Functional Outcome Following Nerve Repair in the Upper Extremity Using Processed Nerve Allograft

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Purpose Reconstruction of peripheral nerve discontinuities with processed nerve allograft has become increasingly relevant. The RANGER Study registry was initiated in 2007 to study the use of processed nerve allografts in contemporary clinical practice. We undertook this study to analyze outcomes for upper extremity nerve repairs contained in the registry database.

Methods We identified an upper extremity–specific population within the RANGER Study registry database consisting of 71 nerves repaired with processed nerve allograft. This group was composed of 56 subjects with a mean age of 40 ± 17 years (range, 18–86 y). We analyzed data to determine the safety and efficacy of processed nerve allograft. Quantitative data were available on 51 subjects with 35 sensory, 13 mixed, and 3 motor nerves. The mean gap length was 23 ± 12 mm (range, 5–50 mm). We performed an analysis to evaluate response-to-treatment and to examine sensory and motor recovery according to the international standards for motor and sensory nerve recovery.

Results There were no reported implant complications, tissue rejections, or adverse experiences related to the use of the processed nerve allografts. Overall recovery, S3 or M4 and above, was achieved in 86% of the procedures. Subgroup analysis demonstrated meaningful levels of recovery in sensory, mixed, and motor nerve repairs with graft lengths between 5 and 50 mm. The study also found meaningful levels of recovery in 89% of digital nerve repairs, 75% of median nerve repairs, and 67% of ulnar nerve repairs.

Conclusions Our data suggest that processed nerve allografts offer a safe and effective method of reconstructing peripheral nerve gaps from 5 to 50 mm in length. These outcomes compare favorably with those reported in the literature for nerve autograft, and exceed those reported for tube conduits. *(J Hand Surg 2012;37A:2340–2349. Copyright © 2012 by the American Society for Surgery of the Hand. All rights reserved.)*

Type of study/level of evidence Therapeutic III.

Key words Nerve graft, nerve injury, nerve regeneration, peripheral nerve, processed nerve allograft.

PERIPHERAL NERVE INJURIES are a common consequence of trauma to the upper extremity. If transected, the nerve requires surgical intervention for functional recovery to occur. If transection injuries are not surgically repaired, the patient can be subjected to lifelong disability, pain, and impaired quality of life.[1–3]

The surgical goal of nerve reconstruction is to achieve a tension-free repair. If direct approximation of

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the nerve ends result in increased tension at the repair site, as a result of the extent of trauma or nerve retraction, interpositioning of a nerve graft is recommended to restore continuity. Autologous nerve graft has long been the preferred material to reestablish nerve continuity. This technique results in the creation of a new nerve injury, increased operative time, and the generation of donor site morbidity, and is hampered by limited sources for donor nerves. These constraints have necessitated the development of alternative methods for restoring nerve continuity. Current alternatives in the surgeon's arsenal include hollow tube conduits or grafting with processed nerve allograft.

Hollow tube conduits and autologous vein provide a protective environment that serves as a physical barrier to isolate the nerve from the surrounding tissue and to contain the fluid that seeps from the cut nerve ends. This fluid creates a provisional fibrin matrix that serves as a substrate or rudimentary bridge for the cells and regenerating axons. This mechanism of action results in a relatively disorganized regeneration and has limited the application of conduits to short-gap, noncritical sensory nerve defects or as a coaptation aide for alignment of the nerve.[4,5]

Processed nerve allografts (Avance Nerve Graft; AxoGen, Inc., Alachua, FL) provide decellularized and predegenerated human nerve tissue for the restoration of nerve continuity. These grafts maintain the microarchitecture inherent to nerve tissue, including the physical structure of the epineurium, fascicles, endoneurial tubes, and microvasculature. They are rapidly revascularized and repopulated with host cells and provide a microenvironment conducive to axonal regeneration. Until recently, limited clinical data have been available to establish the role these grafts play in peripheral nerve reconstruction.[6–9]

We initiated the RANGER Study registry in 2007 as a means to collect data on utilization and outcomes from the use of processed nerve allografts for the reconstruction of peripheral nerve defects. This model was designed to provide a source of data and analysis of adult nerve injuries and repairs to establish additional understanding of applications and expected outcomes. The registry includes 12 studies centers. This comprehensive database includes a robust spectrum of nerve types, mechanisms of injury, and injury locations, including head and neck and upper and lower extremities.[10] We undertook this study to analyze the RANGER Study registry database for outcomes from nerve repairs performed in the upper extremity between 2007 and 2010. Here, we report on the experiences from processed nerve allografts repairs of 71 peripheral nerve injuries in the upper extremity.

MATERIALS AND METHODS

Study design

We performed this investigation and the RANGER Study registry in accordance with our institutional review boards and Good Clinical Practices.[11] All consenting adult subjects implanted with the processed allograft were eligible for the study. We used standardized data capture forms to normalize information from the charts of subjects. Chart reviews were completed in a retrospective fashion to collect subject, injury, and repair demographics as well as outcome measures from surgeon, nursing, and therapy records. We collected data for functional outcomes in an observational manner, because each center followed its own standard practices with regard to postoperative care. In addition, we collected information on adverse experience or complications related to the nerve graft (ie, extrusion, infection, tissue rejection, communicable diseases) occurring intraoperatively or postoperatively. All data were entered into a centralized database and assessed by an independent statistician.

We queried the RANGER Study registry database for all nerve repairs in the upper extremity in subjects reporting sufficient outcomes data to assess a response to the treatment. To qualify for this outcomes population, subjects had to have reported follow-up assessments at a time commensurate with the approximated distance for reinnervation, based on estimated 2-mm/day regeneration.

We analyzed this de-identified dataset as a whole and stratified based on predefined criteria for specific nerves and factors that affect recovery outcomes. We used descriptive statistics to describe the demographics, baseline characteristics, and trends of postimplantation. Continuous parameters (eg, functional scores), total number, mean, median, and standard deviations (SDs) of the mean were recorded. We also recorded categorical parameters (eg, complication rates, adverse events), frequencies, and percentages. We performed chi-square analysis to determine whether there were statistical differences between this group and the study population as a whole.

Study population

We identified a population of 56 subjects in the database presenting with 71 nerves repaired with processed nerve allograft in the upper extremities. This group was composed of 39 men (70%) and 17 women with a mean ± SD age of 40 ± 17 years (range, 18–86 y) and

TABLE 1. Comparison of Outcomes Population With Registry Database

Demographic/Attribute	Outcomes Population (%)	Registry Database (%)
Sex		
Male	70	77
Female	30	23
Age (y):		
18–29	33	39
30–49	39	36
≥ 50	28	25
Time to repair		
Within 3 mo	65	68
After 3 mo	35	32
Concomitant injury		
Yes	69	71
No	31	29

TABLE 2. Nerves Repaired in the Upper Extremity Population

Nerve	Upper Extremity Population
Digital	48
Median	10
Ulnar	6
Radial	2
Palmar cutaneous	1
Musculocutaneous	1
Spinal accessory	1
Axillary nerve	1
Ulnar nerve motor branch	1
Total repairs	71

a mean gap length of 22 ± 11 mm (range, 5–50 mm). Table 1 summarizes the outcomes population studied compared with the entire RANGER Study registry. This population was not statically different from the entire study population. Most repairs were sensory nerves in the hand (69%), with nerves of the forearm accounting for 27% and nerves of the upper arm and shoulder accounting for 4%. Table 2 details the nerves treated in the outcomes population studied. Multiple mechanisms of injury were reported. Lacerations accounted for 68% of the lesions.

We evaluated subject health and smoking history: 93% of the subjects reported no major underlying diseases that may have affected recovery of nerve function. In the remaining subjects, 6 had a history of uncontrolled hypertension and 1 had a history of peripheral neuropathy. Six subjects reported a history of smoking. We observed no demographic or outcome differences between smokers and nonsmokers.

Surgical technique

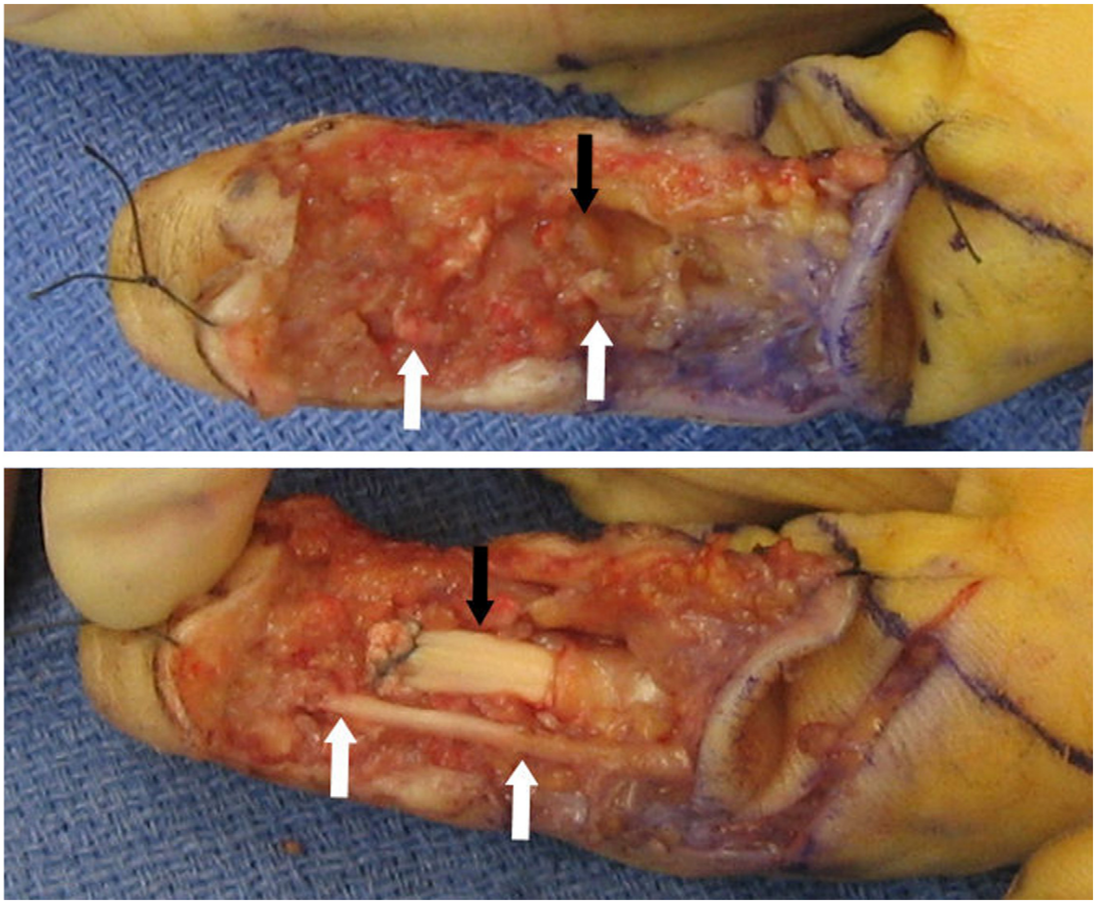
This study did not mandate or require specific surgical techniques. Centers included level 1 trauma, academic, military treatment facilities, community, and ambulatory medical centers that performed nerve repair using processed nerve allografts. All repairs were done under loupe or microscopic magnification, depending on the surgeon's preference and size of nerve involved. Various repair techniques were used, of which epineural sutures were the most predominant (65% of all repairs), followed by group fascicular repair cabling. Most repairs used nylon sutures (74%) with the preferred size of 8-0 or 9-0. In 9 cases, sealants or wraps were used to aid the neurorrhaphy. A total of 69% of subjects had concomitant injuries to vessels, tendon, or bone in the affected area. Figure 1 illustrates the repair of a digital nerve with processed nerve allograft.

Outcomes analysis

Collected outcomes data varied because follow-up measures were based on institutions' standard of care. We conducted an analysis for improvement in nerve function using the sign test to compare reported response relative to baseline for each subject.[12] Quantitative data included static and moving 2-point discrimination, Semmes–Weinstein monofilament testing, range of motion, strength testing, and Medical Research Council Classification (MRCC) scores for sensory and motor function. Qualitative data included pain and subject's or physician's subjective assessments of improvement in function.

We conducted an efficacy analysis for meaningful recovery for subjects providing quantitative data with the Mackinnon modification of the MRCC grading system[2] for sensory and motor recovery. To ensure consistency with most of the relevant literature, meaningful functional recovery was defined as S3–S4 or M3–M5 on the MRCC scale. We analyzed demographics and outcomes for the 3 most commonly treated nerve injuries using descriptive statistics.

We performed further stratification for subgroup analysis to evaluate the level of meaningful recovery for critical factors such as nerve function and nerve gap



A

B

FIGURE 1: A Avulsion injury to the left index finger with soft tissue deficit, tendon (black arrow), and radial digital nerve injury (white arrows). **B** Reconstruction of the radial digital nerve with processed nerve allograft 18-mm long (white arrows) and flexor tendon with tendon graft (black arrow). The wound was then covered with a cross-finger flap.

length. We evaluated statistical significance between subgroups using Fisher's exact test; $P < .05$ was considered significant. We conducted safety analysis on all nerve repairs to determine rates of complications and adverse experiences (infection, rejection, extrusion, and communicable disease). Available data were reviewed from the time of repair through last reported follow-up for incident of adverse events, complications, and revisions.

RESULTS

We conducted an analysis for improvement in nerve function for all subjects based on the last reported follow-up visit. We observed improvement in sensory or motor function in 89% of repairs. There were no reported implant complications, tissue rejections, or adverse events related to the use of the processed nerve allografts. Four injuries (6%) underwent revision. Upon reexploration, 2 subjects had foreign bodies (ie, glass fragments) remaining in the wound bed and 2 subjects reported previously unidentified injuries proximal to the original injury. The surgeon determined these cases to be a technical failure caused by inappreciable internal nerve damage from the original injury.

Of the 71 injuries 51 (35 sensory nerves, 13 mixed nerves, and 3 motor nerves) had quantitative follow-up data suitable for outcomes analysis. Positive qualitative data were reported for 16 of the 20 injuries; however, we excluded these from this analysis because their reported follow-up data were reported as subjective assessments of function. The gap length (mean ± SD [range]) was 23 ± 12 mm (5–50 mm). Overall recovery to S3 or M3 or better was achieved in 86% of these repairs. Table 3 lists the demographic characteristics of subjects in this population. When considering return of sensory functionality to the hand from both sensory (n = 35) and mixed nerves (n = 9) reporting quantitative sensory outcomes, 85% of repairs returned meaningful levels of recovery. The mean static and moving 2-point discriminations reported were both 8 mm (range, 4–15 mm) for the composite sensory results. Return to diminished light touch or better, via Semmes

TABLE 3. Demographics and Outcomes for Subgroup Analysis

Factor	n	Age (y)	Preoperative Interval (d)	Follow-Up (d)	Gap (mm)	Sensory	Mixed	Motor	Complex[a]	Lacerations	Neuromas	Meaningful Recovery[b]
Repairs reporting quantitative data	51	44 ± 16 (18–70)	196 ± 313 (0–1,460)	296 ± 160 (40–717)	23 ± 12 (5, 50)	35	13	3	10	33	8	86%
Nerve function												
Sensory	44[c]	42 ± 15	205 ± 327	300 ± 166	22 ± 11	35	9		9	28	7	86%
Motor	15[d]	39 ± 19	206 ± 245	276 ± 105	32 ± 13		12	3	4	9	2	80%
Gap length (mm)												
5–14	12	47 ± 16	31 ± 49	298 ± 200		10	1	1	2	10	0	100%
15–29	19	42 ± 16	212 ± 390	349 ± 203		16	2	1	4	14	1	74%
30–50	20	42 ± 16	274 ± 296	269 ± 97		9	10	1	4	9	7	90%

[a]Complex mechanisms include amputations, avulsions, and blast injuries.
[b]Meaningful recovery is defined as S3-S4 or M3-M5 on the MRCC scale.
[c]Inclusive of sensory and mixed nerve repairs reporting sensory functional outcomes.
[d]Inclusive of motor and mixed nerve repairs reporting motor functional outcomes.

Weinstein monofilament testing, was reported in 13 of 17 nerve repairs (14 subjects). We evaluated return of motor function for motor (n = 3) and mixed nerve repairs reporting quantitative motor outcomes. Meaningful levels of recovery, defined as M3 or greater, were reported in 80% of these repairs. Electromyography results were also available for 2 of the 3 motor repairs, both of which found successful signs of reinnervation to the target muscle. This was reported in a spinal accessory nerve with a 12-mm gap and a biceps branch of the musculocutaneous nerve with a gap of 15 mm. Figure 2 provides a breakdown of MRCC scores for sensory and motor function. Table 3 provides demographics and outcomes of repairs by nerve function.

Evaluation of outcomes for the 3 most commonly repaired nerves—digital, median, and ulnar—showed that meaningful recovery was reported in 31 of 35 digital nerve repairs (89%), in 6 of 8 median nerve repairs (75%), and in 2 of 3 ulnar nerve repairs (67%). Table 4 provides demographics and outcomes for these specific nerves.

We stratified reported outcomes by nerve gap length into 3 categories (5–14 mm, 15–29 mm, and 30–50 mm) and based them on product code lengths. For nerve gaps under 15 mm, 100% demonstrated meaningful recovery. In gaps between 15 and 29 mm, meaningful recovery was demonstrated in 74% of repairs, and in the long gap group, 90% demonstrated meaningful recovery. When adjusted for known technical failures, the 15- to 29-mm group returned a meaningful recovery rate of 82%. Figure 3 lists the reported MRCC scores by gap length.

DISCUSSION

As an alternative to the classic nerve autograft or hollow tube conduit, nerve allografts provide organized microarchitecture, extracellular matrix constituents, and handling qualities of nerve autograft with the benefit and convenience of an off-the-shelf graft.[13,14] In 1885, Albert[15] described nerve gap reconstitution with whole allograft nerve. Although the concept remained attractive, it was hampered by the need to mitigate the patient's immune response.[13,14] The advent of tissue engineering has since translated the processed nerve allograft into a viable off-the-shelf clinical option.[6–8,10] The Avance processing method (AxoGen Inc, Alachua, FL) for nerve allograft tissue was characterized in animal models using the human process on animal tissues. These studies found that outcomes compared favorably with nerve isograft[16] and were superior to those of tube conduit.[17–19]

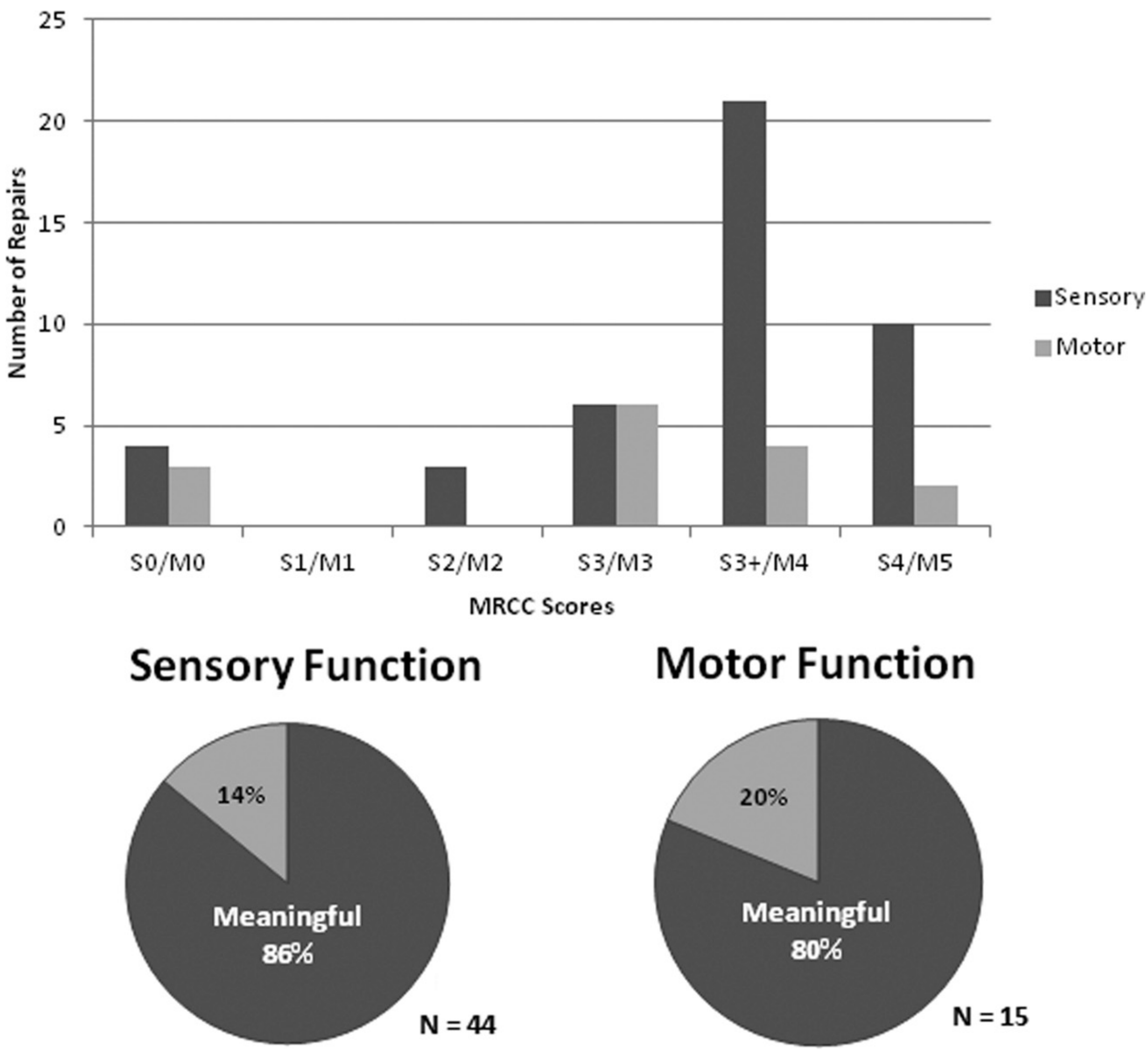


FIGURE 2: Functional sensory and motor outcomes groups expressed by MRCC scores for the outcomes population reporting quantitative measures. Pie charts represent the percentage of subjects reporting meaningful recovery in each group. Bar charts represent the distribution of all MRCC scores for each group. We observed no significant difference ($P > .05$) between groups with $P = .68$.

In the 1920s, the efforts of Huber and Bunnell established nerve autografting as the standard technique for peripheral nerve gap repair. Further understanding of nerve anatomy and microsurgical techniques from the works of Sunderland, Millesi, and Buncke advanced this technique.[20] Despite these advances, meaningful outcomes were often disappointing. For digital nerves repaired with autograft, Kallio[21] reported meaningful recovery in 58 of 103 repairs (56%), whereas Frykman and Gramyk[22] reported an 80% recovery rate. For median and ulnar nerve repairs, Kim et al[23,24] reported on a small number of autograft repairs in more than 30 years of experience, where they observed meaningful recovery in 9 of 15 median nerves (67%) and 4 of 7 ulnar nerves (57%). In larger meta-analyses, Brushart[20] reported meaningful outcomes in 60% of median and ulnar nerve repairs, whereas Frykman and Gramyk found that 80% of median nerves and 60% of ulnar nerves repaired with autograft returned meaningful recovery. Our study found results for processed nerve allografts to be similar to those reported in these studies of autograft, with meaningful recovery observed in 89% of digital nerve repairs (n = 35), 75% of median nerve repairs (n = 8), and 67% of ulnar nerve repairs (n = 3). Continuation of this registry will allow for the inclusion of additional repairs to provide further com-

TABLE 4. Summary of Results of Most Repaired Nerves in the Upper Extremity Reporting Quantitative Data

Factor	n	Age (y)	Preoperative Interval (d)	Follow-Up (d)	Gap (mm)	Complex[a]	Lacerations	Neuromas	Meaningful Recovery[b]
Digital nerves	35	46 ± 14 (23–68)	190 ± 349 (0–1,460)	306 ± 184 (40–717)	19 ± 9 (5–40)	5	24	6	31 of 35 (89%)
Median nerve	8	28.2 ± 7 (20–38)	369 ± 278 (14–725)	230.5 ± 111 (131–442)	33 ± 13 (10–50)	2	4	2	6 of 8 (75%)
Ulnar nerve	3	42 ± 24 (25–70)	27 ± 38 (3–71)	323 ± 54 (270–378)	27 ± 6 (20–30)	2	1	0	2 of 3 (67%)

[a]Complex mechanisms include amputations, avulsions, and blast injuries.
[b]Meaningful recovery is defined as S3-S4 or M3-M5 on the MRCC scale.

parisons between processed nerve allografts and autografts.

Weber et al[25] examined outcomes for tube conduits in digital nerve repairs and found good to excellent outcomes (defined as S3+ to S4) in 91% of the repairs at gaps 4 mm or smaller, whereas they observed good to excellent recovery in gaps between 5 and 25 mm in 67% of repairs. Lohmeyer and colleagues[5] found that 75% of collagen tube conduit repairs provided meaningful recovery; however, all patients with nerve gaps over 15 mm failed to recover sensation. Wangensteen and Kalliainen[4] reported on 126 collagen tube conduits and found that although they were safe to use throughout the body, recovery of static 2-point discrimination was observed in only 24% of repairs. Tube conduits in mixed nerve injuries have been shown to be effective as coaptation aids for gaps less than 5 mm[26]; however their use in longer gaps has not been recommended.[5] A recent study in mixed nerves found 1 in 12 tube conduits provided functional recovery in gaps between 2 and 25 mm.[27] In addition, complication rates ranged from 8% to 35%, with the most common adverse events being extrusion of the conduit or formation of a fistula.[4,25,27–31] Our study found that processed nerve allograft returned a higher level of meaningful recovery compared with the published literature, using comparable outcomes parameters for tube conduits and without their observed complications. Table 5 contains a representative selection of comparable published literature for both autograft and tube conduits.

To allow for historical control comparisons of outcomes from conduit and autograft repairs, we set the criteria for meaningful recovery, S3-S4 or M3-M5 on the MRCC scale, according to what most of the literature has used to categorize successful outcomes. If processed nerve allografts are held to a higher standard, greater than or equal to S3+ (recovery of 2-point discrimination) or greater than or equal to M4 (movement against gravity and some resistance), the percentage of repairs reporting outcomes at these levels is 76% in sensory nerves, 54% in mixed nerves, and 71% in motor nerve repairs. Comparisons from the literature reporting to this level include Weber et al,[25] who reported a 67% success rate with conduits in gaps over 5 mm, and Ruijs et al,[32] who reported a 52% success rate in motor outcomes from mixed nerve repairs.

This study has the same limitations as other observational studies in peripheral nerve. In general, these studies exhibit an increased risk of heterogeneity in the datasets; variability among subjects, injuries, surgical technique, surgeons and centers; attrition; and multiple data sources. To mitigate these risks, we implemented

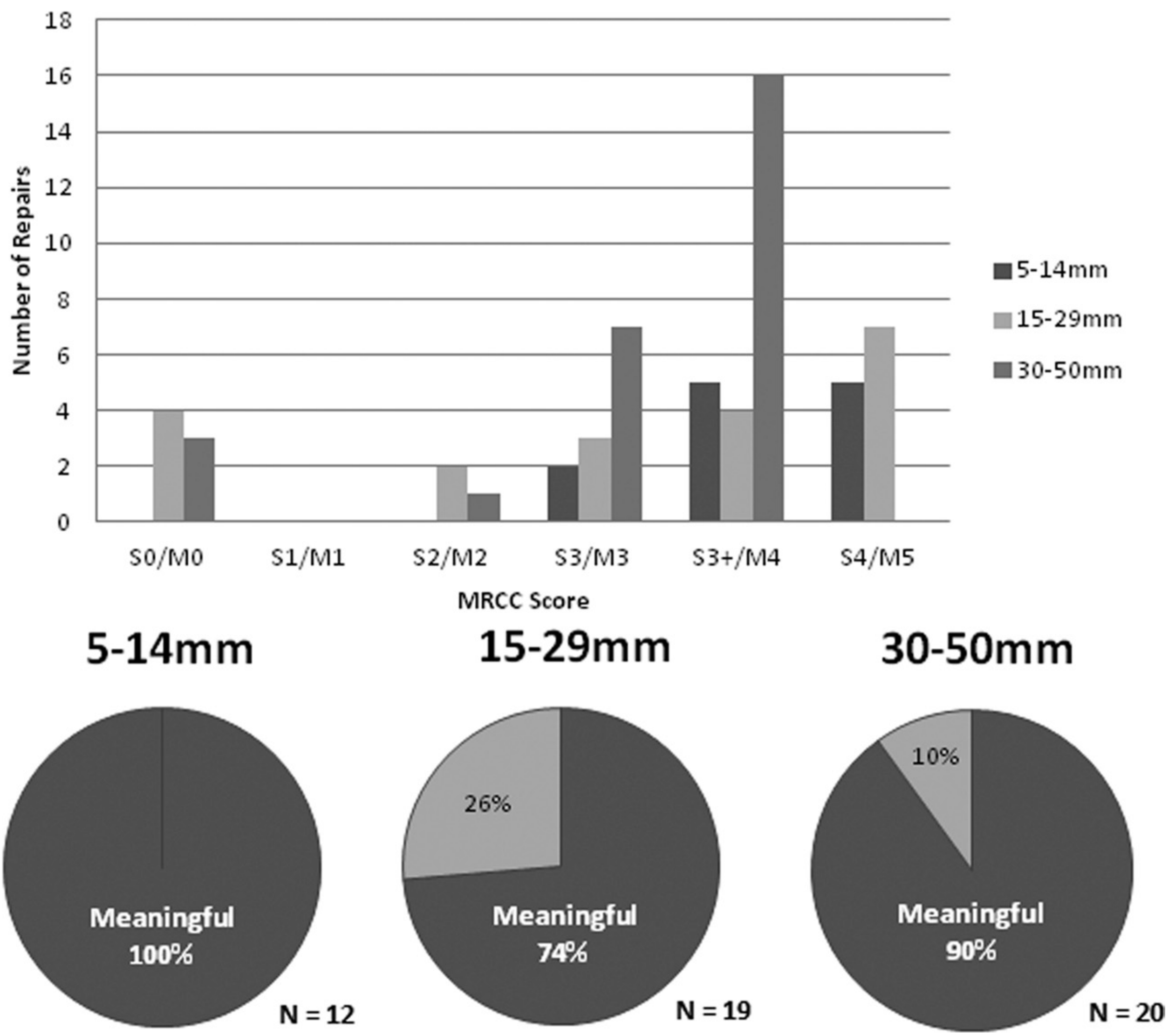


FIGURE 3: Functional sensory and motor outcomes by gap length groups expressed by MRCC scores for the outcomes population reporting quantitative measures. Pie charts represent the percentage of subjects reporting meaningful recovery in each group. Bar charts represent the distribution of all MRCC scores for each group. We observed no significant difference ($P > .05$) among groups: gaps 5 to 14 mm and 15 to 30 mm, $P = .13$; gaps 5 to 14 mm and 30 to 50 mm, $P = .51$; and gaps 15 to 29 mm and 30 to 50 mm, $P = .24$.

several strategies during study planning, enrollment, and data analysis. To improve consistency, limit reporting errors, and allow for uniform data collection, we used comprehensive standardized case report forms across all centers to capture injuries and outcomes. We homogenized data using predefined criteria, and an independent biostatistician completed analysis. In addition, lack of quantitative measurements in 28% of the outcomes population could have potentially affected the meaningful recovery outcome percentages. Benefits of this study model include its multicenter, multisurgeon, multidisciplinary approach and the ability to gather evidence on a representative cross section of injuries typically treated by hand surgeons as well as less common nerve injuries and mechanisms, such as the musculocutaneous nerve or blast injuries.

Results of subgroup analysis demonstrated that processed nerve allografts performed consistently well. Although we observed a slightly higher rate of meaningful recovery with sensory function than with motor function, we observed no significant difference ($P = .68$). Of note, all subjects with processed nerve allografts under 15 mm obtained meaningful levels of recovery. Although not statistically significant,

TABLE 5. Comparison With Historical Reference Literature

Study	n	Gap (mm)	Nerve Injury	Repair Technique	Positive Outcomes[a]
Kallio[21]	77	< 50	Digital	Autograft	60%
Frykman and Gramyk[22]	141	< 50	Digital	Autograft	88%
Kim et al[23]	15		Median	Autograft	67%
Kim et al[24]	7		Ulnar	Autograft	57%
Frykman and Gramyk[22]			Median	Autograft	80%
Frykman and Gramyk[22]			Ulnar	Autograft	60%
Vastamäki et al[33]	14	≤ 35	Ulnar	Autograft	57%
Lohmeyer et al[5]	12	5–18	Digital	NeuraGen[b] type 1 bovine collagen tube	75%
Wangensteen and Kalliainen[4]	64	3–25	Digital and mixed	NeuraGen[b] type 1 bovine collagen tube	43%
Chirac et al[27]	16	2–25	Digital	Neurolac[c] copolyester poly(DL-lactide-ε-caprolactone) tube	44%
Chirac et al[27]	12	2–25	Median and ulnar	Neurolac[c] copolyester poly(DL-lactide-ε-caprolactone) tube	8%

[a]As reported, based on individual study parameters for acceptable recovery: M3-M5 and S3-S4 by MRCC.
[b]Integra LifeSciences, Plainsboro, NJ.
[c]Polyganics; Groningen, Netherlands.

we noted slightly lower response rates in the 15- to 29-mm gap length group (74%). This difference may be attributable to the revision of known technical failures unrelated to the graft in this group (11% in this group vs 6% overall).

Continuation of the registry will allow for increased enrollment, longer-term follow-up from current subjects, and the addition of more study centers, and will provide further evidence for the role of processed nerve allografts in peripheral nerve repair.

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