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Clinical outcomes for Conduits and Scaffolds in peripheral nerve repair

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Abstract

The gold standard of peripheral nerve repair is nerve autograft when tensionless repair is not possible. Use of nerve autograft has several shortcomings, however. These include limited availability of donor tissue, sacrifice of a functional nerve, and possible neuroma formation. In order to address these deficiencies, researchers have developed a variety of biomaterials available for repair of peripheral nerve gaps. We review the clinical studies published in the English literature detailing outcomes and reconstructive options. Regardless of the material used or the type of nerve repaired, outcomes are generally similar to nerve autograft in gaps less than 3 cm. New biomaterials currently under preclinical evaluation may provide improvements in outcomes.

Key words: Plastic surgery; Reconstructive surgical procedures; Nerve tissue; Conduit; Scaffold

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Core tip: Nerve autograft is the gold standard for peripheral nerve reconstruction with gap. However, shortcomings of autograft have led researchers to investigate various biomaterials to improve outcomes. Clinical studies of peripheral nerve reconstruction with conduit other than autograft show similar outcomes in gaps less than 3 cm.

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INTRODUCTION

The gold standard of peripheral nerve repair is primary end-to-end coaptation of nerves. Unfortunately, this treatment is not always feasible in clinical situations. Avoidance of tension during repair is the ultimate goal to enhance potential nerve regeneration[1,2]. Prior studies have shown that injury tends to occur when nerves are stretched to greater than 10% of their original length. It may even initiate the process with stretching as little as 4%-6%[3,4]. Negative outcomes have been reported with tension greater than 25 g[5].

Most surgeons do not attempt primary closure when encountering gaps greater than 4 mm[6]. Tensionless closure is paramount to satisfactory clinical outcomes in nerve repair.

Primary treatment for repair of a nerve gap is autologous nerve grafting[7,8]. However, limited availability of donor tissue, sacrifice of a functional nerve, and possible neuroma formation make this option less than ideal[9-11]. Gluck[12] first reported use of a nerve guide in 1880, bridging with a segment of decalcified bone. Other early attempts were equally unsuccessful. In order to overcome these shortcomings, researchers and surgeons continued to improve nerve repair methods. The ideal conduit must be readily available, biocompatible, size matched to the nerve stumps, prevent axonal escape, and prevents ingress of fibroblasts and inflammatory cells. Simultaneously it should allow growth and chemotactic factors to positively influence axonal growth. Also it should prevent compression and injury to the nerve once healed. The conduit should be flexible, yet resilient enough to resist collapse[13]. Currently, such a conduit remains unavailable. Ongoing studies continue to improve the qualities of available biomaterials. Our goal is to present a survey of clinical studies published in the English literature detailing outcomes and reconstructive options.

REGENERATION BY CONDUIT

Williams *et al*[14] demonstrated the basic steps of nerve regeneration with an inert silicone conduit. In the immediate postoperative period, a fluid containing proteins, clotting factors and growth factors fills within the conduit. By 1 wk, a longitudinally oriented fibrin matrix develops. In the second week, fibroblasts, Schwann cells, macrophages, and endothelial cells enter the matrix. At the same time, axons from the proximal nerve cone extend forward. By four weeks the nerve cone has extended about 10 mm.

RESEARCH

Silicone

Silicone is a non-resorbable, nonporous, biologically inert material. Silicone in medical devices and implants are clinically ubiquitous. Since silicone is non-resorbable, presence of conduit material can lead to compression and decreased axonal conduction[15-17]. For this reason, the tubing is frequently removed[18]. With the advent of resorbable synthetic grafts and processed allografts, clinical utilization of silicone conduits have declined.

Lundborg *et al*[19] first reported in a prospective randomized study the clinical use of silicone tubes in peripheral nerve reconstruction. He reconstructed median nerve gaps of 3 to 5 mm. He then compared silicone conduit to standard repair. He found no differences in motor function. Patients experienced improved sensory recovery within the silicone group. Braga-Silva[20] reported a case series of 26 patients with median, ulnar, or median and ulnar nerve injury. Patients presented with a nerve gap ranging from 2.5 to 5.5 cm. While motor scores for each patient were not published, size of the nerve gap negatively correlated with motor function outcomes.

Expanded polytetrafluoroethylene

Expanded polytetrafluoroethylene (ePTFE) is another nonresorbable, biologically inert material. It is commercially available as Gore-Tex (W.L. Gore and Assoc., Flagstaff, AZ). Like silicone, reports of ePTFE have declined over the years.

Stanec *et al*[21] first reported clinical use of ePTFE in 43 patients exhibiting median and ulnar nerve gaps ranging from 1.5 to 6 cm. Patients with smaller gaps (up to 4 cm) had significantly improved outcomes *vs* larger gaps (78.6% *vs* 13.3% functional recovery).

Pogrel *et al*[22] utilized ePTFE conduits for reconstruction of lingual and inferior alveolar nerve (IAN) injuries in 5 patients. Patients with negative outcomes had nerve gaps greater than 1.0 cm. Pogrel *et al*[22] reported their series of 6 patients with lingual or IAN continuity defects greater than 1 cm. Mixed results were reported.

VEIN

Vein grafts are among the first non-neural biological conduits used for peripheral nerve Usually they are harvested from the dorsum of the hand during digital, median, or ulnar nerve repair. During the regeneration period, they were found to be at risk for kinking or collapse[23-25].

Wrede[26] recorded the first successful use of a vein graft. He repaired a median nerve defect with a 45 mm graft. Platt[27] (1919) also described bridging nerve grafts with autogenous vein. It failed to produce functional return of the musculospiral nerve[27]. Gibb[28] reported a single case of functional restoration using a vein conduit to reconstruct a 1 cm facial nerve gap. It was not until several animal studies demonstrated efficacy that further clinical studies were explored[29,30]. Walton *et al*[25] reported return to normal two point discrimination (2PD; less than 4 mm) in 50% of patients undergoing repair of digital nerves. Nerve gaps ranged from 1 to 3 cm. Poor outcomes were associated with larger gaps. In 1990, Chiu *et al*[24] reported a series of 15 repairs on patients receiving vein grafts for "nonessential" peripheral nerve gaps up to 3 cm. After an average follow-up of 27 mo, the cohort receiving vein graft repair had similar outcomes to autologous nerve graft. However it was inferior to direct repair cohort. Tang *et al*[23] reported 61% good or excellent outcomes in 15 patients undergoing digital nerve repair, with

gaps ranging 0.5 to 5.8 cm[23]. Patients generally had favorable outcomes when gaps were less than 3 cm, thereby corroborating the results from Chiu *et al*[29]. Two years later, Tang published outcomes in median and radial nerve vein grafts. In this study, he inserted nerve fragments from the proximal nerve stump into the vein lumen. His data suggested positive outcomes could be achieved with this technique for gaps up to 4.5 cm[31].

Pogrel *et al*[32] reported a series of 16 patients treated for lingual or IAN nerve defects, ranging from 2 to 14 mm. Using saphenous vein or facial vein, he found that negative outcomes were associated with gaps greater than 5 mm. The author discussed that nerves of trigeminal origin have had poorer outcomes versus other peripheral nerves. It is likely the cause of difficulty in repair of such small gaps (see below).

COLLAGEN

Collagen is a naturally occurring, resorbable structural protein. Purified bovine collagen, the most common source for collagen conduits, has low immunogenicity. Resorption rate can be controlled by the degree of crosslinking induced during preparation. Depending on fabrication method, degradation occurs from 1 to 48 mo[33,34]. Furthermore, preclinical studies have demonstrated that collagen conduits enhance growth and differentiation of many cell types. It is flexible yet durable. This increases its facility as a conduit material[35]. Finally, its permeability allows for diffusion of chemotactic and neurotrophic agents in the extracellular fluid. This type of conduit is commercially available under the name NeuraGen® (Integra LifeSciences, Plainsboro, NJ). Conduit sizes range from 1.5 to 7 mm diameter and are 2 or 3 cm long. Neuromatrix® and Neuroflex® (Collagen Matrix, Inc) are also Type I collagen conduits. No published studies are currently available evaluating its clinical efficacy.

In 2005, Taras *et al*[36] reported the use of commercially available type I bovine collagen in the repair of a variety of peripheral nerves[36]. A prospective series of 22 digital nerve repairs using NuraGen® achieved excellent or good sensory outcomes in 15 of 22 digits. They excluded nerve gaps greater than 20 mm[37].

Ashley *et al*[38] reported treatment of brachial plexus birth injuries with nerve gaps less than 2 cm using collagen conduits. Four of the five patients had favorable outcomes at 2 years postoperative. Lohmeyer *et al*[39] reported a case series of 6 patients undergoing repair of nerve gaps in digital and palmar nerves up to 18 mm. Two-thirds of the patients had excellent 2PD at 12 mo postoperative. They extended follow-up with nine of twelve patients achieving excellent or good sensory scores at 12 mo follow up[40]. Bushnell *et al*[41] reported a series of 12 patients undergoing digital nerve repair for gaps ranging from 1 to 2 cm. Most (88%) had good or excellent 2PD after at least 1 year. In a larger study of 126 nerve injuries in 96 patients, Wangensteen *et al*[42] reported their experience using NeuraGen®. Mean nerve gap was 12.8 (range 2.5 to 20 mm). Overall, nerve function recovery was only 43%. A variety of nerves were repaired, and seven surgeons were involved in the study. Haug *et al*[43] added 45 digital nerve repairs with type Ⅰ collagen to the body of literature. Mean defect was 12 mm (range 5 to 26 mm). All sensory measures improved over 3-, 6-, and 12-mo follow-up interval.

Farole *et al*[44] reported their experience with the NeuraGen® conduit for challenging lingual and IAN repair. In their study, all patients underwent neurolysis with or without resection of neuroma (if present) and placement of the collagen conduit as a "cuff" over coapted nerve ends. They chose this technique to prevent axonal escape, minimize scar ingrowth and nerve entrapment, and to concentrate growth factors at the repair site. Eight of nine patients had improvement after at least one year.

Kuffler *et al*[45] reported a single case of ulnar nerve reconstruction after 3 years. Nerve gap was 12 cm. Using a sheet of collagen, they fashioned a custom-sized conduit. Then they filled it with autologous platelet-rich fibrin. By three months, the patient experienced improvement in neuropathic pain. By 2 years the patient no longer required analgesics. Within 1.5 years, the patient had 4 mm 2PD. Motor function had returned by 2 years. This study showed promising results in the reconstruction of large caliber, mixed function peripheral nerves using collagen conduits. Dienstknecht *et al*[46] recently published a series of 9 patients undergoing median nerve repair. All gaps were 1 to 2 cm long and repaired within 24 h of injury. Average return to work was 8 wk (range 1 to 17). Motor, sensory, pain, and disability scores were satisfactory in 8 of the 9 enrolled patients.

DECELLULARIZED NERVE ALLOGRAFT

Nerve allograft is an alternative to nerve autograft for repair of gaps, but requires the additional administration of immunosuppression for 18 mo. Using a decellularized nerve allograft preserves the three-dimensional collagen scaffolding of a nerve while avoiding immunosuppression[47]. This scaffolding promotes cell migration, nerve fiber elongation, and diffusion of growth factors[48,49]. Laminin, also present, facilitates axonal outgrowth[50]. Human decelullarized nerve is commercially available as Avance® (AxoGen, Inc, Alachua, FL). Available grafts encompass lengths ranging 15 to 70 mm and diameters between 1 and 5 mm.

Karabekmez *et al*[51] were the first to publish clinical data on Avance®. Ten digital nerve repairs were included in the study. Gap length ranged from 0.5 to 3 cm. After an average follow-up of

nearly 9 mo, static 2PD was 5.50 mm and moving 2PD was 4.4 mm. Brooks *et al*[52] then reported a multicenter prospective study with Avance®. These authors examined repair of sensory, motor, and mixed nerves. Of the patients that met follow-up requirements, acceptable outcomes were achieved in every group. Sensory, mixed, and motor nerves recovered at 88.6%, 77%, and 85.7%, respectively. With regards to nerve gap length, short (5 to 14 mm) recovered at 100%, medium (15 to 29 mm) recovered at 76.2%, and long (30 to 50 mm) recovered at 90.9% (mean follow up 265-279 d). Meaningful recovery was defined as S3-4 or M3-5 on the Medical Research Council Classification. Guo *et al*[53] supplemented previous digital nerve repair data with their own case series. Their five patients had a mean nerve gap of 22.8 mm and a mean follow up of 13.2 mo. At the time of final follow up, static 2PD averaged 6 mm and monofilament test ranged positive for monofilaments 4.31 to 4.56. Recently, Taras *et al*[54] reported 18 digital nerve gap repairs treated with processed allograft[54]. Average gap length was 11 mm (range 5 to 30 mm). Overall, 83% of patients had good or excellent results.

Shanti *et al*[55] reported a single case using Avance® for repair of an iatrogenic IAN injury. They did not record the length of the nerve gap. However, they did report improvements in sensory testing at 5 mo postoperative.

POLYGLYCOLIC ACID

Polyglycolic acid (PGA) is a bioabsorbable substance initially used for suture material or mesh[56,57]. Mean resorption time is 90 d[58]. Typically it appears as a tight-weave mesh rolled tube. Its pores are small enough to permit nutrients while impeding invasion by fibroblasts[59]. A tube of PGA is more expensive than suture material used in standard nerve repair[59]. Additionally, PGA is at risk for extrusion prior to complete resorption[59]. PGA is commercially available as Neurotube® (Synovis Life Technologies, Inc.), which has an internal diameter of 2.3, 4, or 8 mm and 2 or 4 cm length.

Initial clinical use of PGA was by Mackinnon *et al*[60] in 1990. Repairing nerve gaps ranging from 0.5 to 3.0 cm, they were able to achieve excellent or good 2PD in 86% of the 15 patients undergoing reconstruction. Weber *et al*[59] (2000) reported his randomized prospective study of 136 nerve injuries treated with either autologous graft or PGA conduit. Although the mean gap length was greater in the PGA conduit group, there was no difference in either moving or static 2PD between the two groups. For either small (less than 4 mm) or large (greater than 8 mm) gaps, the PGA conduit group had better sensory outcomes. Kim *et al*[61] reported successful treatment of a plantar neuroma in an 11-year-old male using a PGA conduit to span a 2.0 cm defect. Pain from the neuroma resolved. Normal sensation returned by 8 mo. In 2005, Navissano *et al*[62] reported their case series of seven patients treated with PGA conduits for traumatic facial nerve terminal branch injuries. Five of seven patients had good or excellent recovery of motor function compared to contralateral side. Nerve gap ranged from 1 to 3 cm.

Battiston *et al*[63] prospectively compared Neurotube® repair of digital nerves to patients treated with vein-muscle grafts. Even though nerve gaps were larger in the Neurotube® group, there were no significant differences in sensory outcomes between the two cohorts. Most (76.9%) of the muscle-vein group had very good results, as did 76.5% of the Neurotube group. Rinker *et al*[64] performed a similar study. They prospectively compared Neurotube repair ® to vein graft repair. PGA conduit group was similar to the vein conduit cohort, including length of nerve gap (9.1 mm mean *vs* 10.3 mm, respectively). There was no significant difference between the cohorts with regards to sensory outcomes. This was true for short (less than 10 mm) or long (greater than 10 mm) gaps.

Rosson *et al*[65] reported 6 cases of PGA used to repair motor nerves. One patient had accessory nerve injury. The remainder had median or ulnar nerve injuries. Nerve gaps ranged from 1.5 to 4 cm (mean 2.8). Follow up ranged from 4 mo to 5.5 years. All patients achieved significant improvement in motor function (rated M3 or greater).

PGA-COLLAGEN

PGA-collagen conduits are composed of a PGA tube coated with 1% amorphous collagen solution. It is then filled with collagen sponge[66]. Fibers usually undergo crosslinking to prevent rapid resorption. To date, this construct is not yet commercially available. Japan was the site of clinical studies of PGA-collagen[67]. Initially it was initially used for reconstruction of intrapelvic nerves damaged during rectal cancer extirpation. Clinical improvement in the patient prompted continued use of the conduit.

In 2004, Nakamura *et al*[67] reported 2 cases using PGA-collagen conduits. The first patient had a 20 mm digital nerve gap. Following treatment, function within normal range by 4 mo. The second patient had a 65 mm superficial peroneal nerve defect with normal sensation by 3 mo. The same group later reported their experience with treatment of Complex Regional Pain Syndrome type Ⅱ[68]. In the two case reports, they described successful resolution of an otherwise challenging clinical entity. It tends to follow a vicious cycle of relapsing pain due to nerve sprouting after injury or resection. The authors theorized that placing the cut ends into the conduit would prevent nerve sprouting and guide the nerve cone to the distal stump. In 2007, Inada *et al*[69] also reported their experience with repair of a frontal branch of the

facial nerve using the same type of conduit, bridging gaps measuring 11 to 30 mm[69]. In both patients, functional recovery was noted by 5 mo. Recently, they also reported chorda tympani nerve reconstruction using their PGA-collagen construct[70]. Average nerve gap was 7 mm among the three patients studied. Electrogustometry measurements returned to normal limits by two weeks postoperative. Dysgeusia resolved between 2 wk to 3 mo.

POLY (DL-LACTIDE-ε-CAPROLACTONE)

Poly (DL-Lactide-ε-Caprolactone) (PLC) is another synthetic bioabsorbable material. Degradation occurs at 1 year. Initial constructs had thicker walls that caused swelling. This negatively impacted nerve healing. Thinner-walled tubes tended to collapse[71]. Increasing the lactide content to 65% reduced the amount of swelling, but lost mechanical strength after 10 wk of implantation[72]. Clinically available PLC may be too rigid for small needles, requiring some softening in water before use[71]. PLC is also transparent, facilitating placement of nerve stumps. It is commercially available by the name of Neurolac® (Polyganics BV, Groningen, Netherlands). They offer 1.5 to 10 mm inner diameters and a length of 3 cm.

After publishing initial clinical studies in 2003, Bertleff *et al*[73] published their follow up findings from a blinded, randomized multicenter trial comparing standard treatment to PLC in repair of peripheral nerve defects of the hand in 54 patients. In treatment of nerve gaps less than 20 mm, they found no significant difference in sensory outcomes compared to controls. Follow up was 12 mo.

FUTURE DIRECTIONS

In addition to the above clinically-tested materials, there is a multitude of materials undergoing preclinical evaluation. These include non-mammalian biodegradable polymers, artificial biodegradable polymers manufactured with electrospinning, conducting polymers, and combinations of the above with Schwann-like neural stem cells and mesenchymal stem cells. Conduits seeded with stem cells, stem-like cells, or support cells theoretically improve nerve regeneration through delivery of growth factors and neurotropic factors into the conduit lumen. Several excellent reviews documenting these advances have been published. They are beyond the scope of the current discussion[74-80].

CONCLUSION

While preclinical studies are essential to bringing new technologies to reconstructive surgeons, further in depth clinical evaluation of materials is warranted. Almost all of the published studies consist of small case series. Outcomes measures are inconsistent from study to study. Furthermore, nerve type, cause of injury, and gap size are extremely variable, making comparison of repair materials and technique difficult. Nevertheless, the above studies suggest that small gaps up to 3 cm can be repaired with available conduits with outcomes similar to nerve autograft. Efficacy of bridging longer gaps with available conduits has yet to be demonstrated. Also, several roadblocks prevent developing technologies from becoming clinically available. Feasibility of stem cell harvest and cost of cutting-edge biomaterials are problematic. These will further delay human studies for these promising therapies.

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