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Collagen Tube Conduits in Peripheral Nerve Repair: A Retrospective Analysis

Kirk J. Wangensteen · Loree K. Kalliainen

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Abstract A chart review was conducted of all patients receiving NeuraGen® conduits from 2002 to 2007 at Regions Hospital, a level I trauma center. Ninety-six patients underwent 126 repairs using NeuraGen® conduits, and 64 patients were seen in follow-up. Repairs were largely of upper extremity sensory nerves but six were repairs of nerves elsewhere in the body. There were no intra-operative complications, but there were two minor postoperative complications and one postoperative pulmonary embolus. Forty of 126 repairs were lost to follow-up. Twenty-six of 126 repairs had follow-up with quantitative testing of nerve recovery (2-point discrimination, Semmes–Weinstein, or EMG testing), with 35% reporting improvement and 31% going on to a revision operation. Sixty of 126 repairs had qualitative testing performed (subjective or objective reporting of sensation or motor function), with 45% reporting improvement and 5% going on to a revision operation. Patients who went on to revision surgery were more likely to have undergone quantitative evaluation of sensation. Overall, sensory recovery was in the 35–45% range in our experience. Our results indicate that NeuraGen® collagen conduits can be used safely throughout the body.

K. J. Wangensteen
Combined MD/PhD Training Program, University of Minnesota, Minneapolis, MN, USA

L. K. Kalliainen (✉)
Department of Plastic and Hand Surgery, Regions Hospital, Mail Stop 11503 B, 640 Jackson Street, St. Paul, MN 55101-2595, USA
e-mail: loree.k.kalliainen@healthpartners.com

L. K. Kalliainen
Departments of General and Orthopaedic Surgery, University of Minnesota, Minneapolis, MN, USA

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Introduction

Damage to peripheral nerves can lead to significant morbidity in manipulating and sensing the environment. With neurotmesis (complete nerve division), there is no spontaneous return of nerve function. Thus, surgical repair is used to approximate nerve ends and restore motor and sensory function. Nerves are repaired by direct end-to-end coaptation or through conduits such as nerve grafts or synthetic tubes. A number of studies suggest that bioabsorbable nerve conduits are at least as effective as nerve grafting for repair of short nerve defects, without the morbidity associated with graft harvest [2, 3, 10–12].

Nerve conduits made of collagen have been shown to be effective in rat and monkey models of nerve repair and are FDA-approved for use in humans [1, 5, 7]. Collagen is an attractive material because it is porous, biocompatible, and absorbable, and it is widely used as a sheet graft to cover wounds. A number of small studies have been published reporting the use of collagen conduits in humans. One study used collagen conduits to repair sensory nerve avulsions in 11 patients and found that, for the six patients with follow-up greater than 12 months, five had improvement by 2-point discrimination and monofilament testing [8]. Another study employed collagen conduits in repair of nine lingual and inferior alveolar nerve injuries, and on evaluation of touch, pinprick, and thermal sensation, they found good improvement in four, some improvement in four, and no improvement in one [6]. A study focused on digital nerve repair with collagen conduits included 12 patients and found good or excellent 2-point discrimination

in eight out of nine patients [4]. Finally, a small prospective study of digital nerve repair with collagen conduits found good or excellent nerve recovery in nine out of 12 patients [9].

To date, there is no other larger, comprehensive study of the efficacy of collagen implants in a typical hospital setting to repair nerve defects in humans. Thus, we performed a retrospective analysis of our results using collagen conduits to repair 126 nerve injuries in 96 patients.

Methods and Materials

IRB approval was granted to retrospectively review the charts of all patients who underwent nerve repair using NeuraGen® nerve conduits at Regions Hospital from 2002 to 2007. Our hospital is a regional level I trauma center that routinely performs reconstructive procedures including nerve repair. We used preoperative, operative, and follow-up notes to record patient age, nerve(s) repaired, time to repair, gap-width spanned, pathology reports, complications, and subjective and objective restoration of nerve function. Specific complications noted included infection, wound dehiscence, hemorrhage, deep venous thrombosis, etc. NeuraGen® conduits are FDA-approved, bovine type 1 collagen tubes of varying caliber. Repair was performed according to manufacturer's recommendations or as a sleeve after primary repair.

Assessments of nerve function on follow-up notes were documented for our analyses. Quantitative measures included Semmes–Weinstein testing, 2-point discrimination, and electromyography. Qualitative descriptions were divided into objective and subjective criteria. Qualitative–objective descriptions were those in which the physician noted a positive Tinel's sign at or distal to the site of the repair and/or testing for light-touch sensation. Qualitative–subjective was the perceived change in sensation or motor function by the patient. Chi-square analysis was performed to determine whether there were statistical differences between groups.

Results

A total of 96 patients underwent 126 nerve repairs using collagen conduits; 29 (30%) were female and 67 (70%) were male. The average age of the patients was 33 years, with a range from 7 to 79 years. The median time from injury to repair was 1 day, with a range from 0 days to 20 years. The median caliber of NeuraGen® tube used was 2 mm, with the range of caliber from 2 to 7 mm. The gap-width spanned was noted in a total of 26 damaged nerves and averaged 12.8 mm (range, 2.5 to 20 mm). Of these, 19 were digital nerves, and the gap averaged 11.7 mm (2.5–20 mm).

Six "iatrogenic" nerve injuries resulted from previous operative procedures (Table 1). There were no intraoperative complications. Postoperative complications included one case with erythema around the wound that resolved with Augmentin, one case of pulmonary embolism after repair of the phrenic nerve, and one case of partial wound dehiscence that resolved with topical Silvadene and local wound care.

The patients' nerves were injured by a variety of mechanisms (Table 1). Injuries were largely to sensory nerves of the upper extremity, with digital nerves injured in 82 out of 126 repairs, other upper extremity nerves in 34 out of 126 repairs and six nerves elsewhere in the body (Table 2). The digital nerve injuries included all of the digits and ranged in location from the common digital nerve proximal to the metacarpal–phalangeal joint to the digital nerves overlying the middle phalanx. There were 23 repairs of non-digital small caliber nerves (2–4 mm) and 21 large-caliber nerves (≥5 mm). Eleven repairs went on to revision, representing 9% of cases, and the percent going on to revision was similar between the categories of digital and non-digital nerves.

A total of 64 out of 96 patients were seen in follow-up; 32 patients were lost to follow-up. Recovery of nerve function was quantified using electromyography, 2-point

Table 1 Mechanisms of injuries.

Mechanism	Number of patients	Number of nerves	Number of revisions
Laceration by saw	15	31	6
Laceration by knife	12	13	1
Laceration by glass	18	22	1
Laceration by scissors, tire, sheet metal, MVC, or jagged rock	9	11	0
Laceration, not otherwise specified	19	23	0
Crush or shear	4	4	0
Cat bite	1	1	1
Gunshot wound	4	4	0
Iatrogenic	6	7	1
Fracture or iatrogenic	1	1	0
Puncture (barb, tool)	2	2	0
Blast	3	4	0
Drill injury	3	3	0
Totals	97[a]	126	11

The mechanisms of injury are listed, as well as the number of patients affected by each, the number of nerves involved, and the number of revisions after NeuraGen® repair. *MVC* Motor vehicle collision

[a] One patient had two separate injuries to nerves

Table 2 List of nerves repaired and revisions.

	Number of nerves	Number of revisions
Digital nerves	82	7 (9%)
Non-digital small caliber nerves (2–4 mm)	23	2 (8%)
Radial nerve sensory branch	6	0
Radial nerve superficial sensory branch	3	0
Medial antebrachial cutaneous nerve	2	0
Medial brachial cutaneous nerve	1	0
Ulnar nerve dorsal sensory branch	6	0
Posterior interosseous nerve	1	0
Supraorbital nerve	3	2 (67%)
Facial nerve buccal branch	1	0
Large-caliber nerves (5+mm)	21	2 (10%)
Median nerve (full)	7	1 (14%)
Median nerve (partial)	7	0
Ulnar nerve	5	1 (20%)
Phrenic nerve	1	0
Deep peroneal nerve	1	0
Total repairs	126	11 (9%)
Total upper extremity	120	9 (8%)
Total non-upper extremity	6	2 (33%)

The specific nerves repaired using NeuraGen® conduits are listed, along with number repaired and the number and percent of revision surgeries performed

discrimination, or Semmes–Weinstein monofilament testing in 26 of the 126 nerve repairs (21%), and improvement was noted in 35% of these patients (Table 3). Qualitative evaluation by either objective examination or subjective report was noted in 60 of 126 nerve repairs (48%), with 45% of these reported as "improved". There was no significant difference in improvement whether quantitative or qualitative evaluation was performed (P=0.37), and 43% of patients overall showed postoperative improvement. Forty of the nerve repairs (32%) were lost to follow-up. The average time to last follow-up among the patients with any follow-up was 256 days.

Of the 26 nerve repairs evaluated by quantitative examination, eight underwent a revision operation. Of the 60 that were evaluated qualitatively, three underwent revision. When quantitative evaluation methods were employed, there was a statistically significant correlation with revision surgery (P=0.001).

Table 3 Evaluation of nerve functional restoration.

Data acquisition method	Number of patients	Number of Nerves	Average days to last follow-up	Overall percent improved (%)	Number of revisions	Percent revisions (%)
Semmes–Weinstein	6	6	295	67	2	33
2-point sensory exam	9	17	371	24	5	29
Electromyography	2	3	449	33	1	33
Objective examination (qualitative)	41	45	249	49	3	7
Subjective report (qualitative)	7	15	158	33	0	0
Lost to follow-up	32	40	36	n/a	0	0
Overall quantitative	17	26	363	35	8	31
Overall qualitative	48	60	226	45	3	5
Total with any documentation	64	86	256	43	11	13

Improvement in nerve function as determined by physical examination. The physical examination measures were stratified based on quantitative measures (Semmes–Weinstein, 2-point discrimination, or electromyography) and qualitative examination. The qualitative findings were divided into objective physical examination findings such as touch sensation, or motor function, and subjective report of sensation. Forty patients were lost to follow-up. The number and percent of patients going on to a revision surgery are noted. Overall, improvement in nerve function was noted in 43% of patients. Although there was no significant difference in the measurement of improvement with quantitative measures versus qualitative measures (P=0.37), there was a statistically significant correlation between quantitative postoperative measurement of nerve function and likelihood of revision surgery (P=0.001)

There were seven revision surgeries to repair 11 nerves (Table 4). Four were revised with NeuraGen® tubules; six were revised with sural nerve grafts, and one was revised with a lateral antebrachial cutaneous nerve graft. The average time to revision was 409 days with a range of 111–730 days.

Pathology reports were obtained for the excised tissue in all revision cases. In one case, pathological examination of excised tissue revealed desmoplastic melanoma with focal perineural extension. In the remainder of cases, the excised tissue was found to be neuroma on pathological examination. There was no mention of inflammation in the pathology reports.

Discussion

Three FDA-approved synthetic conduits are commercially available for nerve repair. They include those made from polyglycolic acid (PGA), polylactide–caprolacton (PLCL), and collagen. Our series of 126 nerve repairs with collagen conduits is the largest group studied to date with this material. Our results indicate that collagen conduits can generally be employed safely. There were no intra-operative complications and two self-limited, minor postoperative complications. One patient had a pulmonary embolus after major surgery to repair the phrenic nerve.

Overall, collagen conduit repair of nerve defects led to recovery of nerve function in 43% of patients with adequate follow-up. Our study had several differences when compared with previous, smaller studies with collagen conduits [4, 6, 8, 9]. Our rate of recovery was less than reported by the smaller studies (75–89%) and may be explained by a number of factors: (1) Our study included a large variety of repairs by seven different surgeons. Our experience may be more typical of the varied experience in a large level 1 trauma center than that presented in prior studies. (2) Our study included various mechanisms of injury. The patient population had a proportionately large number of saw, crush, and gunshot wounds, which may cause more extensive damage to the nerve and surrounding tissue. (3) Our study was not limited to acute injuries, and the mean time to repair of nerves in our study was 1 day post-injury, with a range of up to 20 years. Many of the nerves were repaired acutely, and it is possible that the degree of injury along the length of the nerve was not apparent at the time of surgery. Resultant progressive scarring may have impaired nerve ingrowth.

There were a total of 11 revision procedures in our study. Interestingly, quantitative measurement of nerve function was associated with increased likelihood of revision surgery as compared with qualitative measurement ($P=0.001$). Most likely, this difference was a result of greater concern about the recovery in the patients evaluated quantitatively. It may also be an indication that the patients with larger nerve defects, such as multiple involved nerves or widespread sensory loss, are more likely to be followed more closely by hand therapists, to undergo more thorough sensory examinations, and are more likely to go on to revision surgery if expected progress is not being seen.

Table 4 Nerve revisions.

Age	Mechanism	Nerve	Number of days	Type of repair	Follow-up	Outcome
49	Iatrogenic	Supraorbital	214	Lateral antebrachial cutaneous nerve graft	Adequate	No improvement
51	Iatrogenic	Supraorbital	730	Excision and burial	Adequate	Desmoplastic melanoma with perineural extension
29	Cat bite	4th RDN	230	NeuraGen®	Adequate	Continued pain, no sensory examination, suspected reflex sympathetic dystrophy
34	Laceration by saw	1st UDN	485	Sural nerve graft	Poor	Continued pain, no sensory exam
		1st RDN	485	Sural nerve graft		
		2nd RDN	485	Sural nerve graft		
		2nd/3rd CDN	485	Sural nerve graft		
		3rd/4th CDN	485	Sural nerve graft		
36	Laceration by saw	Ulnar nerve	111	Neuroma repair and NeuraGen® wrap	Last at 236 days post-revision	Advancing Tinel's, weak intrinsic muscles
42	Laceration by knife	5th UDN	210	NeuraGen®	Poor	Lost to follow-up
44	Laceration by glass	Median nerve	582	Sural nerve	Adequate	No improvement

A list of the nerve repairs by NeuraGen® conduits that went on to revision surgeries. The mechanism of injury, nerve damaged, time to repair, type of revision surgery, and outcomes are noted. *RDN* Radial digital nerve, *UDN* ulnar digital nerve, *CDN* common digital nerve

Whatever the case, physicians should perform and document quantitative sensory exams on all patients before and after nerve repair.

Of the 11 revision surgeries, five patients returned for adequate follow-up, and only in one was there documentation of advancing Tinel's sign, highlighting the challenge of nerve revision surgery. Interestingly, the pathology reports of tissue excised from these patients indicated that the tissue was neuromatous, and there was no mention of inflammatory cells or granulomas on histological sections. One of the theoretical problems with collagen tubules is that they could elicit an inflammatory response, as they are foreign bovine biological material. At least, in these cases, it seems that inflammation was not an obvious factor in failure of the nerve to recover.

Our study has the classic problems associated with retrospective studies, namely loss of patients to follow-up, no *a priori* criteria for inclusion or exclusion of patients, and inconsistent evaluation of surgical results in patient follow-up. Practicing physicians may not have a systematic method for following their outcomes in surgery. This study brought to our attention the difficulty in and need for consistency in postoperative evaluation. We are now in the process of implementing an alert system in the electronic medical record to both notify our occupational therapists to contact the patients for evaluation and to remind staff to record 2-point examination and Semmes–Weinstein tests in the postoperative period for patients who undergo nerve repair. The other limitation in our study was our high rate of loss of patients (40 out of 126 nerves repaired). This may be related to the distances that our patients travel and the high number of indigent or transient patients.

No study has compared the various nerve conduits in a randomized, prospective fashion. At least three randomized, controlled, prospective studies have compared bioabsorbable conduits to nerve or vein grafting. A multicenter study of 136 nerve repairs suggested that PGA conduits are at least as effective as nerve grafting for repairing avulsed nerves, with 44% having excellent results, 30% having good results, and 26% having poor results [12]. Another study comparing PGA conduits to muscle–vein grafts found no difference between the two techniques [2]. Finally, a randomized, controlled study of 30 patients with nerves repaired using a PLCL tube or a nerve graft found similar success with either technique [3]. Thus, while there is good prospective evidence that PGA and PLCL conduits are at least as effective as grafting in humans, no similar study has been performed with collagen conduits.

We show here our results with nerve repairs performed using NeuraGen® collagen tubules. Our retrospective study indicates that collagen conduits were safe to use and were effective in 43% of patients. This may represent the outcomes that could be expected with typical use in level I trauma centers. A randomized, prospective study comparing the different commercially available conduits will have to be performed to determine whether they differ in efficacy.

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