

Limitations of Conduits in Peripheral Nerve Repairs

Amy M. Moore · Rahul Kasukurthi ·
Christina K. Magill · H. Francis Farhadi ·
Gregory H. Borschel · Susan E. Mackinnon

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Abstract Nerve conduits have emerged as alternatives to autologous nerve grafts, but their use in large-diameter nerve deficits remains untested. We report four patients who underwent repair of large-diameter nerves using absorbable nerve conduits and discuss the failed clinical outcomes. The reported cases demonstrate the importance of evaluating the length, diameter, and function of nerves undergoing conduit repair. In large-diameter nerves, the use of conduits should be carefully considered.

Keywords Nerve conduits · Nerve regeneration · Peripheral nerve injury

Introduction

Autologous nerve grafting remains the gold standard for the majority of peripheral nerve repairs, particularly in cases where tension on the coaptation precludes a primary repair. However, autologous nerve grafting is limited by the availability of expendable donor nerves and donor site

morbidity. Nerve conduits have emerged as alternatives to autologous grafts, but their use in large-diameter nerve deficits (e.g., median, radial, and ulnar nerves) remains untested both experimentally and clinically. Currently, conduits are typically used for nerve gaps of less than 3 cm involving small-diameter, noncritical nerves (e.g., digital and radial sensory nerves) [3, 14–17].

In this report, the use of absorbable type I collagen conduits and an absorbable polyglycolic acid conduit is described, and the failed clinical outcomes are discussed. The reported cases highlight the necessity of evaluating the length, diameter, and function of nerves before using conduits in repairs. With the success of nerve conduits for the management of short defects in small-diameter nerves, the indications have been extended to large-diameter nerves despite a lack of animal studies to support the use of conduits in large-diameter nerves. The purpose of this manuscript is to draw attention to the possibility that large-diameter conduits may not yield the same success as small-diameter conduits. Thus, the authors advise caution when using conduits in the repair of large-diameter nerves. The Human Research Protection Office at Washington University has reviewed and approved these cases for publication.

No benefit of any kind will be received either directly or indirectly by the authors.

A. M. Moore · R. Kasukurthi · H. F. Farhadi · G. H. Borschel ·
S. E. Mackinnon (✉)
Division of Plastic and Reconstructive Surgery,
Department of Surgery, School of Medicine,
Washington University,
Campus Box 8238, 660 South Euclid Avenue,
St. Louis, MO 63110, USA
e-mail: mackinnons@wustl.edu

C. K. Magill
Department of Otolaryngology, School of Medicine,
Washington University,
St. Louis, MO 63110, USA

Case Reports

Patient 1

A 43-year-old, right-hand-dominant man underwent a right endoscopic carpal tunnel release. Postoperatively, he had progressively worsening numbness resulting in near complete loss of sensation in the median nerve distribution. Electrodiagnostic studies showed decreased nerve conduction compared to preoperative studies. Two months after his

initial surgery, he underwent right wrist exploration by the same surgeon. A complete median nerve transection injury with intervening scar tissue and neuroma were discovered. The affected segment of nerve was resected and a NeuraGen (Integra NeuroSciences) type I collagen nerve conduit (7 mm diameter×2 cm length) was used to repair the defect.

Postoperatively, the patient complained of persistent pain. Repeat electrodiagnostic studies at 1 year suggested persistent loss of median nerve function. Three years after the conduit repair, the patient continued to have significant pain, weakness with debilitating hyperalgesia in the median nerve distribution, and sensitivity at the wrist. At this point, he was referred to the senior author. On exam, he had a positive Tinel's sign at the site of repair, significant weakness, and minimal thumb opposition with thenar wasting. No two-point discrimination was demonstrated in the right median nerve distribution. The patient had pain at the wrist and hyperalgesia in the median nerve distribution.

Approximately 4 years after the conduit repair, the median nerve and the location of the prior nerve conduit repair was reexplored. A large neuroma-in-continuity was noted (Figs. 1a and 2). Intraoperative electrical stimulation failed to show any function across the median nerve. The neuroma was excised, and then by using transverse cuts proximally and distally, the nerve was “breadloafed” until a normal fascicular pattern was obtained (Fig. 1b). The right medial antebrachial cutaneous nerve was used to repair the defect using four cables that were each 7 cm in length (Fig. 1c).

Patient 2

A 22-year-old, right-hand-dominant man sustained a deep glass laceration over the medial–volar aspect of his right midforearm. Emergent intraoperative evaluation revealed complete transection injuries of the ulnar artery, vein, and nerve. Primary repair of the ulnar nerve was not possible and a GEM Neurotube (Synovis, Birmingham, AL, USA)

polyglycolic acid nerve conduit (4 mm diameter×2 cm length) was used to repair the defect.

Postoperatively, the patient showed no evidence of recovery of function and had severe dysesthetic pain over the medial aspect of the right forearm. Seven months after the operation, nerve conduction studies demonstrated absent voluntary motor unit potentials in the ulnar-innervated intrinsic muscles, consistent with severe denervation.

At 9 months postoperatively, the patient was referred to the senior author and complained of severe pain in the ulnar distribution of the hand. Intrinsic ulnar-innervated muscle function was absent. At reexploration, the conduit appeared to be fully degraded and the ulnar nerve was discontinuous with an interstump gap defect of approximately 4 cm (Fig. 3a). The proximal stump ended in a large neuroma (Fig. 4) with the abortive regenerative neuroma extending slightly beyond the proximal suture site (Fig. 3a). After “breadloafing” the proximal and distal stumps to achieve normal fascicular patterns (Fig. 3b), the right medial antebrachial cutaneous nerve was harvested and four separate 6-cm nerve cables were used to achieve a tension-free repair (Fig. 3c).

Patient 3

A 3.5-month-old girl with obstetrical brachial plexus palsy underwent right brachial plexus exploration. The C5–6 roots were coapted using a NeuraGen (Integra NeuroSciences) type I collagen conduit (7 mm diameter×3 cm length).

Postoperatively, the patient failed to develop clinical evidence of motor reinnervation. One year postoperatively, she underwent nerve conduction studies which demonstrated absent motor action potentials in the median, radial, ulnar, musculocutaneous, and axillary nerves. She was also noted to have paralysis of the right hemidiaphragm.

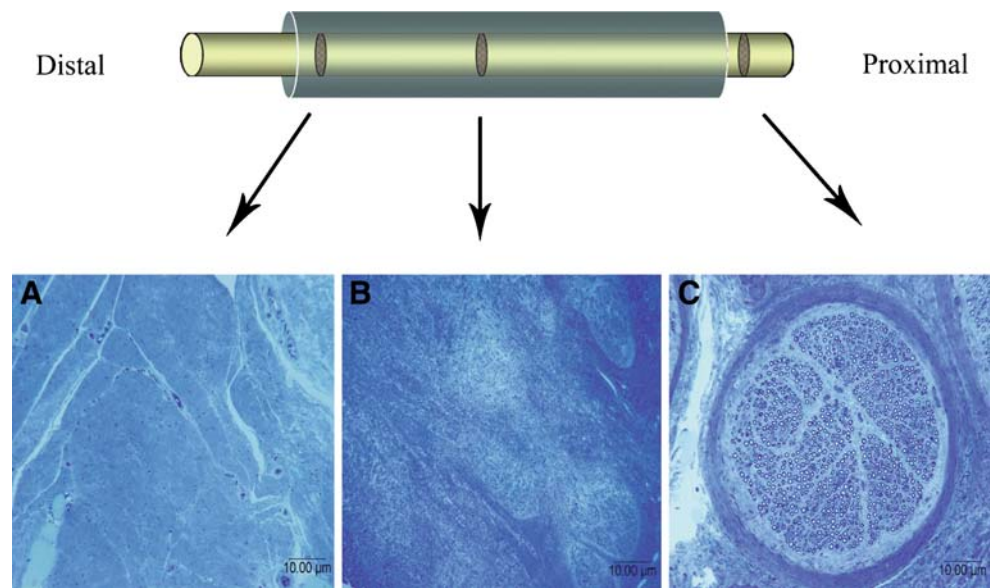
At 2 years of age (21 months postoperatively), she presented to our multidisciplinary pediatric brachial plexus clinic. She demonstrated no function in the median, ulnar, and musculocutaneous nerves and, as a result, had sustained



Figure 1 Patient 1—*intraoperative photos.* **a** Four years after right median nerve repair with a collagen conduit; this *intraoperative view* revealed a large neuroma-in-continuity. **b** A 7-cm gap was developed

before normal fascicular pattern was discovered, and **c** the defect was then repaired using the medial antebrachial cutaneous nerve.

Figure 2 Patient 1—histologic specimens. **a** Histology of the surgical specimen reveals dense fibrinous scar tissue and lack of nerve structures in the section of the distal conduit. **b** The midconduit section shows significant disorganized architecture with no axonal organization, consistent with neuroma. **c** Proximally, normal nerve architecture is demonstrated.



multiple burn injuries to the insensate hand. She also demonstrated no shoulder or elbow function. Further surgery was declined by the family. The family returned to our clinic at age 3 years (33 months postoperatively), at which time her examination was unchanged. The parents again declined further intervention.

Patient 4

A 3-month-old boy with obstetrical brachial plexus palsy underwent left brachial plexus exploration. He was diagnosed preoperatively with a total plexus injury. During the reconstruction, NeuraGen (Integra NeuroSciences) type I collagen conduits (4 mm diameter×3 cm length) were exclusively used for reconstruction. Two conduits were used from the C5 root to the upper and lower trunks, respectively. Another conduit was used from the C6 root to the lower trunk.

Fourteen months postoperatively, the child presented to our multidisciplinary pediatric brachial plexus clinic and

demonstrated no movement in the left upper extremity. The family is currently considering further surgery.

Discussion

Alternatives to autologous nerve grafting have been explored over the last century [13]. Biodegradable nerve conduits avoid donor site morbidity and immunosuppression associated with nerve allografting and have been found to reduce operative time [16, 21].

First-generation conduits composed of nonabsorbable silicone have been associated with nerve compression and long-term sequela from scar tissue and foreign body reaction [17]. Absorbable conduit materials have subsequently been developed to allow greater interaction with the surrounding environment, encourage axonal sprouting, and reduce axonal compression [8, 17].

In the reported cases, absorbable nerve conduits were used to repair large-diameter nerve injuries without successful

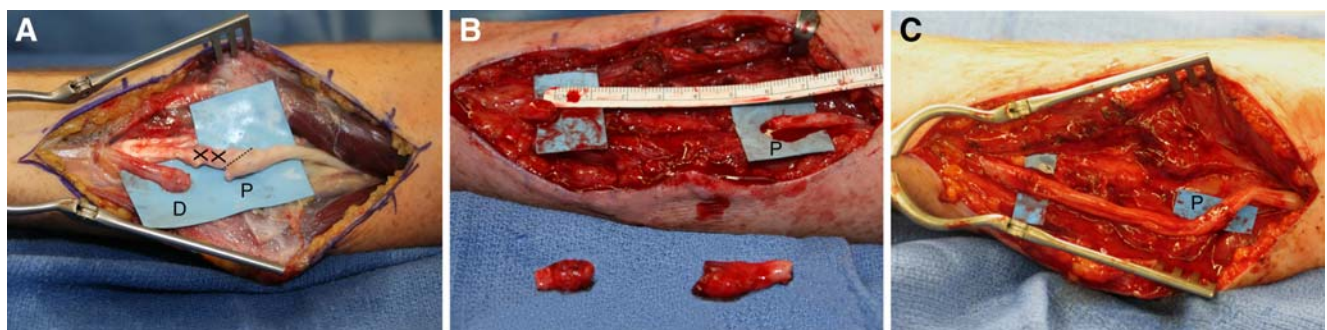
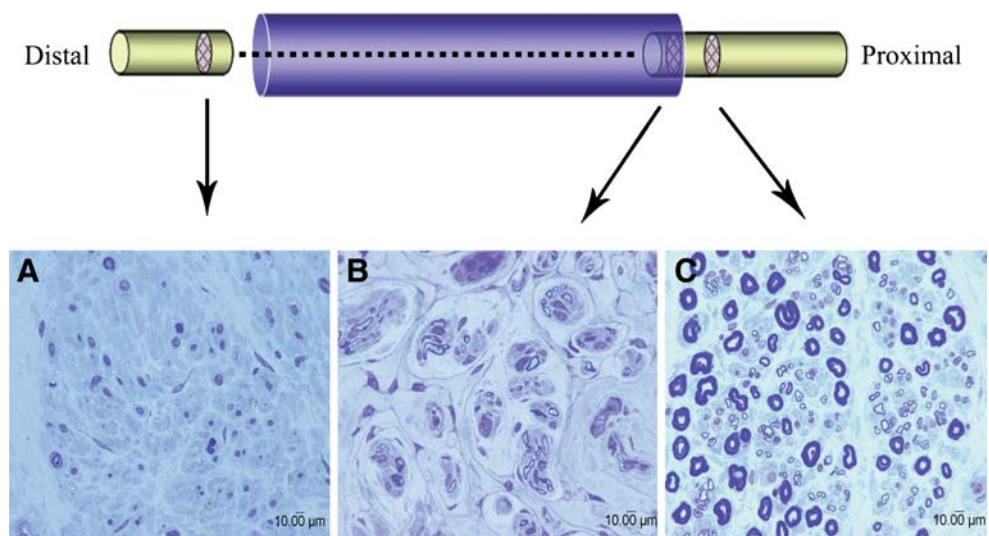


Figure 3 Patient 2—intraoperative photos. **a** Proximal stump (P) ending in a large neuroma discontinuous with distal stump (D) and adjacent to scar tissue on the radial aspect (XX, separated by dashed

line), 9 months postinjury. **b** Trimming of the nerve stumps resulted in a 6-cm gap distance. **c** Four separate medial antebrachial cutaneous nerve channels were used to bridge the gap.

Figure 4 Patient 2—histologic specimens. **a** Histology of the surgical specimen reveals dense fibrinous scar tissue and lack of nerve structures in the section of the distal conduit. **b** The proximal conduit section shows significant disorganized architecture with no axonal organization, consistent with neuroma. No regeneration was seen through the conduit. **c** Proximally, normal nerve architecture is demonstrated.



functional recovery. Technical factors could have contributed to these results, including lack of adequate resection of damaged nerve or failure to properly secure the proximal and distal nerves into the conduit. However, we hypothesize that the large diameter of the involved nerves is likely the most important factor that predisposed these conduits to failure.

The majority of the literature supports the use of conduits for short nerve gaps (equal to or less than 3 cm) in small-diameter, noncritical sensory nerves [14, 16, 17]. A recent review of absorbable conduits highlights the high degree of variability and quality of clinical outcomes data [17] with only isolated studies in humans showing the successful use of conduits in longer nerve gaps (>3 cm) [19, 23].

Animal studies using short nerve gaps with small-diameter nerves have shown conduits to be efficacious [3, 7, 15]. In a nonhuman primate study, a median nerve defect was repaired using collagen conduits of 0.5, 2, and 5 cm in

length, resulting in adequate functional outcomes in the 0.5 and 2 cm groups, but not with the 5 cm distance [8]. A recent study from our laboratory compared NeuraGen (Integra NeuroSciences) type I collagen conduits to decellularized allografts (Axogen) and isograft controls and found that the conduits and processed allografts were not equivalent to the isografts. In a rat short nerve gap (1.4 cm) model at 6 weeks, the conduit (1.5 mm diameter) had significantly less nerve regeneration (49 ± 154 fibers) than the processed allografts ($1,014 \pm 1,035$ fibers) and isograft controls ($2,912 \pm 2,078$ fibers). When the gap length was doubled (2.8 cm), the conduit and the decellularized allografts demonstrated no axonal regeneration distally in all animals, while the isograft group had over 5,000 fibers [24] (Fig. 5). Thus, there are animal studies demonstrating adequate function and regeneration with the use of conduits, but limitations to their use in animal models also exist.

Figure 5 Comparative study findings. A study comparing collagen conduits, processed allografts, and isografts yielded the distal fiber counts illustrated at a 6-week time point. No distal nerve regeneration was demonstrated in the conduit and processed allograft animals when the gap length was doubled [24].

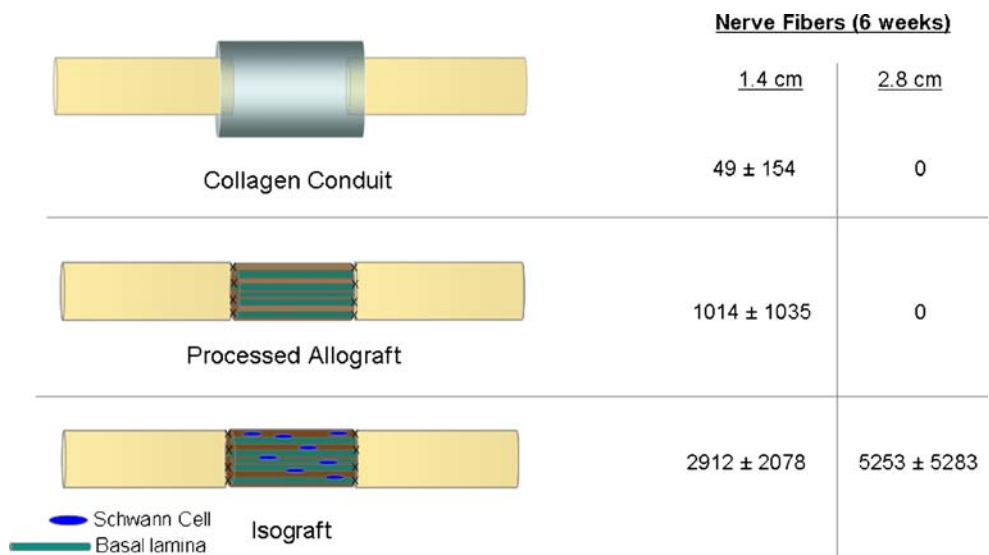
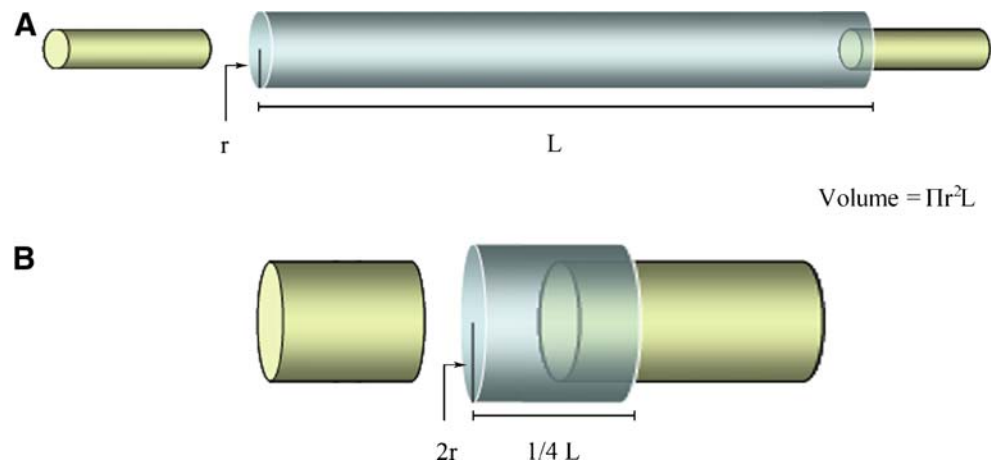


Figure 6 Large-diameter nerves. The figure illustrates the importance of diameter in determining overall volume of a nerve gap. Conduits *A* and *B* are of equal volume. Doubling the radius in conduit *B* gives an equal total volume of conduit *A* with only one-fourth the length according to the formula $V = \pi r^2 L$ where V is the volume, r is the radius, π is the pi (~ 3.14), and L is the length.



When relying on animal studies to support the clinical use of conduits, one must consider the limitations of animal models. Small animals are popular and indispensable in nerve surgery, but rodents demonstrate superior neuroregenerative capacity compared to humans and higher mammals. Thus, in order to recognize true differences between experimental groups, the timing of outcome measurement is critical. Clinical correlation can only be made with earlier time points when both positive and negative control groups are still significantly different. Late time points may show experimental groups (including positive and negative controls) to be equivalent due to the “blow-through” effect in which the superlative rodent regenerative capacity masks true differences between groups [1]. There are examples in the literature of erroneous conclusions drawn from results gathered at late time points when differences between positive and negative control groups are lost due to the enhanced regeneration of the rodent model [1, 22]. For example, Waitayawinyu et al. compared polyglycolic acid nerve conduits and type I collagen nerve conduits [22]. The late time point of 15 weeks could explain the similarity between the isograft controls and the two nerve conduits studied. The slight superiority of the collagen conduit over the polyglycolic acid conduit was likely related to the use of a smaller-diameter collagen type I conduit, which are available at

1.5 mm (inner diameter). The smallest available diameter of the polyglycolic acid nerve conduit is 2.3 mm (inner diameter). Diameter was not noted in this study, which is in keeping with our hypothesis that surgeons are not yet aware of the importance of conduit diameter in nerve regeneration.

Furthermore, data must be interpreted in the context of the small-diameter nerves on which conduits have been tested. Aside from rarely used models such as the porcine sciatic nerve, it is difficult to simulate the large diameter of human nerves using animal models. Even in the subhuman primate model, the ulnar and median nerves are much smaller than in humans and cannot be considered large-diameter clinical nerve models.

While limitations regarding conduit length have been addressed in numerous studies, nerve diameter is an under-recognized contributor to conduit failure. The diameter of the injured nerve and conduit employed in a repair may significantly affect nerve regeneration (Fig. 6). This may be related to a decrease in concentration of neurotrophic factors in the larger volume conduits. Neurotropism is the concept that the distal nerve stump releases substances (neurotrophic factors, nutrients, etc.) that attract the proximal regenerative front [11, 21]. The gradient and availability of diffusible substances released by proximal and distal injured nerves is likely affected by the volume of the conduit, such that, as

Table 1 Options and attributes for the repair of nerve gaps.

Graft type	Immunologically inert	Structure		Contents	
		Cross-sectional ^a	Laminin intact	Schwann cells	Soluble factors
Autograft	+	+	+	+	+
Processed “acellular” allograft	+	+	+/-	-	-
Conduit	+	-	-	-	-

+ present, - not present

^a Cross-sectional structure refers to the interior substructure of endoneurial tubes, which has not yet been replicated in a fully synthetic nerve conduit

volume is increased, the neurotrophic and proregenerative factors are diluted within the space and thus neurotrophism is diminished.

Although a few cases of the successful use of synthetic conduits in large-diameter human nerves do exist, they are rare. Lundborg et al. reported successful ulnar nerve repairs using silicone conduits; however, they involved very short nerve gaps (2–3 mm) and required subsequent removal of the silicone conduit to prevent nerve compression [10, 12]. In 2007, Dellon and colleagues reported the repair of 3-cm ulnar and median nerve defects using polyglycolic acid conduits, using four separate small-diameter conduits in cable formation [4]. More recently, Hung and Dellon reported the successful repair of a 4-cm human median nerve defect with the use of polyglycolic acid conduit. However, in this case, they augmented the long repair by including a slice of autogenous nerve within the conduit [6], a technique that has been successful in augmenting regeneration in the rodent conduit model [5]. To our knowledge, this technique was not used in any of the cases in this report. The use of large-diameter conduits to repair large-diameter nerve defects needs to be further explored. A recent animal study by Shin et al. reported the significant inferiority of a large-diameter conduit (2.3 mm) in comparison to two smaller-diameter conduits (1.5 mm) used in a rat model to repair a 10-mm defect [18]. Shin's study supports the assertion that the diameter of the nerves can cause failure of conduit repairs due to overall volumes that are simply too great to adequately supply the necessary proregenerative gradient and concentration for regenerating axons. Although further studies are needed to confirm these assertions and to establish maximum "volumes" that still support successful regeneration, these factors may account for the conduit failures presented in the reported cases.

Given the limitations of standard conduits, there has been recent interest in exploring options for improvement. Ideally, advances in conduit engineering will create an "autograft substitute" with properties conducive to nerve regeneration (Table 1). In addition to maximizing absorbable properties, research has focused on the addition of substrates (neurotrophic factors and Schwann cells) as well as developing structural matrices for axonal growth within the conduits [2, 9, 20]. However, existing engineered contents have not been proven to significantly affect outcomes, and conduit substrates are yet to be used clinically.

In conclusion, the reported cases illustrate the limitations of conduits in large-diameter, critical nerve repairs. Unfortunately, the appropriate defect length for large-diameter nerve gap repairs has not been established in humans or in an appropriate large animal model. There are also few reported clinical cases of successful reconstruction with large-diameter conduits. The authors encourage surgeons

who are using large-diameter conduits to report their positive results. In the future, advances in engineering may enable conduit use in a wider spectrum of clinical settings; but based on the currently available data, we caution against using nerve conduits to repair large-diameter nerves.

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Conflicts of interest The senior author is codeveloper of the polyglycolic acid conduit (Synovis Micro Companies Alliance, Birmingham, AL, USA), which was used in one of the cases in this report. Our laboratory has also received research funding from Axogen (Alachua, FL, USA) for a study involving processed allografts. This product was not used in these clinical cases, but is marketed as an alternative to autografting and conduit use.

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