

Outcomes of Short-Gap Sensory Nerve Injuries Reconstructed with Processed Nerve Allografts from a Multicenter Registry Study

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Abstract

Background Short-gap digital nerve injuries are a common surgical problem, but the optimal treatment modality is unknown. A multicenter database was queried and analyzed to determine the outcomes of nerve gap reconstructions between 5 and 15 mm with processed nerve allograft.

Methods The current RANGER registry is designed to continuously monitor and compile injury, repair, safety, and outcomes data. Centers followed their own standard of care for treatment and follow-up. The database was queried for digital nerve injuries with a gap between 5 and 15 mm reporting sufficient follow-up data to complete outcomes analysis. Available quantitative outcome measures were reviewed and reported. Meaningful recovery was defined by the Medical Research Council Classification (MRCC) scale at S3-S4 for sensory function.

Results Sufficient follow-up data were available for 24 subjects (37 repairs) in the prescribed gap range. Mean age was 43 years (range, 23–81). Mean gap was 11 ± 3 (5–15) mm. Time to repair was 13 ± 42 (0–215) days. There were 25 lacerations, 8 avulsion/amputations, 2 gunshots, 1 crush injury, and 1 injury of unknown mechanism. Meaningful recovery, defined as S3-S4 on the MRCC scales, was reported in 92% of repairs. Sensory recovery of S3+ or S4 was observed in 84% of repairs. Static 2PD was 7.1 ± 2.9 mm ($n = 19$). Return to light touch was observed in 23 out of 32 repairs reporting Semmes-Weinstein monofilament outcomes (SWMF). There were no reported nerve adverse events.

Conclusion Sensory outcomes for processed nerve allografts were equivalent to historical controls for nerve autograft and exceed those of conduit. Processed nerve allografts provide an effective solution for short-gap digital nerve reconstructions.

Keywords

- ▶ processed nerve allograft
- ▶ digital nerve
- ▶ nerve reconstruction
- ▶ peripheral nerve

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Traumatic disruption of a digital nerve is one of the most common conditions treated by hand surgeons. The mainstays of successful nerve repair have changed little since their description by Ferrara in the 16th century¹ and consist of generous trimming of the nerve to healthy substance, tension-free approximation, and a well-vascularized wound bed. However, it is not always possible to provide a tension-free approximation, especially in the setting of crush or avulsion mechanisms with a wide zone of injury. Yi and Dahlin found that minor and moderate tension, pulling together a 3- or 6-mm gap, results in 29 to 48% impairment in axonal outgrowth as well as apoptosis and decreased Schwann cell activity.² According to Lohmeyer et al, direct repair is not possible in 18% of digital nerve injuries,³ and the resulting gap must be bridged with a graft or conduit. As confirmed by prospective studies of digital nerve repairs, the most common gap length in digital nerve injuries is at the shorter end of the spectrum, between 5 and 15 mm.^{4,5}

Despite the prevalence of the injury and a large body of literature on the subject, no consensus exists as to the optimal management of a digital nerve injury with a short gap.⁶ Nerve autograft is a long-established and reliable means of reconstruction, with the sural nerve and lateral or medial antebrachial cutaneous nerves being the most popular donor nerves.^{7,8} However, nerve graft harvest adds time and complexity to the operative procedure, and donor sites can be associated with significant and longstanding morbidity, including anesthesia, paresthesias, and pain.^{9,10} For these reasons, extensive research has been dedicated to identifying ways to bridge a nerve gap without a nerve autograft. One of the oldest techniques involves constructing a hollow tube conduit to provide a protective environment and to isolate the regenerating nerve from the surrounding tissues. Nerve conduits of various composition, including woven polyglycolic acid (PGA), collagen, and autogenous vein, have been used clinically, with mixed results.^{4,5,11-16}

Processed nerve allografts (Avance Nerve Graft; AxoGen, Inc., Alachua, FL) represent a biologic alternative to nerve autografting and conduits, without donor site morbidity. They consist of decellularized and predegenerated human nerve tissue, with preservation of the internal architecture of epineurium, fascicles, and endoneurial tubes. In experimental studies, they have been shown to rapidly revascularize and repopulate with host cells and provide an environment conducive to nerve regeneration.¹⁷⁻¹⁹ Early clinical data have demonstrated levels of recovery following processed nerve allograft reconstruction of nerve gaps equaling that reported in the literature for nerve autograft and exceeding those reported for conduit.²⁰⁻²² The RANGER Study registry was opened in 2008 and collects data from 18 centers on the utilization and outcomes of processed nerve allografts for the reconstruction of peripheral nerve defects. The registry pools data from a wide cross-section of nerve types, injury type, mechanisms, and practice settings.

Despite the prevalence of digital nerve injuries with a critical gap, the optimal management of these injuries has not been determined. The purpose of this study was to review a large database of patients who underwent nerve reconstruc-

tion with processed nerve allograft to determine the degree of sensory recovery following repair of a short-gap digital nerve injuries and to compare these results with historical controls for nerve autograft and conduit repairs.

Materials and Methods

The RANGER registry is designed to collect utilization and outcome data from the use of processed nerve allografts in sensory, mixed, and motor nerve injuries. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. All adult subjects implanted with processed allograft at participating study centers were eligible for registration into the study. Informed consent, as well as any necessary HIPAA consent, was obtained as required by the institutional review boards of the participating sites. Data were collected in an observational manner from available medical records, as each center followed their own standard of care practices with regard to treatment, postoperative procedures, and assessments. Standardized case report forms were used across all centers to collect subject demographics, nerve injury, and repair information, as well as outcome measures from surgeon follow-up notes, occupational, and therapy records. Additionally, graft-related occurrences of adverse experiences or complications reported intra- or postoperatively were collected. All data were entered into a centralized database and assessed by an independent statistician.

At the time of data analysis, the registry database contained graft utilization data from 263 sensory, mixed, and motor nerve injuries with nerve gaps between 5 and 70 mm in the head and neck, torso, and upper and lower extremities. There were 101 sensory nerve injuries reporting follow-up from the utilization data. This dataset was queried for digital nerve injuries with gaps between 5 and 15 mm from subjects completing a minimum of 6 months follow-up and reported quantitative outcome data. Available data were reviewed from the time of repair through last reported follow-up. Descriptive statistics were used to describe the demographics, baseline characteristics, and trends of postimplantation. For continuous parameters (e.g., functional scores), *N*, mean, median, and standard deviations of the mean were recorded. For categorical parameters (e.g., complication rates, adverse events), the frequencies and percentages were also recorded.

Completed outcomes assessments included static and moving two-point discrimination, Semmes-Weinstein monofilament testing, and Medical Research Council Classification (MRCC) scores for sensory function. Outcomes analysis for meaningful recovery was conducted with the Mackinnon modification of the MRCC grading system for sensory recovery.²³ Meaningful recovery was defined to be S3-S4 on the MRCC scale. Further analysis was performed to evaluate for higher levels of recovery, return of two-point discrimination, and touch sensibility. Safety outcomes were reviewed on all nerve repairs to determine rates of complications and adverse experiences (infection, rejection, extrusion, and communicable disease).

Results

Twenty-four subjects, 21 males and 3 females, were identified in the database presenting with 37 digital nerve injuries repaired with processed nerve allograft with a gap between 5 and 15 mm. ► **Fig. 1** shows the nerve distribution of these repairs. The mean \pm SD (minimum, maximum) age was 43 ± 15 years (23, 81) and a mean gap length of 11 ± 3 mm (5, 15). Fifteen subjects reported no pertinent medical conditions that may have affected recovery of nerve function. In the remaining nine subjects, seven had a history of uncontrolled hypertension, one subject reported both hypertension and diabetes, and one subject reported a history of seizures. The majority of the population ($n = 18$) reported no smoking history. The remaining subjects included three current smokers, one previous heavy smoker, and two subjects with an unknown smoking history. Multiple mechanisms of injury were reported. There were 17 saw-related lacerations, 7 sharp-type lacerations, 1 laceration of unknown mechanism, 8 amputations/avulsions, 1 crush-type injuries, 2 gunshot injuries, and 1 injury sustained during a tornado. Concomitant injuries to vessels, tendon, or bone were reported in 28 of the 37 repairs. ► **Table 1** describes the breakdown of concomitant injuries by repair. A majority of subjects were repaired at acute or subacute periods with an average time to repair of 13 ± 41 (0–215) days. All repairs were completed via epineural suture under magnification utilizing an appropriately size-matched processed nerve allograft according to product instructions for use (see ► **Figs. 2** and **3**). The average subject follow-up time was approximately 16 months. The most prevalent quantitative assessment tools utilized were static two-point discrim-

Table 1 Summary of nerve repairs with concomitant injuries

Concomitant Injuries	Nerve repairs
Tendon	2
Vascular	1
Fracture requiring skin grafting	2
Vascular and fracture	1
Tendon and fracture	8
Tendon, vascular, and fracture	13
Tendon, vascular, fracture requiring skin grafting	1
Total	28

ination (s2PD), moving two-point discrimination (m2PD), and Semmes Weinstein monofilaments. Meaningful recovery of S3 or greater was reported in 92% of repairs with 84% reporting recovery at the S3+ or S4 level. ► **Fig. 4** breaks down the distribution of MRCC scores by repair. The average s2PD was 7.1 ± 2.9 (2–15) mm, $n = 19$. The average moving was 6.7 ± 3.3 (2–15) mm, $n = 17$. There were 32 repairs reporting Semmes-Weinstein monofilament (SWMF) outcomes. Return of protective sensation or greater was reported in 29 of 33

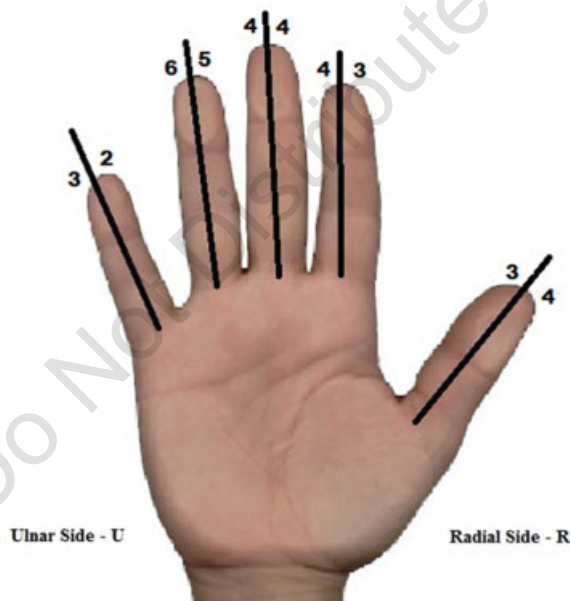


Fig. 1 Each value represents the distribution of nerve repairs performed in each digit on the radial or ulnar side. One repair was a common digital nerve in the fourth web space; therefore, that repair was counted twice, once in the radial nerve in the small finger and once in the ulnar nerve in the ring finger.

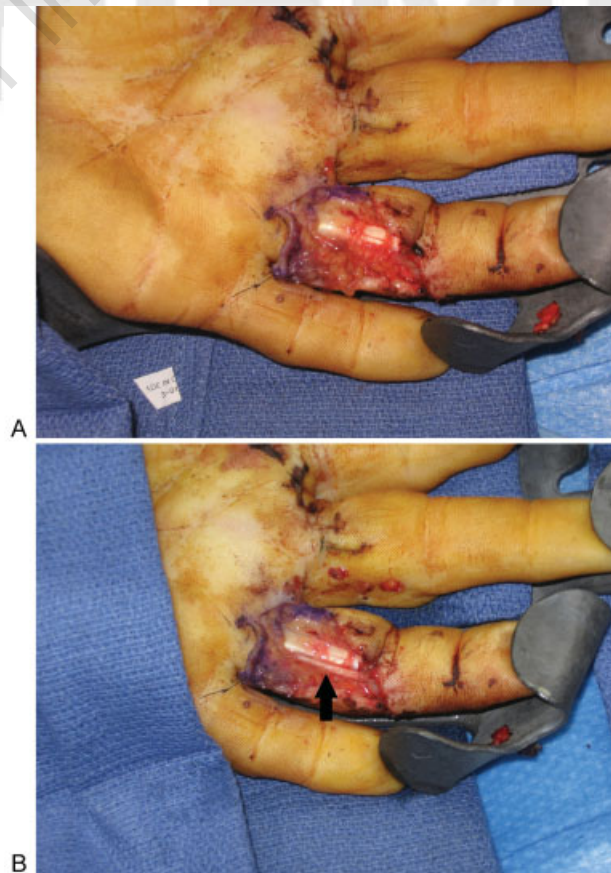


Fig. 2 (A) A 42-year-old man who sustained a table saw injury to the left ring finger. The ulnar digital nerve is severed with a gap length after debridement of 15 mm. (B) Following repair using a processed nerve allograft (black arrow), 2 mm diameter, 15 mm length.

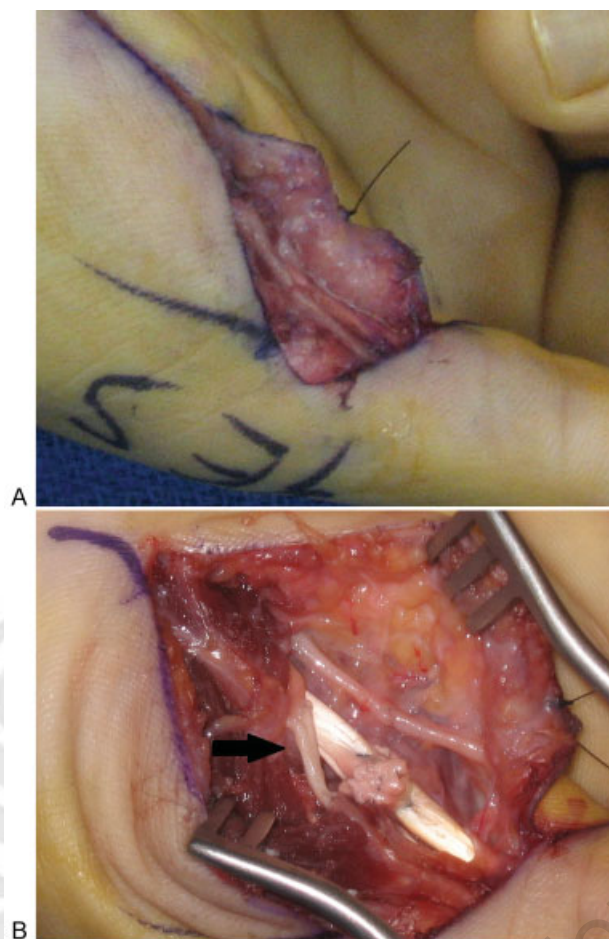


Fig. 3 (A) A 30-year-old man who sustained a deep laceration of the thumb following a fall on a piece of broken glass. The flexor pollicis longus (FPL) tendon is severed and has been retrieved at the wrist pursuant to repair. The ulnar digital nerve is partially cut and the radial digital nerve is severed with a gap length of 10 mm. (B) Following repair of the FPL tendon, direct repair of the ulnar digital nerve, and repair of the radial digital nerve with a processed nerve allograft, 3 mm diameter and 10 mm length.

repairs with light touch and normal sensation returning in 16 and 7 of those repairs, respectively. ▶ **Table 2** stratifies recovery of nerve function by quantitative examinations.

There were no reported implant complications, tissue rejections, or adverse events related to the nerve graft. One subject reported a postoperative infection at the nail bed 1 month after left thumb replantation at the proximal phalanx from a panel saw injury. The infection was resolved with oral antibiotics and was determined to be unrelated to the nerve graft. There were three subjects not reporting recovery to S3 or greater. One amputation and one saw injury recovered to a level of S1 and one 8-month-old crush injury recovered to S2. We found no differences in patient or injury demographics between these patients and patients reporting meaningful recovery.

Discussion

Management of a critical nerve gap has been recognized as a problem since the earliest days of surgical nerve repair, yet

the optimal method of bridging a nerve gap has not been determined. In 1870, Philipeux and Vulpian reported the first experiments with peripheral nerve autografts, noting that the nerve graft could lead to nerve regeneration distally. The landmark work of Bunnell and Huber established nerve autografting as a clinical reality, and by the 1940s, nerve autografts had become the standard repair technique when primary suture was not possible.²⁴ However, the resulting nerve deficiency following autograft harvest can sometimes be problematic. For that reason, nerve allografts have always been an attractive alternative for surgeons treating peripheral nerve lesions. In fact, clinical nerve allografts have a history which exceeds autografts, dating back to 1885 when Albert reported the use of a nerve allograft from an amputated limb to bridge a 3-cm gap in the median nerve following resection of a sarcoma.²⁵ For many years, however, nerve allografts did not gain broad acceptance due to the need for immunomodulatory therapy and the risk of disease transmission.^{26,27} However, these problems have been surmounted with the processed nerve allograft, which has been commercially available in the United States since 2007.^{20–22} Processed nerve allografts have many advantages. They are biocompatible, easy to use, do not require immunosuppression, and avoid a donor site deficit. In the present study, there were no adverse events reported.

The RANGER multicenter registry study was initiated in 2007 to collect utilization and outcome data from the use of processed nerve allografts. It pools data from 18 clinical sites and 36 surgeons spanning a wide range of practice environments, including both urban and rural settings, academic, nonacademic, and military medical centers. It includes a wide spectrum of nerve injury types, locations, and nerve gap ranges. Some early outcomes from the registry have been previously published. Brook et al reported on the first data milestone of the registry and Cho et al reported quantitative outcomes from sensory, mixed, and motor nerve repairs in the upper extremity including a subgroup analysis digital nerve gap repairs, 5 to 40 mm ($n = 35$).^{21,22} Since the time of its publication, additional data were collected from both new and established centers allowing for further subgroup analysis of digital repairs.^{21,22} For the present study, the database was queried for all digital nerve repairs with a gap length between 5 and 15 mm and sufficient follow-up time to allow assessment of recovery. This gap length was chosen because it is a common clinical scenario faced by hand surgeons, and to allow comparison with existing studies on alternative repair techniques.^{4,28–31}

In the present study, meaningful recovery was defined as achieving sensory recovery to the S3 level, or greater, using the Mackinnon modification of the MRCC grading system.²³ Thirty-four of the 37 repairs where quantitative outcomes were reported attained this level. These outcomes were attained despite the high incidence of complex injuries (5 amputations, 2 avulsions, 16 saw, and 2 gunshots), which historically are associated with poorer outcomes. We found these outcomes and those reported in the digital repair subgroup from Cho et al were comparable with meaningful recovery reported at 92 and 89%, respectively. Higher levels of

Distribution of MRCC Sensory Scores of Repairs with Processed Nerve Allograft

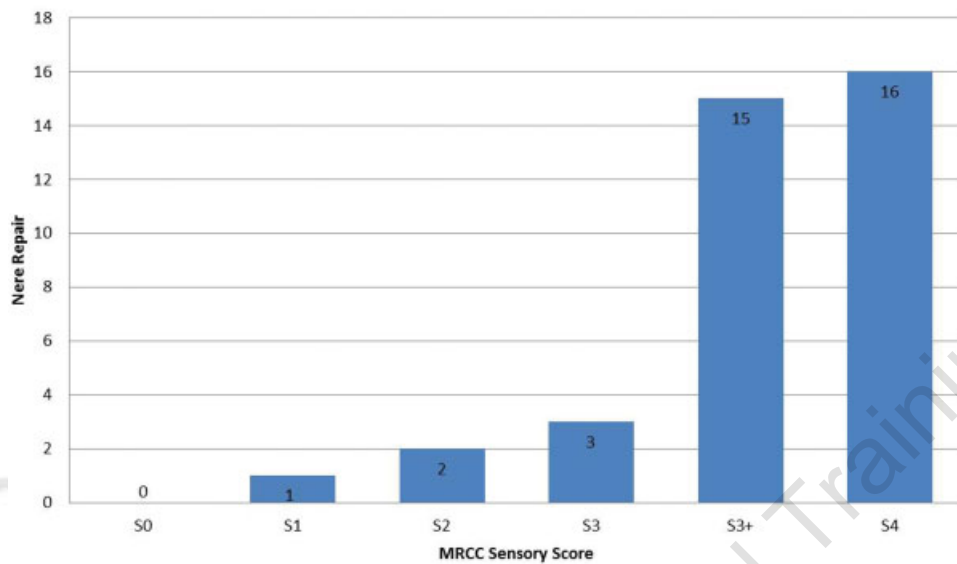


Fig. 4 Distribution of MRCC sensory scores by nerve repair.

sensory recovery were also reported at the S3+ and S4 levels. The S3+ level of recovery is defined as the recovery of pain and touch sensibility with disappearance of over response and good localization of stimulus, with a two-point discrimination ranging from 7 to 15 mm with the S4 level regaining two-point discrimination between 2 and 6 mm. In our study, higher levels of meaningful recovery were achieved in 84% of repairs. The greatest impediment to making meaningful comparisons across retrospective studies is the fact that different methods are employed for measuring recovery. However, several prior studies provide sufficient individual recovery data that MRCC scores can be assigned and a comparison made. Using this analysis, sensory recovery following the repair of short gaps in digital nerves using processed allograft was found to be equivalent to historical results for autografts. Nunley et al, in 1989, published a series of 21 digital nerve gaps repaired with medial antebrachial cutaneous nerve autografts. Recovery of at least 15-mm 2PD was reported in 86% of patients; however, some gaps longer than 15 mm were included.³² Two years later, Frykman and Gramyk reported at least S3+ recovery in 95% of patients in a

series of 73 patients with digital nerve gaps treated with autografting. Again, patients with gap lengths up to 3 cm were included.²⁹ In 1993, Kallio presented a series of 254 digital nerve repairs in 95 patients. Of these, there were eight nerve repairs where autografting was performed for a gap less than 2 cm, all of which achieved sensory recovery to at least the S3+ level.³¹ Repair of digital nerve gaps with synthetic conduits is an attractive option due to the convenience and lack of donor deficit. In general, the rate of recovery in the present study for processed nerve allograft compares favorably to those published for conduits; however, the rates of sensory recovery for conduit repairs have varied widely among the published retrospective studies. See ▶Table 3 for a breakdown of historical literature by recovery criteria. In a multicenter prospective study, Weber et al reported a meaningful recovery rate of 74% in 56 digital nerve repairs using woven PGA conduits with a gap length of less than 25 mm.⁴ Also using PGA conduits, Battiston reported recovery to the S3+ level in 75% of eight patients with a gap length less than 15 mm.³³ Chiriack et al using copolyester poly (DL-lactide-e-caprolactone) tubes (NeuroLac PCL) reported

Table 2 Evaluation of nerve function

Outcome assessment method	Number of patients	Number of repairs	Average gap (mm)	Average follow-up (d)	Repairs reporting S3 or greater
Static two-point discrimination	14	19	12.3 ± 2.9	534 ± 240	19
Moving two-point discrimination	11	17	12.8 ± 2.4	556 ± 252	17
Semmes–Weinstein monofilament	19	32	11.3 ± 3.4	481 ± 225	29

Note: Some subjects completed multiple assessments.

Table 3 Comparisons to historical controls by recovery criteria

Studies reporting meaningful recovery ($\geq S3$)			
Study	Digital nerve gap (mm)	Test article	MRCC $\geq S3$
Our findings	Up to 15 mm, $n = 37$	Avance Nerve Graft	92%
Karabekmez et al 2009	Up to 30mm, $n = 9$	Avance Nerve Graft	100%
Taras et al 2011	Up to 17mm, $n = 22$	NeuraGen Nerve Guide	76%
Chiriac et al 2011	Gaps < 15mm, $n = 15$	NeuroLac PCL tube	36%
Lohmeyer et al 2009	Up to 15mm, $n = 9$	NeuraGen Nerve Guide	100%
Studies reporting higher threshold levels of meaningful recovery ($\geq S3 +$)			
Study	Digital nerve gap (mm)	Test article	MRCC $\geq S3 +$
Our findings	Up to 15 mm, $n = 37$	Avance Nerve Graft	84%
Lohmeyer et al 2014	Mean gap 12 mm, $n = 40$	NeuraGen Nerve Guide	63%
Haug et al 2013	Mean gap 12 mm, $n = 42$	NeuraGen Nerve Guide	40%
Bushnell et al 2008	Up to 20 mm, $n = 9$	NeuraGen Nerve Guide	100%
Battiston et al 2005	Gaps < 15 mm, $n = 8$	Neurotube PGA tube	75%
Weber et al 2000	Mean gap 7 mm, $n = 56$	Neurotube PGA tube	74%

recovery to S3 level in 36% of 15 subjects with gap lengths less than 15 mm.³⁴ For type 1 bovine collagen conduits, retrospective reports have also varied. Bushnell et al, in 2008, reported 100% recovery to the S3+ level in 11 patients with gap lengths less than 20 mm, and Lohmeyer et al reported a 100% in the subset of patients in their study ($n = 9$) with gap lengths less than 15 mm.^{3,35} In 2013, Haug et al reported recovery to S3+ or greater in 40% of digital nerve repairs at an average gap of 12 mm³⁶ and in 2014 Lohmeyer et al reported S3+ or greater in 63% of repairs. Furthermore, Schmauss et al in 2014 found that long-term recovery of sensibility after tubulization was dependent on gap length with better results in repairs less than 10 mm.^{37,38} Reported complications with the conduit include persistent paresthesias, uncomfortable foreign body feeling, wound infection, and product extrusions.^{3-5,39}

In a clinical scenario where a digital gap cannot be directly repaired, 5 mm or greater, the financial implications of different repair modalities should also be considered in the treatment algorithm for short digital sensory nerve defects. Currently, the shortest available nerve allograft is 15 mm in length. While a cost analysis as a data point was not included in the registry, current list pricing in 2014 for a 15 mm for Avance Nerve Graft and a 20-mm collagen tube conduits were comparable at \$1,400 and \$1,470, respectively. The average cost of operating room time, exclusive of anesthesia and surgeon fees, is reported at \$65 to \$166 per minute in 2005 dollars.⁴⁰ In 2011, a procedure similar to the isolation of nerve autograft, the isolation of a vein conduit, was estimated at a \$1,220 at one of the study facilities with no allocation for additional surgical complications.⁵ The additional time required and surgical site necessary to harvest a nerve autograft make nerve allograft a cost-effective alternative source for nerve grafting.

The present study has some limitations. It is retrospective in nature, and subject to selection bias. Specifically,

only patients with sufficient follow-up have been included limiting the sample size. This may tend to select patients with more complex injury patterns or complications, who require long-term follow-up. In addition, the choice of repair technique (processed allograft, autograft, or conduit) was not randomized but was left to the discretion of the treating surgeon and patient. While gap lengths reported in the study are reflective of postresection to healthy fascicular structure, the surgical technique and outcome measurements were not standardized. Despite these limitations, the data obtained from the RANGER registry is valuable, as it represents the first attempt to gather a large array of data regarding usage patterns within a common digital gap range seen in everyday clinical practice to allow for comparisons of outcomes with existing repair methods. Prospective studies are underway which will shed more light on the comparative effectiveness of processed nerve allograft repair and define more clearly their role in peripheral nerve reconstruction.

Conclusion

In a retrospective outcome study, processed nerve allografts performed very well in short-gap reconstructions for digital nerves in the hand. There were no reported adverse events. These outcomes compare favorably to historical data from the literature on nerve autograft and conduits. This study is currently in open enrollment, and continuation of the RANGER registry will provide additional insight into the expanding utility of processed nerve allografts.

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