PROCESSED NERVE ALLOGRAFTS FOR PERIPHERAL NERVE RECONSTRUCTION: A MULTICENTER STUDY OF UTILIZATION AND OUTCOMES IN SENSORY, MIXED, AND MOTOR NERVE RECONSTRUCTIONS

DARRELL N. BROOKS, M.D.,[1*] RENATA V. WEBER, M.D.,[2] JEROME J. CHAO, M.D.,[3] BRIAN D. RINKER, M.D.,[4] JOZEF ZOLDOS, M.D,[5] MICHAEL R. ROBICHAUX, M.D.,[6] SEBASTIAN B. RUGGERI, M.D.,[7] KURT A. ANDERSON, M.D.,[8] EKKEHARD E. BONATZ, M.D., PH.D.,[9] SCOTT M. WISOTSKY, M.D.,[10] MICKEY S. CHO, M.D.,[11] CHRISTOPHER WILSON, M.D.,[11] ELLIS O. COOPER, M.D.,[11] JOHN V. INGARI, M.D.,[12] BAUBACK SAFA, M.D.,[13] BRIAN M. PARRETT, M.D.,[13] and GREGORY M. BUNCKE, M.D.[13]

Purpose: As alternatives to autograft become more conventional, clinical outcomes data on their effectiveness in restoring meaningful function is essential. In this study we report on the outcomes from a multicenter study on processed nerve allografts (Avance® Nerve Graft, AxoGen, Inc). *Patients and Methods:* Twelve sites with 25 surgeons contributed data from 132 individual nerve injuries. Data was analyzed to determine the safety and efficacy of the nerve allograft. Sufficient data for efficacy analysis were reported in 76 injuries (49 sensory, 18 mixed, and 9 motor nerves). The mean age was 41 ± 17 (18–86) years. The mean graft length was 22 ± 11 (5–50) mm. Subgroup analysis was performed to determine the relationship to factors known to influence outcomes of nerve repair such as nerve type, gap length, patient age, time to repair, age of injury, and mechanism of injury. *Results:* Meaningful recovery was reported in 87% of the repairs reporting quantitative data. Subgroup analysis demonstrated consistency, showing no significant differences with regard to recovery outcomes between the groups ($P > 0.05$ Fisher's Exact Test). No graft related adverse experiences were reported and a 5% revision rate was observed. *Conclusion:* Processed nerve allografts performed well and were found to be safe and effective in sensory, mixed and motor nerve defects between 5 and 50 mm. The outcomes for safety and meaningful recovery observed in this study compare favorably to those reported in the literature for nerve autograft and are higher than those reported for nerve conduits. © 2011 Wiley Periodicals, Inc. Microsurgery 00:000–000, 2011.

Severe nerve injuries frequently result in motor and sensory deficits with life altering outcomes for patients. The reconstruction of segmental loss after trauma or resection poses a significant surgical challenge. Continuity of the damaged nerve must be restored after transection or avulsion injuries to permit regeneration and axonal reinnervation into distal motor and sensory end-organs. Traditionally, in cases where a secure and tension free end to end nerve coaptation is not possible, a segment of another healthy nerve from a less critical area of the patient is sacrificed to provide the missing tissue. This autograft tissue serves as a bridge, providing a three dimensional physical environment to guide and support the regenerating axons across the deficit.[1] While the benefits of the nerve architecture and microenvironment in an autograft are well established,[1–8] the harvesting and subsequent donor site morbidity leads to functional loss as well as an increased risk of scarring, symptomatic neuroma formation, additional anesthesia time, and higher facility costs associated with a second surgical site.[9] Even with these risks, the potential for functional recovery in a critical area often outweighs the risks involved with harvest of the donor nerve.[1]

Extensive research efforts have focused on identifying alternatives to the classical nerve autograft. Processed nerve allografts have shown promise in numerous animal studies and in early clinical explorations.[10–16] While processed nerve allografts are acellular, they contain many of the beneficial characteristics of the nerve autograft, such as physical macrostructures, three dimensional microstructural scaffolding and protein components inherent to nerve tissue.[2,5,6,12,17–19] Commercially available processed nerve allografts (Avance® Nerve Graft, AxoGen) are manufactured from donated human peripheral nerve tissue. The tissue is detergent processed to selectively remove cellular components and debris, pre-wallerian degenerated to cleave growth inhibitors and then terminally sterilized.

[1]The Buncke Clinic; San Francisco, CA, USA
[2]Department of Plastic and Reconstructive Microsurgery, Montefiore Medical Center, Albert Einstein College of Medicine; Bronx, NY, USA
[3]Department of Plastic Surgery, Albany Medical Center; Albany, NY, USA
[4]Division of Plastic Surgery, University of Kentucky; Lexington, KY, USA
[5]Arizona Center for Hand Surgery; Phoenix, AZ, USA
[6]Baton Rouge Orthopaedic Clinic; Baton Rouge, LA, USA
[7]Affiliated Arm, Shoulder and Hand Clinic; Phoenix, AZ, USA
[8]Orthopaedic Specialty Clinic of Spokane; Spokane, WA, USA
[9]Southlake Orthopaedics; Birmingham, AL, USA
[10]Tampa Bay Orthopaedic Specialists; Pinellas Park, FL, USA
[11]Department of Orthopaedics & Rehabilitation, Brooke Army Medical Center; Fort Sam Houston, TX, USA
[12]The San Antonio Hand Center; San Antonio, TX, USA
[13]The Buncke Clinic; San Francisco, CA, USA

Grant sponsor: AxoGen, Inc.; Alachua, FL

*Correspondence to: Darrell N. Brooks, M.D., The Buncke Clinic, 45 Castro St. Ste 121, San Francisco, CA 94114. E-mail: Rangerstudy@gmail.com

Received 19 September 2011; Revision accepted 5 October 2011; Accepted 6 October 2011
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/micr.20975

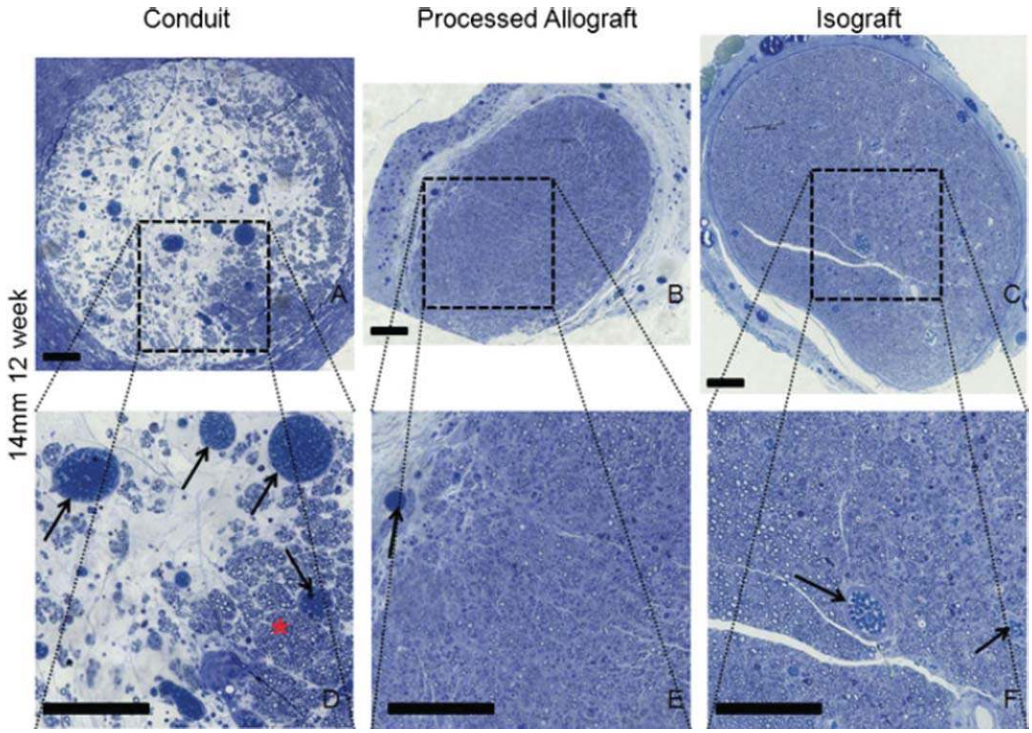

Figure 1. Excerpt from Johnson et al, Journal of Reconstructive Microsurgery. Histological cross sections of midgraft regenerating nerve from the 14-mm 12-week study. The figure shows representative micrographs from conduits in the 14-mm group (A, 10x and D, 20x), processed allografts from the 14-mm group (B, 10x and E, 20x), and isografts from the 14-mm group (C, 10x and F, 20x). Scale bar represents 100 mm. Red asterisk indicates a portion of the clustering fibers seen in the conduit groups (D). Black arrows indicate blood vessels found in the lumen of the conduits and in the interior of the processed allograft and isografts. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Animal studies have compared processed nerve allograft to both nerve isograft and collagen nerve tubes. The processed nerve tissue was found to be similar to isograft and superior to collagen tubes. One study found that the processed allograft supported a statistically superior number of myelinated fibers at the midgraft and distal nerve in a rat sciatic nerve model at 14- and 28-mm nerve gap.[10] In a subsequent study examining nerve fiber density, it was found that the processed nerve allograft and isograft had nerve fibers evenly distributed across the cross section of the nerve.[5] This was superior to collagen nerve conduit, whose regeneration was found to be sparse and irregularly clustered through-out the cross section, see Figure 1 an excerpt from Johnson et al.[5]

Early clinical studies have shown that processed nerve allografts are safe and effective in sensory nerves up to 30 mm.[12,14] Mayo Clinic published on 10 nerve injuries and found that all ten subjects recovered two-point discrimination of 6 mm or better.[12]

To date there are no comprehensive clinical studies published in the literature on the utilization and efficacy outcomes for processed nerve allografts in sensory, mixed and motor nerve injuries. Here we report our findings from a multicenter, retrospective study evaluating the utilization, safety, and efficacy outcomes of a processed human nerve allograft (Avance® Nerve Graft, AxoGen).

MATERIALS AND METHODS

Patient Population

Between 2007 and 2010, 12 centers were identified with a potential population of 123 subjects treated with processed nerve allograft. IRB approval was obtained and 108 adult subjects presenting with 132 nerve repairs were enrolled in the study. All repairs were performed by experienced plastic or orthopedic surgeons who at a minimum completed a fellowship in hand or hand and microsurgery. Study centers followed their own standard of care for subject treatment, rehabilitation regime, and follow-up measures. To capture clinical experience in a diverse population of injuries, eligibility criteria were nonrestrictive with the exception of subjects less than 18 years of age and subjects who did not provide consent. All adult subjects treated with processed nerve allografts were open to participate in the study. Chart reviews were completed in a retrospective fashion to collect subject, injury and repair demographics. Follow-up data points for safety and functional outcomes were

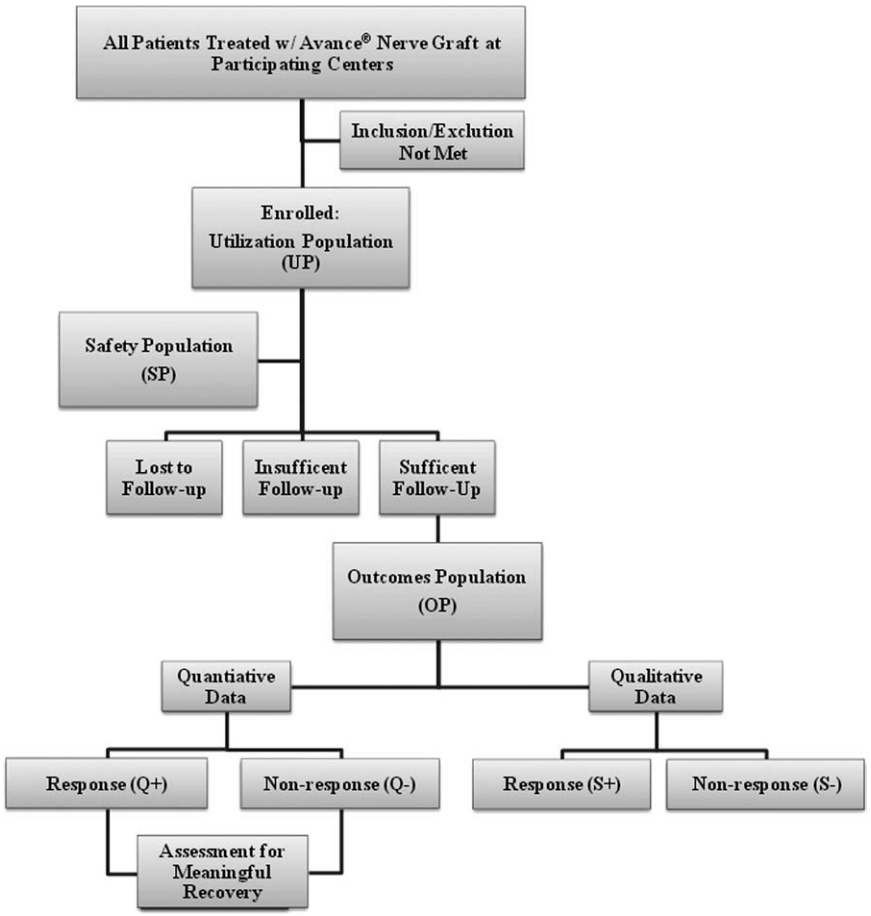

Figure 2. Subject population schema.

Table 1. Population Summary

Follow-up status	IFU	LFU	SFU	Total
Subjects	34 (31%)	15 (14%)	59 (55%)	108
Repairs	37 (28%)	19 (14%)	76 (58%)	132
Adverse events related to the nerve graft	0	0	0	0

IFU, insufficient follow-up; LFU, lost to follow-up; SFU, sufficient follow-up.

collected in an observational manner and are described in the Clinical Evaluation section below. Data was segregated to perform population analysis for utilization, safety, and efficacy outcomes. Figure 2 is a graphical representation of this distribution.

The total population (Utilization Population, UP) in the study was comprised of 83 males (77%) and 25 females (23%). The mean ± SD (minimum, maximum) age is 38 ± 16 (18–86). Leading up to surgical repair, the mean preoperative interval is 163 ± 331 (0–2,461) days. Two of the subjects had a preoperative interval of 2,461 and 1,460 days, accounting for the degree variability in the preoperative interval. The mean graft length was 27 ± 14 (5–50) mm.

Subjects who provided sufficient follow-up assessments (SFU) to evaluate functional outcomes were placed into the Outcomes Population (OP). To qualify for this population, subjects had to have reported follow-up assessments at a time-point commiserate with the approximated distance for reinnervation, based on estimated 2 mm/day regeneration. The OP consisted of 59 subjects with 76 nerve repairs. There are 42 males (72%) and 17 females (28%). The rest of the subjects either had data that was Insufficient Follow-Up (IFU) or Lost to Follow-Up (LFU). Table 1 summarizes the total study population by follow up status, number and incidence of repairs. Table 2 details the nerves treated in the UP and OP. Demographic characteristics of subjects in the OP are summarized in Table 3. The mean age of subjects in the OP is 41 ± 17 (18 to 86) years. Prior to surgery, the subjects had a mean preoperative interval of 172 ± 283 (0–1,460) days. One subject had a preoperative interval of 1,460 days which contributed to the degree of variability.

The mechanism of injury for subjects in the OP was distributed throughout many categories with blunt saw-like lacerations having the greatest incidence, 29% of all

Table 2. Nerves Repaired by Population

Nerve	Utilization population	Outcomes population
Digital	73	48
Median	22	11
Ulnar	15	6
Radial	4	2
Peroneal	5	2
Musculocutaneous	1	1
Anterior interosseous	1	0
Facial	3	3
Tibial	2	0
Sciatic	1	0
Spinal Accessory	2	1
Posterior Interosseous	1	0
Axillary nerve	1	1
Ulnar nerve motor branch	1	1
Total Repairs	132	76

the nerve repairs. The majority of the repairs were digital nerves in the hand (60%) and upper extremity nerves (32%). A smaller number occurred in the head/neck region (5%), and the lower extremities (3%). Table 4 provides a breakdown of mechanism of injury by nerve type for the Outcome Population.

Overall subjects in the OP were considered healthy with 88% of the subjects reporting no significant underlying diseases. In the remaining 12% of the subjects reporting an underlying health issue that could be a contributing factor to the overall outcome, six had a history of uncontrolled hypertension and one had a history of peripheral neuropathy. Only 10 subjects reported a history of prior or current smoking. The remainder either reported being a nonsmoker or did not indicate a smoking history. No demographic or outcome differences were observed between smokers and nonsmokers. An analysis of the demographics between subject, injury and repair found the Outcomes Population to be comparable to the Utilization Population, as seen in Table 5. This indicates the Outcome Population is representative of the entire population in this study to date.

Surgical Technique

Centers enrolling subjects in the study included Level 1 trauma centers, academic medical centers, military medical centers, community medical centers and ambulatory surgical centers that actively performed nerve repair utilizing processed nerve allografts (Avance® Nerve Graft). This study did not mandate or require specific surgical techniques. Information regarding the extent of injury, repair type, graft sizes, suture size and placements, adjunct repair aides (i.e., wraps, sealants, glues) and concomitant injuries was collected on standardized case report forms (CRFs) for each subject.

In the Outcomes Population, various repair techniques were utilized with epineural sutures being the most predominant (66% of all repairs) followed by group fascicular repair (cabling). The majority of the repairs used nylon sutures (74%) with the preferred size of an 8–0 or 9–0. In the majority of the cases (75%), no sealant or wrap was used. In 11% of the cases an anastomatic cuff or wrap was utilized as a coaptation aid. Sixty-four percent of the subjects had other concomitant injuries, such as vascular, tendon, or bony injuries, in the affected area. Figure 3 is an example of a bilateral digital nerve repair following degloving injury. Table 6 summarizes nerve repair methods by nerve type in the outcomes population.

Clinical Evaluation

Each study site followed their own standard of care regimen for subject treatment, rehabilitation, and follow-up measures. This clinical investigation was performed in accordance with the protocol, the FDA Good Clinical Practices including 21CRF part 312, 601, 50, 56, ICH E6, and the Helsinki Declaration of 1975. Standardized CRFs were used to capture information from the charts of subjects meeting the inclusion and exclusion criteria. Data was collected and reported to the extent available in the medical records. Preoperative, operative, post-operative follow-up and physical therapy notes were the main source documentation. Data collected included general subject demographics, details of the nerve injury, the nerve repair(s) performed, concomitant treatments, and all available follow up evaluations performed with the corresponding outcomes. Additionally, information on adverse experience or complications occurring intra/post-operatively were collected.

Follow-up assessments utilized throughout the sites included a variety of quantitative and qualitative measures for both sensory and motor deficits. Quantitative measures included static 2-point discrimination, moving 2 point discrimination, Semmes–Weinstein Monofilament testing, range of motion, strength testing, and MRCC scores for sensory and motor function. Qualitative measures include pain assessment and subject/physician subjective assessment of improvement in function.

Although not all sites completed the same battery of assessments following repair, consistencies allowed for data analysis of results. Static 2PD and strength testing were the most prevalent for sensory and motor evaluations. Additionally, data from nerve conduction studies was available in 3 subjects with motor nerve repairs.

The Mackinnon modification of the Medical Research Council grading system[1,20,21] was used for evaluation of sensory and motor recovery. Outcomes of assessments from subjects with sufficient follow-up were reviewed to determine level of recovery attained. To ensure consistency with a majority of the relevant literature, meaningful functional recovery was defined to be S3-S4 or M3-M5 on the MRCC scale.

Outcomes from this study were then compared to the available historical literature for other nerve gap repair

Table 3. Outcomes Population: Result Summary

Factor	N	Age (years)[a]	POI[b] (days)[a]	Follow-up (days)[a]	Gap (mm)[a]	Sensory	Mixed	Motor	Lacerations	Neuromas	Complex	Response Rate[c]	Meaningful Recovery[d]
OP by Repair	76	41 ± 17 (18, 86)	172 ± 283 (0, 1460)	264 ± 152 (40, 717)	22 ± 11 (5, 50)	49	18	9	51	9	16	89.5%	87.3%
Nerve Type													
Sensory	49	41 ± 14	182 ± 323	276 ± 169	19 ± 8	–	–	–	36	6	7	91.8%	88.6%
Mixed	18	38 ± 19	170 ± 234	205 ± 115	29 ± 12	–	–	–	9	3	6	83.3%	77.0%
Motor	9	45 ± 20	160 ± 164	341 ± 72	29 ± 13	–	–	–	6	0	3	88.8%	85.7%
Gap Length (mm)													
5–14	16	44 ± 16	94 ± 191	270 ± 185	–	13	2	1	14	0	2	100%	100%
15–29	34	40 ± 18	149 ± 317	279 ± 186	–	25	5	4	25	2	7	85.3%	76.2%[e]
30–50	26	41 ± 17	231 ± 274	265 ± 105	–	11	11	4	12	7	7	88.5%	90.9%
Time to Repair													
Acute	42	42 ± 17	–	274 ± 181	20 ± 9	29	8	5	33	0	9	92.9%	87.1%
Delayed	7	40 ± 13	–	246 ± 88	25 ± 13	3	4	0	12	9	6	85.7%	100 %
Chronic	27	40 ± 18	–	263 ± 127	26 ± 12	17	6	4	6	0	1	85.2%	83.3%
Subject Age[f] (years)													
18–29	19	–	222 ± 371	226 ± 128	22 ± 10	9	8	2	10	2	7	84.2%	70%[e]
30–49	22	–	160 ± 224	270 ± 148	22 ± 13	17	4	1	17	2	3	90.9%	88.2%
50+	16	–	131 ± 259	310 ± 188	22 ± 11	10	3	3	10	2	4	93.8%	92.9%
Mechanism of Injury													
Complex	16	37 ± 17	202 ± 371	292 ± 171	27 ± 12	7	6	3	–	–	–	87.5%	81.8%
Laceration	51	42 ± 15	103 ± 173	249 ± 149	20 ± 9	36	9	6	–	–	–	90.2%	88.9%
Neuroma	9	43 ± 26	542 ± 286	291 ± 126	31 ± 10	6	3	0	–	–	–	88.9%	87.5%

[a] *Report in mean ± SD.*
[b] *POI, preoperative interval.*
[c] *Response rate includes quantitative and/or qualitative data.*
[d] *Meaningful Recovery calculated from the subjects providing quantitative measures of recovery.*
[e] *Inclusive of 2 of the 4 revisions deemed unrelated to nerve graft.*
[f] *Two subjects did not report age.*

Table 4. Mechanism of Injury and Nerve Type in the Outcomes Population

Mechanism of injury	Sensory	Mixed	Motor	Total
Complex				
Amputation/Avulsion	3	1	0	4
Blast	0	4	0	4
Compression/Crush	4	0	3	7
Gunshot	0	1	0	1
Lacerations				
Blunt/saw	18	3	1	22
Sharp	7	4	1	12
Laceration-Unknown	11	2	4	17
Neuroma	6	3	0	9
Total	49	18	9	76

Table 5. Comparison of OP with Total Study Population

Demographic/attribute	OP (%)	UP (%)
Gender		
Male	72	77
Female	28	23
Age, years		
18–29	33	39
30–49	39	36
+50	28	25
Time to repair		
Acute	55	57
Delayed	9	11
Chronic	36	32
Most prevalent mechanism of injury		
Laceration (blunt/saw)	29	23
Laceration (sharp)	16	15
Laceration (unknown)	18	15
Location		
Upper	32	36
Digital	60	55
Lower	3	6
Head/Neck	5	3
Nerve type		
Sensory	64	58
Motor	12	10
Mixed	24	32
Concomitant injury		
Yes	64	71
No	36	29

alternatives. A search was conducted on Medline and the available literature for nerve autograft and nerve tube style conduits were reviewed for studies that reported outcomes based on the Mackinnon modification of the Medical Research Council grading system. Outcomes from the published literature were then compared with the outcomes from this study with regard to meaningful recovery rates and revision rates. Table 7 contains the selected historical literature.

Statistical Methods

Data was gathered and compiled into a centralized study database. Each subject was assigned a unique identifier. Collected data was primarily evaluated in a blinded manner for utilization, safety and outcomes as a whole then unblinded to test for site and surgeon effect. SAS/STAT® software was utilized for the data analysis (Statistical Analysis Systems, 2011).

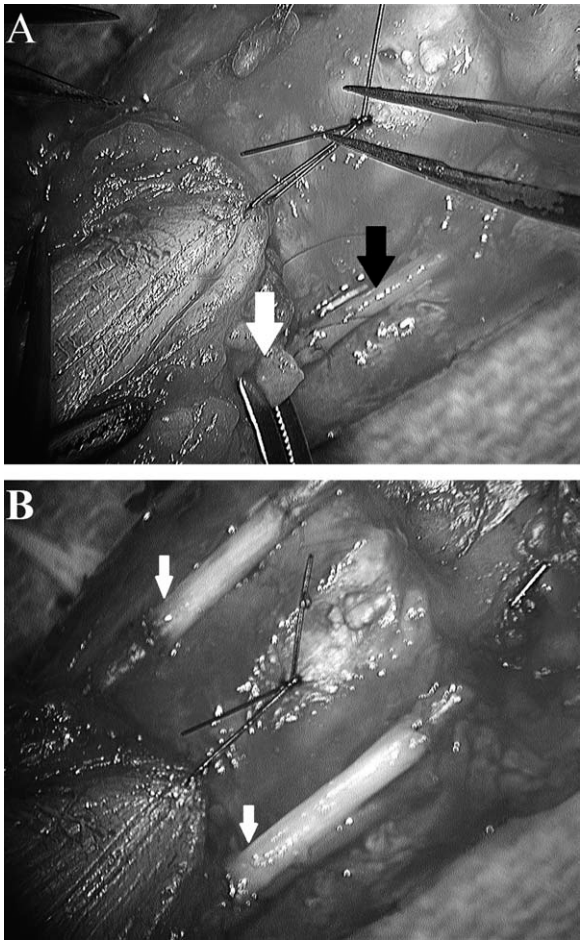

Figure 3. ***A:*** *Incomplete degloving injury to the left long finger, revascularization with 3 cm vein graft to the Ulnar Digital Artery (black arrow) and bilateral digital nerve avulsion that was resected back to healthy nerve tissue (white arrow).* ***B:*** *Reconstruction of the ulnar and radial digital nerves with processed nerve allograft, 10 mm and 15 mm respectively (white arrows).*

Subjects were placed into classifications based on the level of follow-up obtained at the time of this initial analysis. Subjects were considered LFU if they did not return for any post-operative follow-up visits. Subjects were considered to have IFU if the only available follow up data was at a time point where recovery would not be expected based on parameters of injury (i.e., appropriate amount of time has not passed to adequately assess regeneration, assumed at 2 mm/day, to reach the target organ), or the only available follow up was not applicable to the repaired nerve. Subjects were considered SFU if collected follow-up assessments were during a minimum

time point where recovery would be expected and was applicable to the nerve repaired. Table 1 summarizes the total study population by follow up status.

Descriptive statistics were used to describe the demographics, baseline characteristics, quality of data collected, and trends of post implantation. Continuous parameters (e.g., functional scores), N, mean, median, standard errors of the mean were recorded. Categorical parameters (e.g., complication rates, adverse events), the frequencies, percentages were also recorded. Subgroup analyses (e.g., by gender, type of nerve injury, age) was also explored.

The study population was divided into three subpopulations: Utilization Population (UP) and Safety Population (SP) comprised of all subjects enrolled at the participating sites and Outcomes Population (OP) consisting of a subset of UP that reported sufficient follow-up data to assess a response to the treatment. Chi-square analysis was performed to determine whether there was statistical difference between populations.

Patient experience was ranked Q+ (quantitative data demonstrated response to treatment), Q− (quantitative data demonstrating no response to treatment), S+ (qualitative data demonstrated response to treatment), and S− (qualitative data demonstrated no response to treatment). Predefined analysis parameters were in place and if conflicting data was reported for quantitative and qualitative measures, the quantitative data supplanted the qualitative data.

Table 6. Repair Technique by Nerve Type in the Outcomes Population

Repair technique	Sensory	Mixed	Motor	Total
Method				
Epineural	37	6	7	50
Cabling	2	4	–	6
Fascicular	–	4	–	4
Not specified	10	4	2	16
Sealant or wrap used	2	6	6	14

The sign test was used to compare response relative to baseline for each subject when analyzing the data from the OP.[21] Function prior to surgery was assigned a score of zero. Recovery postsurgery was based on the composite scores of qualitative and quantitative assessments where (Q+) or (S+) was assigned a score of 1 and (Q−) or (S−) was assigned a score of −1.

Additional subgroup analysis for subjects providing quantitative data was performed to evaluate the level of meaningful recovery based on MRCC scales for sensory and motor function. Statistical significance between subgroups was evaluated using Fisher's Exact Test; $P < 0.05$ was considered significant.

RESULTS

Efficacy Analysis for Response to Treatment

In the Outcomes Population 89.5% of all subjects reported a positive response to the treatment. The responder group was comprised of 54 subjects with 68 individual nerve injuries. The mean age was 42 ± 17 (18–86). The mean nerve gap was 22 ± 10 (5–50) mm and the mean time-to-repair was 137 ± 213 (0–949) days. When examining the type of nerve being repaired, a positive response was seen across 45 sensory, 8 motor, and 15 mixed nerve repairs. Table 8 summarizes the response to treatment of all repairs in the OP by nerve type.

No response to treatment was reported in eight subjects across five sites and six surgeons. Group characteristics (e.g., nerve type, nerve gap, time-to-repair) compared similarly to repairs reporting recovery. The mean age was 33 ± 15 (18–65). The mean nerve gap was 26 ± 12 (15–50) mm and the mean time-to-repair was 383 ± 514 (0–1,460) days. Injuries occurred in the upper extremity with four sensory, three mixed, and one motor nerve. There were five lacerations, one crush, one neuroma, and one blast injury. Five repairs reported no recovery via quantitative assessments and three reported no recovery qualitatively. Four subjects underwent revision; however,

Table 7. Comparison to Historical Reference Literature

Study	Year published	Number of repairs	Nerve injury types	Test article	Positive Outcomes[a]
Wangensteen and Kalliainen	2009	64	Sensory, mixed and motor nerve injuries	NeuraGen® Type 1 Bovine Collagen Tube	43%
Kim and Kline	2001–2006	52	Sensory and mixed nerves	Direct Suture and Autograft	67–86%
Frykman and Gramyk	1991	91	Mixed nerves	Direct Suture and Autograft	75–78%
Frykman and Gramyk	1991	384	Sensory nerves	Autograft for Digital Nerve Injury under 5 cm	80%
Weber et al.	2000	62	Sensory nerves	Neurotube® PGA Tube	74%
Weber et al.	2000	74	Sensory nerves	Direct Repair and Autograft	86%
Kallio et al.	1993	254	Sensory nerves	Autograft and Direct Repair	70%
Lohmeyer et al.	2009	12	Sensory nerves	NeuraGen® Type 1 Bovine Collagen Tube	75%

[a]*As reported, based on individual study parameters for acceptable recovery: M3-M5, S3-S4 by MRCC.*

Table 8. Outcome Population (OP) Response to Treatment Summary

Nerve type	N	Q+	S+	Q−	S−	Positive response
Sensory	49	32	13	2	2	91.8%
Motor	9	8	0	0	1	88.9%
Mixed	18	12	3	3	0	83.3%
Overall	76	52	16	5	3	89.5%

Q, quantitative assessment; S, qualitative/subjective assessment; +; positive response; −, no response.

the operative surgeon deemed causality to be unrelated to the processed nerve allograft and are discussed in the Safety Section below.

Of the four remaining subjects that had a repair that did not respond to treatment, three of the subjects had originally sustained injury to multiple nerves. These injuries were also repaired with processed nerve allograft and did report meaningful recovery.

For responders and nonresponders, no demographic differences were found with regard to patient age, preoperative interval, mechanism of injury, nerve type gap length, or repair techniques. With regards to statistical significance, the calculation of power post-hoc was done based on the following parameters: significance Level = 0.05 and sample size = 76. From these parameters, it is determined the power = 0.9999, indicating that a statistically meaningful positive response was reported from the implant of processed nerve allografts (Avance® Nerve Graft).

The Outcome Population was further stratified for additional subgroup analysis to evaluate the response rate and level of meaningful recovery for critical factors such as nerve type, nerve gap length, subject age, preoperative interval, and mechanism of injury. The characteristics of these subgroups are summarized in Table 3.

Efficacy Analysis for Meaningful Recovery

To further evaluate the level of response, subjects reporting quantitative data measures were analyzed for meaningful levels of recovery. The criteria for determining the levels of recovery considered "meaningful" were defined from the available literature[22–30] as return of motor recovery to M3 or greater and sensory recovery to S3 or greater. When subjects reported quantitative data, meaningful recovery was achieved in 87.3% of repairs. Figure 4 provides a breakdown of MRCC scores for sensory and motor outcomes.

Meaningful Recovery by Nerve Type Cohort

This subgroup population was comprised of 35 Sensory nerves, 13 Mixed nerves, and 7 Motor nerves. Meaningful recovery was seen in 89% of the sensory, 86% of the motor, and 77% mixed nerve repairs. When looking at outcomes from sensory assessments for digital and mixed nerve repairs, static 2-point discrimination was

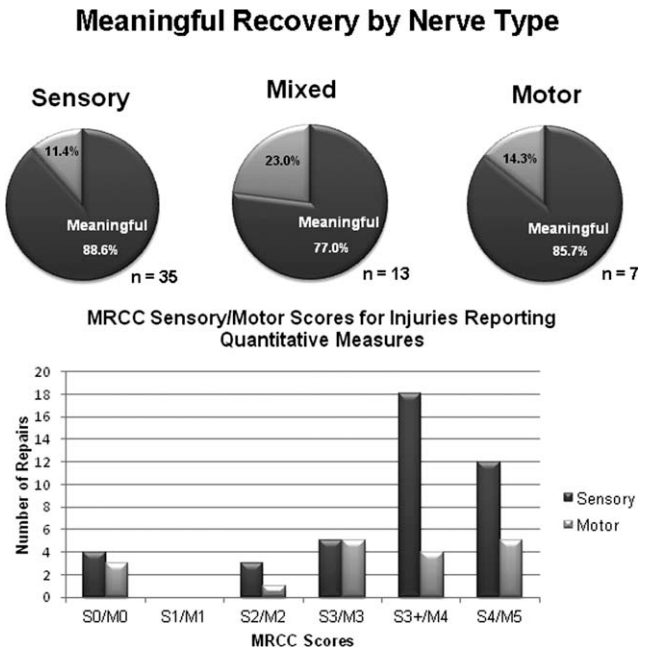

Figure 4. Functional sensory and motor outcomes by nerve type groups expressed by MRCC scores for outcomes population reporting quantitative measures. Pie charts represent the percentage of subjects reporting Meaningful Recovery in each group. Bar Charts represent the distribution of all MRCC scores for each group. No significant difference (P > 0.05) was observed between the three groups with Sensory-Mixed: P = 0.160, Sensory-Motor: P = 0.999, Mixed-Motor: P = 0.526.

evaluated in 26 of the nerve repairs with an average score of 8 mm (4–15 mm). Moving 2PD, reported in 11 repairs, was 8 mm (4–15 mm). SWMF testing was conducted in 14 subjects with return to diminished light touch or better reported in 13 of 17 nerve repairs.

Electromyography (EMG) results were available for three of the seven motor nerve repairs. Reinnervation to the target muscle was reported in all cases after the repair of a spinal accessory nerve with a 12 mm gap, a biceps branch of the musculocutaneous nerve with a gap of 15 mm and a common peroneal nerve with a gap 40 mm.

A majority of the mixed nerve injuries occurred in the median, ulnar, and radial nerves at the forearm level with nerve gaps ranging from 10 to 50 mm. Of the 19 cases reporting motor scores, return of meaningful motor function was observed at the level of M4-M5 in nine of the cases and M3 in six cases. Figure 4 provides a breakdown of meaningful recovery by nerve type. No significant differences were found between cohort groups ($P = 0.24$).

Meaningful Recovery by Gap Length Cohort

It is well established that the length of the nerve gap treated is a factor affecting the expected rate and level of recovery following peripheral nerve repair.[1,17,20,25–29,31–33]

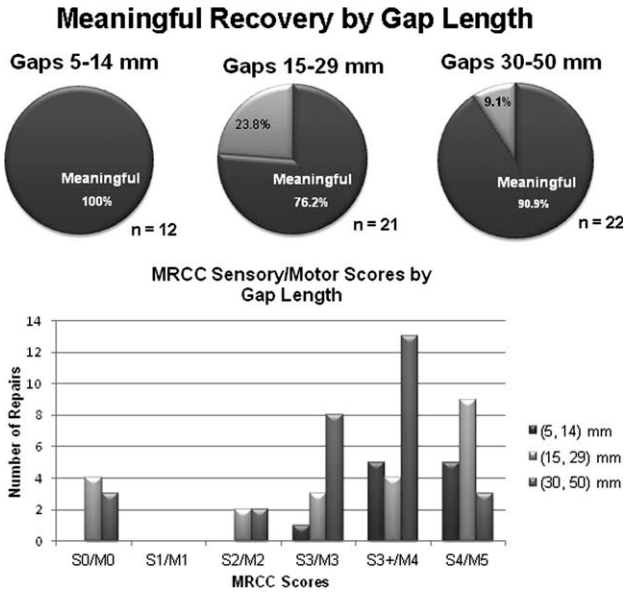

*Figure 5. Functional sensory and motor outcomes by gap length groups expressed by MRCC scores for outcomes population reporting quantitative measures. Pie charts represent the percentage of subjects reporting meaningful recovery in each group. Bar Charts represent the distribution of all MRCC scores for each group. No significant difference (*P *> 0.05) was observed between the three groups with Gaps 5–14 mm-Gaps 15–30 mm:* P *= 0.535, Gaps 5–14 mm-Gaps 30–50 mm:* P *= 0.999, Gaps 15–29 mm-Gaps 30–50 mm:* P *= 0.999.*

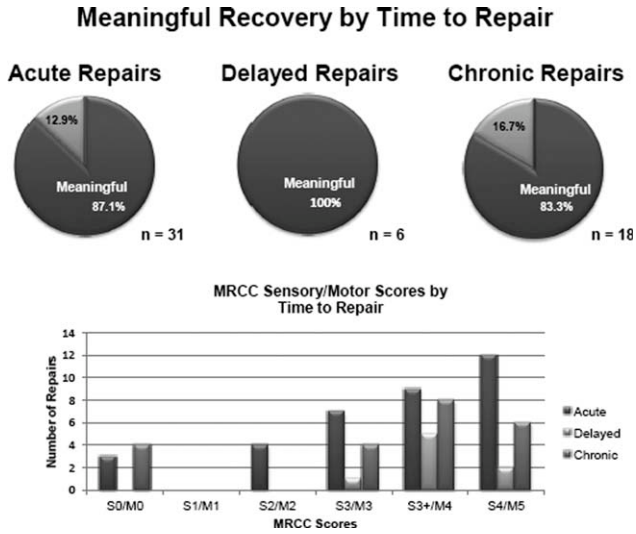

*Figure 6. Functional sensory and motor outcomes by subject age groups expressed by MRCC scores for outcomes population reporting quantitative measures. Pie charts represent the percentage of subjects reporting meaningful recovery in each group. Bar charts represent the distribution of all MRCC scores for each group. No significant difference (*P *> 0.05) was observed between the three groups with 18–29 years to 30–49 years:* P *= 0.999, 18–29 years to 50+ years:* P *= 0.999, 30–49 years to 50+ years:* P *= 0.438.*

Here, the subjects reporting quantitative data were grouped by treated gap length into three categories. The categories were based on the associated graft product code and were: 5–14 mm, 15–29 mm, and 30–50 mm. For nerve gaps under 15 mm, 12 out of 12 repairs (100%) demonstrated meaningful recovery. For gaps between 15 and 29 mm meaningful recovery was demonstrated in 16 of the 21 repairs (76%). In the long gap group, 20 out of 22 repairs (91%) demonstrated meaningful recovery. Figure 5 lists the reported MRCC scores by gap length. No significant differences were found between cohort groups ($P = 0.83$).

Meaningful Recovery by Time to Repair Cohort

Time to repair was divided into three groups. Acute: repairs occurring within three weeks from the original injury, Delayed: repairs occurring after three weeks but within three months of the original injury, and Chronic: repairs occurring after three months of the original injury. Meaningful recovery was seen across all groups with 87, 100, and 83% in acute, delayed, and chronic repairs. Figure 6 lists the reported MRCC scores by time to repair. No significant differences were found between cohort groups ($P = 0.38$).

Meaningful Recovery by Subject Age Cohort

Subject age is associated with the rate of and level of recovery. This particular study excluded pediatric subjects as they typically have a greater probability of recovery related to their regenerative potential and brain plasticity. The adult population in this study was divided, based on quartile calculations, into three different age subgroups: young adults (18–29 years), middle aged (30–49 years) and older adults (50+ years). Table 3 summarizes the characteristics of this subgroup. In the Young, Middle and Older subgroups, 70, 88, and 93% respectively demonstrated meaningful recovery. Figure 7 lists the reported MRCC scores by subject age. No significant differences were found between cohort groups ($P = 0.19$).

Meaningful Recovery by Mechanism of Injury

The mechanism of injury is a contributing factor that can affect outcomes after nerve repair. Here the mechanisms were divided into three groups and was based on the potential complexity of the injury and difficulty of the repair. The first group consisted of lacerations, both sharp and blunt as well as lacerations of unknown origin. In these repairs, 89% reported meaningful recovery. The second group was injuries resulting from neuroma that required resection. Meaningful recovery was achieved in 88% of these repairs. The last group was complex reconstructions, which consists of amputations, avulsions, blasts, crushes and compressions, and gunshot injuries. Meaningful recovery was reported in 82% of these repairs. Figure 8 lists the reported MRCC scores by

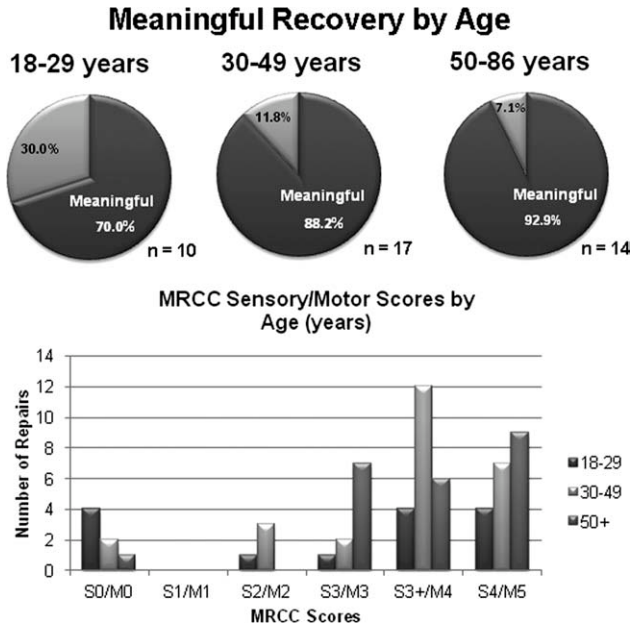

*Figure 7. Functional sensory and motor outcomes by time to repair groups expressed by MRCC scores for outcomes population reporting quantitative measures. Pie charts represent the percentage of subjects reporting meaningful recovery in each group. Bar charts represent the distribution of all MRCC scores for each group. No significant difference (*P > *0.05) was observed between the three groups with Acute-Delayed:* P = *0.999, Acute-Chronic:* P = *0.348, Delayed-Chronic:* P = *0.554.*

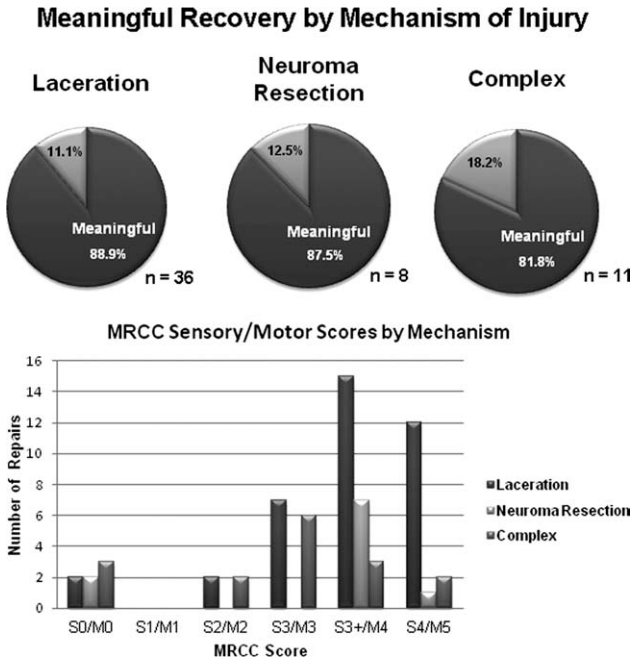

*Figure 8. Functional sensory and motor outcomes by mechanism of injury groups expressed by MRCC scores for outcomes population reporting quantitative measures. Pie charts represent the percentage of subjects reporting meaningful recovery in each group. Bar charts represent the distribution of all MRCC scores for each group. No significant difference (*P > *0.05) was observed between the three groups with Lacerations-Neuroma Resection:* P = *0.461, Laceration-Complex:* P = *0.284, Neuroma Resection-Complex:* P = *0.999.*

mechanism of injury. No significant differences were found between cohort populations ($P = 0.39$).

Safety Analysis-Complications and Revisions

There were no reported implant complications, tissue rejections, or adverse events related to the use of the processed nerve allografts.

Four injuries (5% of OP) underwent revision. While this revision rate is lower than revision rates reported in the literature for other repair alternatives,[25,26,30,34,35] an analysis to determine common contributing factors and causality was warranted. There were two mixed and two sensory nerves revised. Repairs reporting a revision tended to be more chronic with the mean time to repair at 674 days with one subject seeking repair four years after original injury. Two subjects, presenting with lacerations from glass injuries, reported having glass shards remaining in the wound bed. One subject presenting with a four-year-old crush injury to the index finger was repaired with processed nerve allograft after neuroma excision. Upon re-exploration, it was noted that the radial digital artery was thrombosed with no active circulation and a neuroma was present in the host nerve proximal to the graft coaptation. The operative surgeon determined causality to be due to additional internal nerve damage from the original injury. One subject originally repaired with a collagen nerve conduit in the median nerve after sustaining injuries to the forearm with a circular saw, presented with a neuroma two years later and was revised with processed nerve allograft. Following the four month follow-up visit, the subject was re-explored and a neuroma was identified 15 mm proximal to the original repair at a previously unidentified injury site. In the four revision cases, the operative surgeon deemed causality to be unrelated to the processed nerve allograft. At revision, three of the subjects were reconstructed with processed nerve allograft and one subject was reconstructed with autogenous nerve graft.

DISCUSSION

Processed nerve allografts are currently distributed as a human tissue allograft by AxoGen®. These nerve grafts have been available for clinical use since 2007. While several smaller case series have been presented on the safety and efficacy, this project is currently the largest multicenter study of its kind for both allografts and peripheral nerve repair. The major findings thus far were the following: Processed nerve allografts are a safe and

effective alternative for nerve reconstruction with meaningful recovery reported in 87.3% of cases reporting quantitative data. Subgroup analysis also shows that these allografts provide functional recovery in sensory, mixed, and motor nerve injuries in gaps up to 50 mm.

Although not all of the repairs in the Utilization Population reported sufficient follow-up for outcomes analysis, data collected around the nerve injury and repair provided insight on the use and safety of processed nerve allografts in today's clinical practice. Implantation of the allograft was completed using standard microsurgical techniques similar to autograft and direct suture repairs. The reported mechanism of injury was well distributed across numerous categories with the greatest number in Lacerations at 53% (70 of 132 repairs). A majority of the nerves treated were sensory nerves (64%), with approximately one quarter of the injuries being mixed nerves (24%) and pure motor nerves comprising the remaining 12%. As expected with traumatic nerve injury, a majority of the repairs involved the digital nerves in the hand (61%), with the remaining upper extremity injuries constituting an additional 32%. The remaining comprised of lower extremity nerves (3%), and the head/neck region (5%). This utilization distribution compares similarly to the rates and frequencies of peripheral nerve injuries in general[36–38] suggesting that processed nerve allografts are becoming increasingly well accepted as a repair method for all appropriate types of peripheral nerve injuries.

Frykman and Gramyk[30] identified several contributing factors to the outcome of nerve repair, such as location of injury, nerve type, nerve gap length, time-to-repair, patient age, and mechanism of injury. As this study covered a large patient population, further subgroup analysis was possible in some instances to assess what effect these factors had on recovery after repair with processed nerve allograft.

Subjects in the study were generally healthy with only nine reporting an underlying health condition that could impact recovery outcomes; eight being uncontrolled hypertension and one with peripheral neuropathy. Seven of these subjects demonstrated meaningful recovery and two subjects with uncontrolled hypertension reported insufficient follow-up.

Both mechanism of injury and location of injury were relatively consistent, with a majority of the injuries caused by lacerations and the location of the injuries occurring reasonably distal in the course of the given nerve. Mechanism of injury may have played a role in the outcome of subjects in the Young Adult group (18–29 years). In this study, the young adult cohort (18–29 years) presented with more complex injuries as compared to the other two age groups with seven complex injuries. The middle aged population (30–49 years) contained only three and the older population (50 years and older) contained four complex injuries. Interestingly, all of the blast injuries were sustained by the 18–29 years age group.

Nerve type played a limited role in observed outcomes. Sensory nerves returned a slightly higher rate of meaningful recovery, however no significant difference was observed at this time. This could be related to the larger number of subjects in the sensory nerve subgroup as compared with that of the mixed and motor nerve subgroups.

The relationship between nerve gaps was evaluated as a factor on recovery outcomes. In this dataset all (100%) subjects with nerve grafts under 15 mm returned meaningful levels of functional recovery. By comparison, nerve grafts from 15 mm to less than 30 mm in length and the 30–50 mm graft length groups both returned meaningful recovery rates of 76% and 91%, respectively. Outcomes stratified by time-to-repair were similar among the groups. As is the case in the published literature, chronic motor nerve injuries that were repaired after one year from the original injury tended to provide less recovery than those with a shorter time-to-repair.[3,8,20,30,34,39,40]

There is no obvious conclusion regarding the relationship between gap length, patient age, or nerve type and outcomes at this time. Per the literature, we would have expected to see a statistically significant relationship between gap length, subject age, and nerve type with regard to outcomes. In this dataset, this may be attributed to the number of subjects in each group, the distribution of covariates across the groups or may be directly related to the function and impact of the processed nerve allograft on regeneration and in the surgeon's approach. As the study continues, additional enrollment should elucidate any potential relationships.

While a low revision rate was reported, their affect on subgroup analysis was noted. While not statistically significant, slightly lower response rates were noted in the 15–29 mm gap length cohort and the 18–29 years of age cohort. Additional analysis revealed that two of the four revision cases were located in each of these cohorts. These revisions were determined by the operative surgeon to the unrelated to the nerve graft, with two reporting glass shards remaining in the wound and two reporting inadequate resection beyond the original zone of injury. If these cohorts are adjusted for the revision cases, the rates for meaningful recovery would actually be 85% and 87.5%, respectively. These rates fall in line with the outcomes seen in the other related cohorts.

This study suffered from the same limitations as other studies of similar type. In general, observational studies exhibit increased risk of heterogeneity in the datasets; variability between subjects, injuries, surgeons and sites; subject attrition; and multiple sources of data. Observational studies also suffer from the fact that they do not lend themselves to being conducted in a prospective, randomized fashion.

To control for these risks, detailed standardized case report forms were used across all centers to improve consistency, limit reporting errors and allow for center to center testing for potential bias. Population and subgroup analysis was performed to ensure each were representative of the whole. Chi square testing found no significant differences among centers and study populations. Additional safeguards were placed around the entry and analysis of the study data and an independent biostatistician was utilized for data analysis. Data was homogenized to assess subject response rate followed by quantitative subset population analysis to determine the extent of recovery. Subgroup and covariate analysis was performed for contributing factors such as nerve type, nerve graft length, subject age and time-to-repair. The processed nerve allograft performed consistently well across each population and subgroup.

Benefits of this model include its multicenter, multisurgeon, multidiscipline design and the ability of an observational study to gather evidence on a representative cross section of injuries typically handled by hand surgeons. This included less commonly injured nerves such as radial, peroneal, and spinal accessory nerves, as well as less common mechanisms such as blast injuries from improvised explosive devices.

The average follow-up time for subjects in the OP is 264 ± 152 days. Consideration should be given to this timing as many of these subjects are likely still in the active regeneration/recovery phase of their nerve injuries. While this is adequate for many of the distal repairs, we continue to follow and collect data on subjects, converting them from IFU to SFU and further define the granular levels of recovery within the OP.

As this study was inclusive of all types of peripheral nerve injuries, the completed assessments and frequency of follow-up varied widely and contributed to the somewhat large standard deviations for certain measures. Of note, static 2PD was the preferred sensory assessment tool, utilized over Semmes Weinstein Monofilaments at a ratio of 3:1. For motor assessments, functional range of motion, and strength testing were the predominate form of assessing outcomes, followed by EMGs for pure motor nerves.

Historically, peripheral nerve repair research has been limited to small case series or large single center retrospective studies. Unfortunately, multicenter projects are seldom undertaken, and prospective, randomized, controlled studies are even rarer. As a result, surgeons have come to rely on experiential data from expert and institutional publications when determining expected outcomes or forming an evidenced based approach for treatment peripheral nerve injuries.

For the classic nerve autograft, a wealth of single center experiential data is available. The individual works from Sunderland, Seddon, Buncke, Wilgis, Millesi, and Kline set the foundation for the understanding of modern day peripheral nerve surgery.[7,25–29,41–44] This foundational work has been expanded upon and contemporary expectations, while variable, are available for the nerve autograft.[2,3,17,33,39,45,46]

In a review by Frykman and Gramyk, meaningful functional recovery was reported in 80% of nerve autograft repairs in digital nerve gaps less than 50 mm. Mixed nerves of the forearm (Median, Ulnar and Radial) were found to return meaningful levels of motor function in 63% to 81% of cases, and meaningful levels of sensory function in 75–78% of injuries.[30]

Ruijs et al. completed a meta-analysis of published literature on median and ulnar nerve reconstructions. Results were compiled from 23 studies with a total of 623 injuries, with 322 median, and 301 ulnar nerves repaired with either direct suture or autograft. Recovery to S3+/S4 and M4/M5 was noted in 42.6–51.6% of the injuries, respectively.[47]

The 30+ years of experience from Louisiana State University Health Sciences Center reports on outcomes for surgical repair of 49 "not-in-continuity" and 80 "in-continuity" mixed nerves of the upper extremity treated with nerve autograft. The study found that 72% of mixed nerves treated with nerve autograft returned to meaningful levels of functional recovery.[34]

Kallio et al reported on 254 digital nerve repairs performed across a 16-year period and found that return to meaningful sensory recovery was seen in 79.5% of subjects with direct suture and 56.3% of the subjects with autograft.[22]

For autograft alternatives the largest published randomized controlled study was Weber et al. in 2000. This study examined the outcomes of nerve conduit as compared with direct suture and autograft for sensory only digital nerve repairs. The study found that nerve conduits performed very well in a gap of 4 mm or less, with 11 of 11 subjects reporting meaningful recovery of 2-PD. As the gap length increased, the outcomes became less consistent with 34% of repairs between 5 mm and 25 mm gap reporting poor outcomes, nearly twice what was reported for the control.[31]

Lohmeyer and associates reported that 75% of digital nerve treated with a type-1 bovine collagen conduit (NeuraGen®, Integra Life Sciences, Plainsboro, NJ), reported meaningful recovery, however all tubes over 15 mm reported no recovery of protective sensation and failed to regain any discrimination.[48]

Wangensteen and Kalliainen report a single center, multisurgeon retrospective study of outcomes from the general use of collagen tubes for nerve repair. This study collected utilization data on 126 nerve injuries in the upper extremity, lower extremity as well as the head and neck. It contained sensory, mixed and motor nerves as a representative cross section of nerve injuries treated at

Level 1 trauma centers. Their experience found collagen tubes (NeuraGen®) were safe to use and effective in 43% of nerve injuries. Additional findings noted that when quantitative outcome measures were available, a 31% revision rate was observed.[35]

The outcomes from our study compare favorably with those reported in the literature for nerve autograft and the processed nerve allograft returned a higher rate of meaningful functional recovery than those reported in the literature for nerve conduits.

CONCLUSION

This study establishes a foundational understanding on expected outcomes for processed nerve allografts. In our study, the outcomes population consisted of 49 Sensory, 18 Mixed, and 9 Motor nerves treated with processed nerve allograft for nerve gap lengths from 5 mm to 50 mm. Meaningful levels of recovery were achieved in 87% of the subjects reporting quantitative data. When examined by nerve type meaningful levels of functional recovery were achieved in 89% of Sensory, 77% of Mixed and 86% of Motor nerve injuries. No graft related adverse experiences were reported and a 5% revision rate was observed.

Continuation of this study will allow for the enrollment of additional subjects, longer term follow-up, and a greater number of contributors. Furthermore, efforts are being made to increase the frequency of follow-up, reduce the attrition rate, streamline data collection, and obtain more structured prospective evaluations with the goal of constructing an increasingly robust database to provide additional evidence on the role of processed nerve allografts in peripheral nerve repair.

ACKNOWLEDGMENTS

This study was part of the RANGER research program: A *R*egistry Study of *A*vance® *N*erve Graft *E*valuating Outcomes in Nerve *R*epair. We would like to thank the members of our individual study research teams who participated in data organization and collection as well as Steven Bramer Ph.D. and Amanda Richards M.S., for their contributions in data analysis. Patient selection, treatment decisions and study evaluations were performed at the discretion of the authors or their institution's staff and the data analysis was performed by independent biostatisticians.

REFERENCES

1. Mackinnon SE, Dellon AL. Surgery of the Peripheral Nerve. New York: Thieme Medical; 1988.
2. Lundborg G. Nerve Injury and Repair: Regeneration, Reconstruction and Cortical Remodeling. Philidelphia: Elsevier; 2004.
3. Hentz VR. Peripheral nerve repair and regeneration. West J Med 1989;150:75–76.
4. Hudson TW, Evans GR, Schmidt CE. Engineering strategies for peripheral nerve repair. Orthop Clin North Am 2000;31:485–498.
5. Johnson PJ, Newton P, Hunter DA, Mackinnon SE. Nerve endoneurial microstructure facilitates uniform distribution of regenerative fibers: A post hoc comparison of midgraft nerve fiber densities. J Reconstr Microsurg 2011;27:83–90.
6. Millesi H, Schmidhammer R, editors. How to Improve the Results of Peripheral Nerve Surgery. New York, NY: Springer Wein New York; 2007.
7. Seddon H. Nerve Injuries. Med Bull (Ann Arbor) 1965;31:4–10.
8. Steinberg DR. Factors Affecting the Results of Peripheral Nerve Repair. In: Gelberman R, editor. Operative Nerve Repair and Reconstruction. Philadelphia: Lippincott 1991. p 349–364.
9. FF IJ, Nicolai JP, Meek MF. Sural nerve donor-site morbidity: Thirty-four years of follow-up. Ann Plast Surg 2006;57:391–395.
10. Whitlock EL, Tuffaha SH, Luciano JP, Yan Y, Hunter DA, Magill CK, Moore AM, Tong AY, Mackinnon SE, Borschel GH. Processed allografts and type I collagen conduits for repair of peripheral nerve gaps. Muscle Nerve 2009;39:787–799.
11. Graham JB, Qing-Shan X, Neubauer D, Muir D. A chondroitinase-treated, decellularized nerve allograft compares favorably to the cellular isograft in rat peripheral nerve repair. J Neurodegen Regen 2009;2:19–29.
12. Karabekmez FE, Duymaz A, Moran SL. Early clinical outcomes with the use of decellularized nerve allograft for repair of sensory defects within the hand. Hand (NY) 2009;4:245–249.
13. Neubauer D, Graham JB, Muir D. Chondroitinase treatment increases the effective length of acellular nerve grafts. Exp Neurol 2007;207:163–170.
14. Shanti RM, Ziccardi VB. Use of decellularized nerve allograft for inferior alveolar nerve reconstruction: A case report. J Oral Maxillofac Surg 2011;69:550–553.
15. Gunn S, Cosetti M, Roland JT Jr. Processed allograft: Novel use in facial nerve repair after resection of a rare racial nerve paraganglioma. Laryngoscope 2010;120 (Suppl 4):S206.
16. Kvist M, Sondell M, Kanje M, Dahlin LB. Regeneration in, and properties of, extracted peripheral nerve allografts and xenografts. J Plast Surg Hand Surg 2011;45:122–128.
17. Isaacs J. Treatment of acute peripheral nerve injuries: Current concepts. J Hand Surg Am 2010;35:491–497.
18. Johnson PJ, Newton P, Hunter DA, Mackinnon SE. Nerve endoneurial microstructure facilitates uniform distribution of regenerative fibers: A post hoc comparison of midgraft nerve fiber densities. J Reconstr Microsurg 2011;27:83–90.
19. Mackinnon SE, Doolabh VB, Noval CB, Trulock EP. Clinical outcomes following nerve allograft transplantation. Plastic Reconstruct Surg 2001;107:1419–1429.
20. Mackinnon SE, Dellon AL. Results of Nerve Repair and Grafting. Surgery of Peripheral Nerve, 1st ed. New York: Thieme Medical; 1988.
21. Mendenhall W, Wackerly DD, Scheaffer RL.Mathematical Statistics with Applications. Boston: PWS-Kent Pub. Co.; 1990.xiv, 818 p. p.
22. Kallio PK. The results of secondary repair of 254 digital nerves. J Hand Surg 1993;18B:327–330.
23. Kallio PK, Vastamäki M. An analysis of the results of late reconstruction of 132 median nerves. J Hand Surg Br 1993 Feb;18:97–105.
24. Vastamki M, Kallio PK, Solonen KA. The results of secondary microsurgical repair of ulnar nerve injury. J Hand Surg (Br Eur) 1993;18:323–326.
25. Kim DH, Han K, Tiel RL, Murovic JA, Kline DG. Surgical outcomes of 654 ulnar nerve lesions. J Neurosurg 2003;98:993–1004.
26. Kim DH, Kam AC, Chandika P, Tiel RL, Kline DG. Surgical management and outcomes in patients with median nerve lesions. J Neurosurg 2001;95:584–594.
27. Kim DH, Kam AC, Chandika P, Tiel RL, Kline DG. Surgical management and outcome in patients with radial nerve lesions. J Neurosurg 2001;95:573–583.
28. Kim DH, Murovic JA, Kim YY, Kline DG. Surgical treatment and outcomes in 45 cases of posterior interosseous nerve entrapments and injuries. J Neurosurg 2006;104:766–777.

29. Kim DH, Murovic JA, Kim YY, Kline DG. Surgical treatment and outcomes in 15 patients with anterior interosseous nerve entrapments and injuries. J Neurosurg 2006;104:757–765.
30. Frykman G, Gramyk K. Results of nerve grafting. In:Gelberman R, editor. Operative Nerve Repair and Reconstruction. Philadelphia: JB Lippincott; 1991.
31. Weber RA, et al. A randomized prospective study of PGA conduits for digital nerve reconstruction in humans. Plast Recon Surgery 2000;106:1036–1045.
32. Dvali L, Mackinnon S. Nerve repair, grafting, and nerve transfers. Clin Plast Surg 2003;30:203–221.
33. Mackinnon SE. Surgical management of peripheral nerve gap. Clin Plast Surg 1989;16:587–603.
34. Murovic JA. Upper-extremity peripheral nerve injuries: A Louisiana State University Health Sciences Center literature review with comparison of the operative outcomes of 1837 Louisiana State University Health Sciences Center median, radial, and ulnar nerve lesions. Neurosurgery 2009;65(4 Suppl):A11–A17.
35. Wangensteen KJ, Kalliainen LK. Collagen tube conduits in peripheral nerve repair: A retrospective analysis. Hand (NY) 2009;5:273–277.
36. Hoxie SC, Capo JA, Dennison DG, Shin AY. The economic impact of electric saw injuries to the hand. J Hand Surg Am 2009;34:886–889.
37. Robinson LR. Traumatic injury to peripheral nerves. Muscle Nerve 2000;23:863–873.
38. Asplund M, Nilsson M, Jacobsson A, von Holst H. Incidence of traumatic peripheral nerve injuries and amputations in Sweden between 1998 and 2006. Neuroepidemiology 2009;32:217–228.
39. Lee SK, Wolfe SW. Peripheral nerve injury and repair. J Am Acad Orthop Surg 2000;8:243–252.
40. Vanderhooft E. Functional outcome of nerve grafts for the upper and lower extremities. Hand Clin 2000;16:93–104.
41. Buncke HJ Jr. Digital nerve repairs. Surg Clin North Am 1972;52:1267–1285.
42. Millesi H. Nerve Grafting. Clin Plast Surg 1984;11:105–113.
43. Sunderland S. A classification of peripheral nerve injuries producing loss of function. Brain 1951;74:491.
44. Wilgis EF, Maxwell GP. Distal digital nerve grafts: Clinical and anatomical studies. J Hand Surg Am 1979;4:439–443.
45. Chiu DT, Ishii C. Management of peripheral nerve injuries. Orthop Clin North Am 1986;17:365–373.
46. Ducic I, Endara M, Al-Attar A, Quadri H. Minimally invasive peripheral nerve surgery: A short scar technique. Microsurgery 2010;30:622–626.
47. Ruijs AC, Jaquet JB, Kalmijn S, Giele H, Hovius SE. Median and ulnar nerve injuries: A meta-analysis of predictors of motor and sensory recovery after modern microsurgical nerve repair. Plast Reconstr Surg 2005;116:484–494; discussion 495–486.
48. Lohmeyer JA, Siemers F, Machens HG, Mailander P. The clinical use of artificial nerve conduits for digital nerve repair: A prospective cohort study and literature review. J Reconstr Microsurg 2009;25:55–61.