Nerve Conduits

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ABSTRACT: The evolution of peripheral nerve repair is reviewed with respect to the development of the nerve conduit. The rationale and available scientific evidence to support the use of nerve conduits is presented. Therapy evaluation and treatment protocols for patients with peripheral nerve repairs with nerve conduits are detailed. The authors present clinical experience to date with 73 cases of peripheral nerves repaired with the NeuraGen® collagen nerve conduit.

J HAND THER. 2005;18:191–197.

PART 1: SURGERY AND RATIONALE

Introduction

Transected peripheral nerves are injuries commonly faced by the surgeon managing hand injuries. These lesions are often responsible for longstanding and severe impairment of hand function. After complete axonal transection, the neuron undergoes various degenerative processes, followed by an attempt at regeneration. The regenerating proximal growth cone searches for connections with the degenerating distal fibers. All of this occurs within a posttraumatic milieu of inflammation and altered anatomy.

Primary tensionless repair has been the standard of care treatment for transected peripheral nerves. Advancements in microsurgical tools and techniques have provided the surgeon with the technical skills to repair these peripheral nerve injuries in the early post injury period.

Numerous factors, including loss of nerve substance, delay in operative repair, and severe concomitant injuries, may preclude early primary repair. In these instances, autogenous nerve grafting has been an effective means of repair and reconstruction in overcoming the neural gap.[1–3] Harvesting a donor nerve graft, however, can have significant morbidity and consequence.[4–6] There can often be associated scarring at the donor site, neuroma formation, and loss of donor site function. As such, there remains an impetus to develop an alternative method towards managing peripheral nerve injuries which are not amenable to the ''gold standard'' primary tensionless epineural repair.

The purpose of this article is to review the development and clinical results in the use of nerve conduits for bridging gaps in lacerated peripheral nerves, to present our clinical experience, and to discuss postoperative therapy considerations.

History and Rationale

As early as 1880, Gluck[7] attempted to bridge nerve gaps with decalcified bone. Nearly one decade later, Buenger[8] reported on the use of cadaveric brachial artery to repair canine sciatic nerves. In the early 1900s, Formatti and Nageotte used vein as bridge graft material in rodents.[9,10] In the 1920s, Platt[11] performed early work with fascial and vein grafts in humans. Nerve conduits composed of nonbiologic materials including gelatin, agar, bone, metal, and rubber were also explored, albeit with no recognizable clinical success.[12] Not until the post–World War II era was there a renewed interest and resurgence in

NeuraGen is a registered trademark of Integra Neuro Sciences (Plainsboro, NJ). Dr. Taras has received research funding and honorarium from Integra Neuro Sciences.

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doi:10.1197/j.jht.2005.02.012

the search for and use of vessels and synthetic materials as nerve guide channels.

Nerve guide channels are either natural or synthetic tubular conduits that enable the bridging of a nerve gap between injured nerve stumps. They direct axonal sprouting from the regenerating proximal cone, retard infiltration of fibrous tissue, and provide a conduit for diffusion of neurotropic and neurotrophic factors that are secreted by the damaged nerve endings. Added benefits include decreased suture line tension and increased concentration of endogenous proteins. Conduits can also selectively inhibit or permit the diffusion of macromolecules between the lumen of the channel and the surrounding tissues.[13]

Nerve conduits should possess several key properties. They must be readily formed into a conduit having a desired diameter. They should require minimal effort to implant. They must be able to be sterilized. An ideal nerve conduit should be pliable, maintain its shape during regeneration, and it must resist collapse during implantation and manual activity.[12]

The basic features of nerve regeneration to bridge a 10-mm gap in rat, in a general inert synthetic conduit such as silicone, have been demonstrated by Williams and associates.[14] Within hours of implantation, the conduit fills with a clear fluid secreted by the blood vessels in the severed nerve cable. This fluid is rich in proteins, clotting factors, and soluble factors that enhance regeneration. Within one week's time, the nerve gap is bridged by a longitudinally oriented matrix of fibrin. In the second week, fibroblasts, Schwann cells, macrophages, and endothelial cells enter the fibrin matrix. Axons from the proximal nerve cone sprout to elongate along the matrix. After some four weeks, axons reach the distal nerve stump and become myelinated. Once the gap is bridged, the axons elongate down the preserved endoneurial tubes of the distal nerve segment towards their final target destination.

In 1982, Chiu et al.[15–17] presented the first in a series of reports that demonstrated the success of venous nerve conduits for short nerve gaps. In 1990, Chiu and Strauch[18] showed that nerve gaps of 3 cm or less, in "nonessential cutaneous nerves," provided return of good sensibility as measured by two-point discrimination (2pd) and the Ten Test, an analogue scale for sensibility. Their study found that direct nerve repair was superior to the autogenous venous nerve conduits. They could not, however, make valid the same assumption with regards to autogenous nerve grafts.[15] Tang and associates[19] further reaffirmed the efficacy of autogenous venous conduits in digital nerve reconstruction. Eighteen digital nerve gaps, ranging from 0.5 to 5.8 cm, were bridged with venous nerve conduits during tendon surgery in zone II. A technique of using normal nerve slices for defects greater than 2 cm was used in an attempt to potentiate the autogenous vein nerve conduit. In another study conducted two years later, Tang et al.[20] presented a series of 16 peripheral nerve reconstructions with nerve gaps measuring up to 5.8 cm. A single vein graft was used in median nerves and one radial nerve and one sensory radial nerve. The results suggested that vein nerve conduits with interposition of nerve tissue could be a practical and reliable procedure for deficits up to 4.5 cm. Under similar guises, Brunelli and associates[21] studied vein conduits filled with muscle, a means to prevent the collapse of the conduit lumen. Their findings suggested that veins with muscle interposition were superior to vein and fresh muscle conduits alone both functionally and histologically. These studies suggest that for nerve gaps greater than 3 cm, application of vein conduits should be considered if the vein conduit is potentiated to promote axonal growth. A potential drawback of vein grafts with interposition tissue was demonstrated by Khouri and associates.[22] Their findings suggested that although the additional collagen and laminin of the adventitial layers of the conduit and interposition material may be beneficial, the inherent presence of fibroblasts may lead to delayed intraluminal fibrovascular proliferation or fibrosis. As a result of this inflammatory fibrosis, short term gains may be lost over time.

At the turn of the 19th century, the Spanish biologist Ramón y Cajal[23] postulated the concept of neurotropism: the idea that chemical agents from the distal nerve stump could attract the regenerating proximal axons. Years later, the concept of neurotropism was disputed by Weiss and colleagues[24] in a series of experiments using Y-shaped arterial conduits for nerve regeneration. Weiss et al. postulated that contact guidance was more important than neurotropism as a factor in nerve regeneration. It was not until the 1980s that more sophisticated experiments demonstrated that both neurotropism and contact guidance are important in the regenerating nerve.[25–28] With these fundamental principles in mind, Lundborg and Dahlin,[29] in the early 1990s, presented their results of a study comparing conventional microsurgical technique to the use of silicone tubes in the repair of median and ulnar nerve transections in the human forearm. In 18 cases with gaps measuring 3–4 mm, 11 undergoing silicone tubulization and seven undergoing primary repair, early results demonstrated no difference between either techniques with regards to sensory or motor functioning of the hand for intervals up to one year after repair. These techniques, however, have not proven useful for bridging extensive gaps as demonstrated in several experimental studies.[30] In addition, complications associated with the clinical use of silicone chambers have been chronic nerve compression, irritation at the chamber site necessitating removal, and inflammatory or fibrotic reaction that compromised nerve regeneration and function.[31,32]

Considerable research has been focused on developing conduits that stimulate improved regeneration over longer, more clinically relevant nerve gap lengths. An ongoing search continues to find synthetic materials that can optimize the regenerative process. Several biodegradable materials have demonstrated abilities to support nerve regeneration. Polyesters such as polylactic acid, polyglycolic acid were early choices for investigation. Mackinnon and Dellon,[33] using a bioabsorbable polyglycolic tube to bridge nerve gaps of 3 cm or less, reported good to excellent functional sensory recovery. Weber and colleagues[34] reported on 136 digital nerve reconstructions comparing polyglycolic acid conduits to primary repair with either an end-to-end or nerve graft technique. Their results indicated an improved outcome in sensory recovery for the conduit treated group with nerve gaps of 4 mm or less when compared with the primary epineural repair group. In those gaps greater than 8 mm, treatment consisted of either polyglycolic conduit or autogenous nerve grafting. Comparative results of these two groups also demonstrated improved 2pd for the conduit group. In both studies, however, gaps were once again limited to 3 cm.

Alternative interest has been focused on devising nerve conduits from more natural and biologic materials so as to improve biocompatibility, decrease possible toxic effects, and actively enhance the migration of Schwann cells and axons during regeneration. Conduits derived from biologic molecules such as laminin, fibronectin, and collagen have all demonstrated improved regeneration. Archibald and associates[35,36] have demonstrated the effectiveness of nerve guides constructed from purified type I bovine collagen in the regeneration of a 5 mm nerve gap in the nonhuman primate. Despite its reported success in primate trials, no human clinical trials have been reported in the literature to date. This product has become commercially available marketed under the name NeuroGen®. These conduits are available in diameters of 2, 3, 4, 5, and 6 mm and are 2.2 cm in length.

Conclusion

The standard treatment for fresh peripheral nerve transactions remains the primary tensionless repair. Unfortunately, numerous factors prevent such a repair from being possible. These conditions include loss of nerve substance, delay in repair, and severe concomitant injury. Autogenous nerve grafting has been and remains an effective technique for the reconstruction and repair of the neural gap. Overall, primary end-to-end and nerve grafting in adults have resulted in a broad range of excellent results reported from 0% to 67% of the patients reconstructed.[37,38] In addition, the associated donor site deficits associated with nerve grafting have stimulated interests in alternative means of bridging the nerve gap during repair and reconstruction in the hopes of improving overall results and decreasing associated morbidities. One of these potential methods has been through the use of nerve conduits. Nerve guide repair offers several potential advantages as compared to nerve graft repair. Nerve conduits offer the ability to have readily available prostheses that can be size-matched to fit at the nerve repair site. As mentioned previously, a second surgical procedure to harvest the donor nerve is avoided along with the associated risks. Nerve conduits also provide for the ability to prevent axonal escape at the suture sites. In addition, as numerous studies have suggested, the regenerating axons are able to align themselves as a result of various neurotropic and neurotrophic factors.[25,26,39–41] In theory, allowing a severed nerve ending to grow across a confined gap enables growth factors to influence the proximal growth cone. This would result in a more accurate alignment of nerve endings.[42]

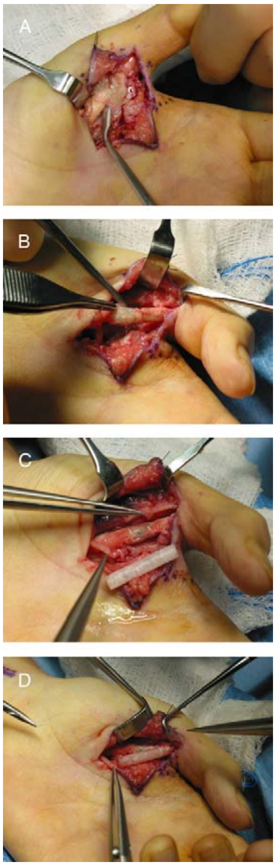

FIGURE 1. Along with a tenolysis of the flexor pollicis longus, a failed primary nerve repair is treated by resection of the neuroma and reconstruction of the 2-cm defect with a NeuroGen® collagen nerve conduit, resulting in restoration of sensation and 6-mm two-point discrimination.

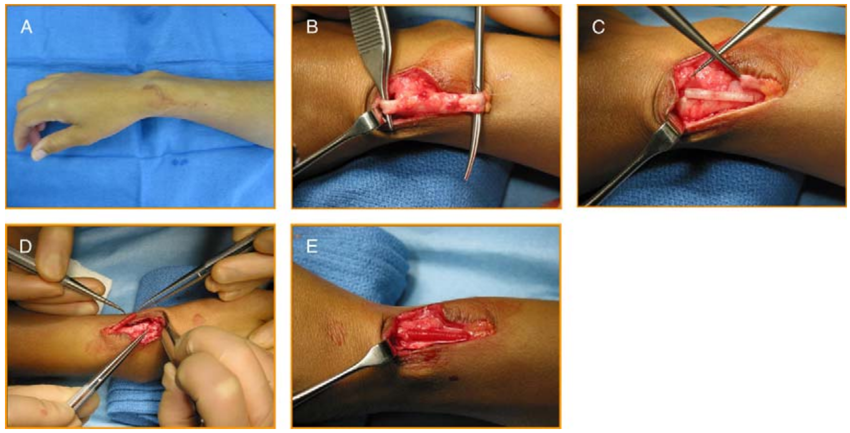

FIGURE 2. Neglected superficial radial nerve laceration resulting in very painful neuroma managed by resection of intervening scar tissue and reconstruction with NeuroGen® collagen nerve conduit. This effectively eliminated the pain and restored sensation in nerve territory.

Despite these advantages, an important obstacle that still persists is overriding the size of the maximal neural gap that can be successfully bridged while maintaining acceptable functional sensory and motor recovery. Considerable research is being currently devoted to the creation of optimal nerve guidance channels that will promote nerve regeneration over larger deficits. Advances in areas of biomaterials and biotechnology, as well as an increasing understanding of the molecular biology about the nerve growth phenomenon, will undoubtedly enhance the success of nerve regeneration and repair.

Clinical Experience

Figures 1–3 illustrate cases which reflect the senior author's experience with the repair of 73 peripheral nerves utilizing the NeuroGen® collagen nerve conduit. Repaired nerves include median, ulnar, radial, posterior interosseous, common digital, proper digital, and the superficial radial sensory nerve. His clinical impression has been very positive with results appearing more favorable to those of direct repair or nerve grafting. Currently, we are conducting a clinical study documenting the outcomes of the use of collagen nerve conduits in nerve repair and reconstruction.

PART 2: POSTOPERATIVE MANAGEMENT: THERAPY CONSIDERATIONS FOLLOWING PERIPHERAL NERVE REPAIR WITH NERVE CONDUITS

Introduction

A formal review of current literature reveals that to date there has been no formal scientific investigation of the effects of traditional hand therapy on the outcomes of peripheral nerve repair with nerve conduits. Based on their early and frequent clinical encounters with this patient population, hand therapists are situated optimally within the health care continuum to evaluate the effects of therapeutic techniques and modalities and the recovery of sensibility and function in this group of patients. The purpose of the following discussion is to provide guidelines for the postoperative therapy program of patients following nerve repair with nerve conduits and to encourage hand therapists to formally investigate this patient population.

Evaluation

An accurate history is essential to evaluation and treatment of the nerve-injured patient. Patient demographics including age, occupation and avocations, date of injury or onset of condition, and date of surgery should be documented to ensure that clinical data can be accurately interpreted and analyzed. The mechanism of injury and history of concomitant injury should be documented to aide in determining expected rate and extent of recovery. Concomitant medical conditions should be recorded with special consideration to those effecting the immune system and tissue healing. Medications should also be noted for the physiologic effect if any on nerve recovery. Patients should be questioned regarding their present symptoms and how they compare with the preoperative period. Valid, reliable pain and function scales are recommended as an objective method for recording subjective patient information that bears great significance in evaluating patient outcomes. An accurate history guides the clinician in choosing the appropriate physical evaluation parameters to perform. Data gathered during the clinical evaluation are used to develop an effective treatment plan. In general, patients who have had peripheral nerve

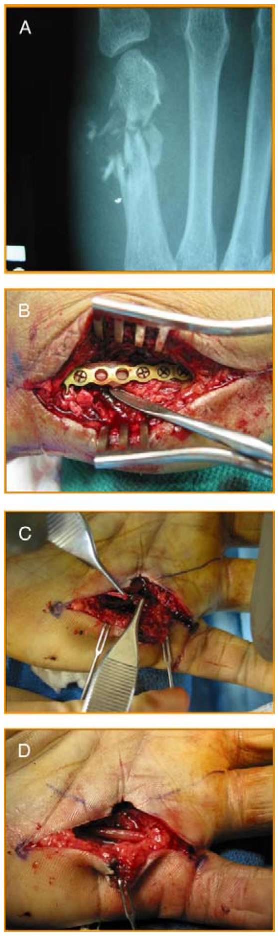

FIGURE 3. This police officer had a gunshot wound resulting in a segmental defect of the fifth metacarpal and radial digital nerve. Reconstruction of the nerve defect utilized a collagen nerve conduit to bridge the gap.

repairs with nerve conduits are evaluated and treated following protocols for tensionless peripheral nerve repair.

To begin the physical examination, the patient's upper extremity is placed in a safe and comfortable position. In general, when the nerve repair is volar, a position of protected flexion should be assumed, and when the nerve repair is dorsal the upper extremity should be placed in relative extension. Visual inspection is the initial physical assessment as it can be accomplished without physical contact with or discomfort to the patient. Visual inspection should include measurement and description of wounds, skin integrity, color, and description of any visible edema and muscle atrophy. If significant edema is appreciated visually, an objective measurement should be taken and documented in the patient record. Next, palpation should include evaluation of skin temperature with subjective comparison to the contralateral limb. After peripheral nerve repair with a nerve conduit, a firm mass can be appreciated with palpation of the surgical site for up to one year. In more superficial areas, and in thin individuals, this mass can be appreciated on visual inspection.

Objective range of motion (ROM) testing of individual joint motion and composite joint motions (concomitant range of motion of metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints) can be tested in the early postoperative period (initial four weeks) as patients with nerve repair with nerve conduits can be considered to have a tensionless repair. Evaluation of motor function is generally deferred in the initial postoperative period due to the possibility of disruption of the operative site. At four weeks after surgery, manual muscle testing can be performed. Manometer testing such as grip and pinch dynamometer testing is not recommended to begin until six weeks after surgery.

Sensory evaluation can safely be performed at any point in the postoperative period. This testing can begin on the immediate postoperative visit to establish baseline values. Tools specific to the modality being evaluated should be used in sensory evaluation to assure accuracy of testing. Evaluation should include slowly adapting skin receptors (Merkel cell neurite complex and Ruffini end organ) that respond to static touch, and quickly adapting receptors (Meissner and Pacinian corpuscles) that respond to moving touch and discharge impulses according to the stimulus frequency. Meissner corpuscles respond to frequencies up to 30 Hz; Pacinian corpuscles respond to higher frequencies.[43]

Quickly adapting receptor threshold is assessed through the use of tests of vibration. Vibration is tested at the digit pulp. With vision occluded, the patient should be asked to identify when and where vibration is felt. The vibration should then be stopped by the therapist placing pressure over the vibrating surface of the tuning fork and the patient is instructed to indicate when they feel the vibration cease. This process is repeated for all digit tips and is compared bilaterally. Two tuning forks are necessary to fully assess vibratory sensation; 30 cps is used to test the Meissner corpuscles and 256 cps is used for Pacinian corpuscles.[44]

Slowly adapting receptor (Merkel cell neurite complex and Ruffini end organ) threshold is assessed through cutaneous touch-pressure tests such as the Semmes-Weinstein monofilaments. Testing should include a bilateral comparison.[44]

Innervation density and tactile discrimination is measured by 2pd.[44] It is thought that this test more accurately reflects the number of innervated sensory receptors.[45] Static 2pd is performed at each finger pulp. The patient's vision is occluded, and with just enough pressure to deform the patient's skin pressure is applied with one or two points to the fingertip with the points placed perpendicular to the digit for 5 seconds. The patient is asked to identify one or two points. The smallest distance that the patient can correctly identify as two points is considered the static 2pd value. Moving 2pd is evaluated by placing the points perpendicular to the digit and moving them longitudinally along the digit pulp from proximal to distal.

A strong correlation has been reported between object identification and static and moving 2pd.[45–47] Object identification is a function of hand sensibility and has been used as a functional outcome to evaluate patient recovery after nerve reconstruction. Because return to function is the ultimate goal following nerve reconstruction, object identification and 2pd may be the sensory tests of choice for this patient population. It is recommended that patients be reevaluated every four to eight weeks after nerve conduit surgery for one year after surgery.

Treatment

Patients are seen for the first postoperative visit two to three days after nerve conduit placement at which time the surgical dressing is removed and the wound is inspected. Referral to therapy is made at this time for preliminary exercises and splinting if indicated. In the case of digital nerves with a tensionless conduit repair, no splint is required, instead a light gauze or stockinette dressing is applied. If the therapy referral lacks complete information regarding the surgical repair or when splinting is specifically requested, the blocking splint described below for repairs with tension should be applied. This splint may also be indicated in the case of the unreliable patient or with an individual who is likely to overuse the operated hand.

At this first session with the therapist, the patient is instructed in a home exercise program consisting of short arc ROM exercises and gentle composite fisting. Short arc ROM can be accomplished by instructing the patient to assume a neutral wrist, then actively flex the fingertips to the tip of the abducted thumb, then back to full extension. Patients are typically instructed to perform 15 repetitions five times per day. Patients are advised to avoid functional hand activities until four postoperative weeks. Patients should be instructed to observe for edema and to monitor for other signs of inflammation which would require modification of the exercise program. At two postoperative weeks, sutures are removed and formal therapy is instituted if ROM deficits are apparent. Passive ROM can safely be performed to alleviate any joint or scar contracture. Dynamic splinting is not recommended as the forces created may have the potential to deform or displace the nerve conduit. At four weeks post operative, the patient may ease back into normal functional activities of the hand.

Though the guidelines for conduit placement recommend tensionless repair, it should be recognized that the limits for gap length may be exceeded by some surgeons creating tension at the repair site. For digital nerve repairs with some degree of tension as well as for median or ulnar nerve repairs with a nerve conduit, a standard, forearm based dorsal blocking splint is fabricated with the wrist in neutral to 30 degrees of flexion, MP joints in 45 degrees of flexion and IP joints in neutral. This splint is fabricated on the first post operative visit and altered to accommodate any concomitant injury requiring alternate positioning. This splint is worn continuously except for hygiene and exercise sessions for four weeks. Patients are instructed during the first post operative visit in active ROM exercise within the limits of the post operative splint. At 2 weeks, formal therapy is instituted for edema control, wound and scar care, and protected passive ROM exercise consisting of isolated and composite digital range of motion with the wrist held passively in 30–40 degrees of flexion, and isolated wrist range of motion with the digits relaxed. At four postoperative weeks, the splint may be discontinued or replaced with an appropriate supportive or functional splint to accommodate the specific nerve deficit.

Scar massage should be avoided for six to eight weeks after surgery to prevent external stress that may disrupt the conduit placement. Topical scar applications such as silicone and gel pads may be safely used over nerve conduits which are semi-rigid and do not deform easily when light external pressure is applied. Ultrasound is not recommended for use over the conduit site, because the effect of sound energy and deep heat on conduit degradation is not known.

At six postoperative weeks, composite digital and wrist range of motion and resistance are introduced into the therapy program. Current investigations suggest that early introduction of sensory reeducation prior to reinnervation may aide in modulating the changed sensory code from the hand to the brain after injury and in doing so may enhance the ultimate recovery post nerve repair.[48] This work is worthy of review and may lead to improved functional outcomes following nerve injury and repair.

Clinical Experience

Therapeutic observations of the aforementioned 73 peripheral nerve repairs utilizing the NeuraGen® collagen nerve conduit have yielded no conduit rejection and only two cases of scar sensitivity. Patients tolerate splinting and ROM exercise, and resisted exercise on the timelines described here without negative clinical consequences. All patients demonstrate a palpable mass in the area of conduit placement for up to six months after surgery. Our current clinical study is focused on evaluation of rate of return of 2pd, object and texture identification, and return to work/function.

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