibres regenerate into the correct microtubule. It is clear that multiple factors influence the regeneration of nerve fibres and that a gap between nerve ends allows growth factors to be expressed, lending biological control to the regeneration process.

Research work with the Neurotube®, a bioabsorbable, flexible, corrugated woven tube made of polyglycolic acid, began in primate animal models in the late 1980s. Nerve regeneration in a rodent is limited to about 1cm, so Mackinnon and Dellon examined regeneration in primates with bioabsorbable conduits of varying materials and lengths. They were the first to identify that nerve regeneration could occur in conduits and up to a limit of 3cm in primates.[6] A further study compared regeneration across a 3cm deficit between polyglycolic acid (PGA) nerve conduits and ulnar nerve graphs, examining electrophysiologic and histologic parameters. There was no significant difference between the conduit and graft groups. This study demonstrated that regeneration across a 3cm distance was equal in quality to the traditional nerve graft technique.[7]

1. *P Weiss and A C Taylor, "Further experimental evidence against "neurotropism" in nerve regeneration",* J. Exp. Zool., *95 (1944), pp. 289–300.*
2. *R S Cajal (1928),* Degeneration and regeneration of the nervous system, *Vo. 1. London: Oxford University Press.*
3. *G Lundborg, "A 25-year perspective of peripheral nerve surgery: Evolving neuroscientific concepts and clinical significance",* J. Hand. Surg., *25A (2000), pp. 391–414.*
4. *V Doolabh, M C Hertl and S E Mackinnon, "The role of conduits in nerve repair: a review",* Rev. Neurosci., *7 (1996), pp. 47–84.*
5. *T M Brushart and W A Seiler, "Selective reinervation of distal motor stumps by peripheral motor axons",* Exp. Neurol., *97 (1987), pp. 289–300.*
6. *S E Mackinnon and A L Dellon, "A study of nerve regeneration across synthetic (Maxon) and biologic (collagen) nerve conduits for nerve gaps up to 5 cm in the primate",* J. Reconstr. Microsurg., *6 (1990), pp. 117–121.*
7. *A L Dellon and S E Mackinnon, "An alternative to the classical nerve graft for the management of the short nerve gap",* Plast. Reconstr. Surg., *82(5) (1988), pp. 849–856.*

The Neurotube® was used to form a conduit to secondarily reconstruct median and digital nerve in a small pilot study carried out in human patients in Canada.[8] All were secondary reconstructions with gaps up to 3cm. Over 50% of these nerve reconstructions had excellent functional sensation results, comparing favourably to the classic nerve graft technique, while avoiding the need for a nerve graft and avoiding donor site morbidity. Subsequently, the successful clinical reconstruction of the inferior alveolar nerve with a PGA absorbable conduit was reported.[9]

The strong evidence that an absorbable conduit (Neurotube®) could be used instead of the traditional nerve graft techniques to reconstruct lacerated nerves led to US Food and Drug Administration (FDA) approval of an Investigational Device Exemption clinical trial for Neuroregen, LLC in the US, starting in 1994. Five clinical trial sites enrolled patients over a four-year period in Texas, Mississippi, Kentucky and Illinois. Five principal investigators enrolled a total of 98 patients with 136 nerve reconstructions. This was a randomised, prospective, multicentre study comparing the use of an absorbable conduit to the traditional nerve repair techniques. A subject with a complete laceration to the common or proper digital nerves in the hand was enrolled into the study, and the nerve was randomly assigned a standard repair or experimental repair group. An injured nerve in the standard repair group was repaired end to end if the gap between the nerve ends was 4mm or less, or repaired with a nerve graft if the gap was 5mm or greater. Both standard and experimental repair groups were limited to a maximum deficit of 30mm. In the experimental repair group, the Neurotube® was placed between the transacted ends with a minimum gap of 5mm in the conduit. Patients were followed for one year, with sensory measurements of moving and static two-point discrimination made every three months. These measurements were grouped as excellent, good and poor results following the British standard grading system.

For the Neurotube to be cleared for clinical use, the trial must demonstrate that the device is safe when implanted and that the function outcomes with its use are at least comparable with the standard repair technique. PGA is the same formulation as vicryl suture and was easily demonstrated to be safe when implanted. When comparing the Neurotube® with the standard end-to-end repair when the gap was 4mm or less, the standard technique resulted in a 49% excellent sensory functional result, while the Neurotube had 91% excellent measurements – a significant difference. Comparing the Neurotube to the nerve graft technique for gaps greater than 8mm, there were no excellent results reported with the grafts, in sharp contrast to 42% excellent results using the Neurotube – also a significantly better difference. The data from the study was published in the October 1990 issue of PRS.[10] The authors, clinical trial investigators, concluded that repairing a transacted nerve with the Neurotube® offers the possibility of improved sensation compared with the standard end-to-end technique. It was also concluded that the Neurotube® is superior to nerve grafting for reconstruction of digital nerve deficits of less than 3cm, since it clearly offered better sensory function with no donor site morbidity, thus avoiding the need to harvest a graft from some other site with the associated loss of function, scarring and other possible complications. The Neurotube® was cleared for use in the US by the FDA in March 1999. The CE Mark for the Neurotube® was obtained for use in Europe in April 1998.

The opportunity to perform a secondary reconstruction will likely present from a failed primary repair or some trauma, resulting in a painful neuroma in continuity. The Neurotube® can be used to reconstruct peripheral nerves throughout the body, allowing the complete resection of damaged nerve tissue and deficits of less than 3cm to be repaired without a nerve graft. Not only digital nerves in the hands and feet, but also any appropriately sized nerve such as radial sensory, calcaneal, deep or superficial peroneal or inferior alveolar nerves can be reconstructed readily. Larger-diameter nerves in which groups of fascicles can be identified, such as the median or ulnar nerve, can be reconstructed with multiple Neurotubes instead of using cable nerve grafts. Brachial plexus lesions have been repaired as well. Nerves in the lower extremity, which traditionally tend to be left unrepaired because of their size and the contraindicated need to sacrifice some other nerve as a graft, can also be repaired with the Neurotube®. A recent case report addressed the resection of a painful post-trauma neuroma of the medial plantar nerve and reconstruction with the Neurotube®. The benefits of this approach include

8. *S E Mackinnon and A L Dellon, "Clinical nerve reconstruction with a bioabsorbable polyglycolic acid tube",* Plast. Reconstr. Surg.*, 85(3) (1990), pp. 419–424.*
9. *W A Crawley and A L Dellon, "Inferior alveolar nerve reconstruction with a polyglycolic acid bioabsorbable nerve conduit",* Plast. Reconstr. Surg.*, 90(2) (1992), pp. 300–302.*
10. *R A Weber, W C Breidenbach, R E Brown, M E Jabaley and D P Mass, "A randomized prospective study of polyglycolic acid conduits for nerve reconstruction in humans",* Plast. Reconstr. Surg.*, 106(5) (2000), pp. 1,036–1,045.*

allowing nerve regeneration across the 2cm gap without a graft, the prevention of the reformation of another neuroma and restoration of sensory function to the patient's toe.[11]

There are numerous advantages to using the Neurotube® to repair damaged nerves in contrast to the traditional techniques. An improved functional result is obtained by using a chamber that allows a gap to be situated intentionally between nerve ends, allowing the intrinsic nerve growth factors to exert their influence on the regenerating axons as they sprout in that confined chamber. Use of the Neurotube® allows for a tension-free repair site, which encourages the complete resection of damaged nerve tissue, also adding to the improved functional outcome. With a large deficit up to 3cm, reconstruction is accomplished without the need to harvest a nerve graft, eliminating donor site morbidity (loss of sensation, potential for neuroma formation, scar at incision site) and added operating room anaesthesia time to harvest a graft. The Neurotube® is absorbable and, like Vicryl, has minimal inflammatory response and is totally absorbed in the body by hydrolysis. In contrast, non-absorbable materials cause an inflammatory response, scar formation around the material and other tissue reaction, much like a silicon implant, and can compress the nerve, much like a nerve entrapment syndrome. The PGA material is a porous mesh, which allows the infiltration of oxygen to support the regeneration process. The Neurotube® is flexible and corrugated, which allows the device to bend if placed over joints and prevents occlusion of the device from the pressure of surrounding muscle or soft tissue.

The surgical technique required to reconstruct a damaged nerve with the Neurotube is straightforward and does not require the use of a microscope. The nerve is exposed under tourniquet, the nerve ends resected to remove all damage, the tourniquet released and haemostasis obtained, and the gap between the nerve ends measured carefully. The Neurotube is trimmed with scissors to the length of the gap plus 1cm, which allows the nerve ends to be inserted 5mm into each end of the tube. With loupes and micro instruments, a horizontal mattress stitch is placed with 8-0 nylon to draw the nerve end into the lumen of the Neurotube. The device is irrigated with heparinised saline before the second nerve end is placed into the Neurotube. With a shelf life of three years, the Neurotube can be stored in the OR, ER or clinic for convenient use as the need arises. Available for the past five years with a 2.2mm diameter width, the Neurotube will soon also have sizes of 4mm and 8mm diameters. ■

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11. *J Kim and A L Dellon, "Reconstruction of a painful post-traumatic medial plantar neuroma with a bioabsorbable nerve conduit: a case report",* J. Foot Ankle Surg.*, 40(5) (2001), pp. 318–323.*