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# A Multicenter, Prospective, Randomized, Pilot Study of Outcomes for Digital Nerve Repair in the Hand Using Hollow Conduit Compared With Processed Allograft Nerve

**Kenneth R. Means Jr[1], Brian D. Rinker[2], James P. Higgins[1], S. Houston Payne Jr[3], Gregory A. Merrell[4], and E. F. Shaw Wilgis[1]**

**Abstract**

**Background:** Current repair options for peripheral nerve injuries where tension-free gap closure is not possible include allograft, processed nerve allograft, and hollow tube conduit. Here we report on the outcomes from a multicenter prospective, randomized, patient- and evaluator-blinded, pilot study comparing processed nerve allograft and hollow conduit for digital nerve reconstructions in the hand. **Methods:** Across 4 centers, consented participants meeting inclusion criteria while not meeting exclusion criteria were randomized intraoperatively to either processed nerve allograft or hollow conduit. Standard sensory and safety assessments were conducted at baseline, 1, 3, 6, 9, and 12 months after reconstruction. The primary outcome was static 2-point discrimination (s2PD) testing. Participants and assessors were blinded to treatment. The contralateral digit served as the control. **Results:** We randomized 23 participants with 31 digital nerve injuries. Sixteen participants with 20 repairs had at least 6 months of follow-up while 12-month follow-up was available for 15 repairs. There were no significant differences in participant and baseline characteristics between treatment groups. The predominant nerve injury was laceration/sharp transection. The mean ± SD length of the nerve gap prior to repair was 12 ± 4 mm (5-20 mm) for both groups. The average s2PD for processed allograft was 5 ± 1 mm (n = 6) compared with 8 ± 5 mm (n = 9) for hollow conduits. The average moving 2PD for processed allograft was 5 ± 1 mm compared with 7 ± 5 mm for hollow conduits. All injuries randomized to processed nerve allograft returned some degree of s2PD as compared with 75% of the repairs in the conduit group. Two hollow conduits and one allograft were lost due to infection during the study. **Conclusions:** In this pilot study, patients whose digital nerve reconstructions were performed with processed nerve allografts had significantly improved and more consistent functional sensory outcomes compared with hollow conduits.

**Keywords:** processed nerve allograft, nerve conduit, digital nerve, nerve reconstruction, peripheral nerve

## Introduction

Although the standard for treatment of peripheral nerve injuries is tensionless primary nerve repair, the nature of the injury often necessitates extensive resection and debridement to obtain healthy nerve tissue, resulting in a gap in the nerve.[16,17,20] Deficits that cannot be directly approximated require reconstruction with a material to bridge this gap.[5,17,21] Current nerve gap bridging options include autograft nerve, autologous vein, and commercially available off-the-shelf alternatives such as processed nerve allograft or hollow tube conduits. Autografts are most often the standard of care, but required harvesting of donor nerves increases operative time and introduces the potential for a host of donor site complications, such as sensory loss, hypertrophic scarring, and painful neuroma formation.[10,19]

Off-the-shelf nerve graft alternatives offer benefits over autograft techniques, including no donor deficit, avoidance of multiple suture lines, convenience, and proven effectiveness in the right situations. These include hollow conduits and, more recently, processed human nerve allograft. Hollow conduits are most commonly composed of polyglycolic acid, collagen, or poly(DL-lactide-ε-caprolactone).[18,25]

[1]Curtis National Hand Center, Baltimore, MD, USA
[2]University of Kentucky Division of Plastic Surgery, Lexington, KY, USA
[3]Georgia Hand, Shoulder & Elbow, Atlanta, GA, USA
[4]Indiana Hand to Shoulder Center, Indianapolis, IN, USA

**Corresponding Author:**
Kenneth R. Means Jr, The Curtis National Hand Center, Medstar Union Memorial Hospital, 3333 N. Calvert St. 200 JPB, Baltimore, MD 21218, USA.
Email: anne.mattson@medstar.net

Conduits share the common characteristics that they are semirigid, to resist collapse and kinking; semipermeable, to allow the diffusion of oxygen and nutrients that support nerve regeneration; and absorbable. The entubulation technique provides an enclosed chamber to trap and collect fibrin, which provides a rudimentary scaffold for cellular migration during nerve regeneration.[15]

Commercially available processed human nerve allograft (Avance® Nerve Graft; AxoGen Inc, Alachua, Florida, USA) mitigates concerns of donor site morbidity from nerve autografts while providing a 3-dimensional microstructural scaffolding and protein composition inherent to nerve tissue structure. Controlled decellularization protocols overcome issues with immune rejection while leaving the extracellular matrix intact. This process yields grafts with a preserved internal architecture of the epineurium, fascicles, and endoneurial tubes. The intact laminin in processed nerve allograft offers axon support and guidance cues not found in hollow conduit, and animal studies have reported several equivalent outcomes compared with autograft.[9,12,22,26]

Early clinical data and outcomes reported from an ongoing registry on processed nerve allograft have demonstrated meaningful levels of recovery in nerve gaps up to 50 mm in length.[2,4,7,13,23] The purpose of our study was to compare the outcomes for digital nerve gap reconstruction with hollow conduit versus allograft in a multicenter prospective, randomized, double-blind pilot study.

## Materials and Methods

Our pilot study involved participation between 4 treatment centers, utilizing a prospective randomization of either processed nerve allograft (Avance® nerve graft; AxoGen Inc) or commercially available hollow conduits (NeuroGen™, NeuroMatrix™, or NeuroFlex™) for the reconstruction of digital nerve injuries in the hand. 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. Informed consent was obtained in writing from all patients included in the study.

Participants were limited to consenting male and female adults older or equal to 18 years and younger or equal to 70 years, who had sustained injuries requiring repair of at least one digital nerve distal to the superficial palmar arch that resulted in a nerve gap of more than or equal to 5 mm and less than or equal to 20 mm after resection to healthy nerve. Patients were excluded if meeting any of the following criteria: distance from injury site to sensory target more than 125 mm, injury to nerve was a crush or avulsion, incomplete nerve transections, replantation of the injured digit required, contralateral injuries corresponding to the target digit, nerve injuries in limb present proximal to crease of wrist, end to side nerve repair required, injuries with significant vascular damage that may impair adequate perfusion of the target limb, participants who are undergoing treatment with chemotherapy, radiation therapy, or other treatment known to affect the growth of neural and/or vascular structures, use of bovine collagen–based hollow nerve conduit (NeuroGen™, NeuroMatrix™, or NeuroFlex™) in a participant with known or suspected bovine sensitivity, history of neuropathy, uncontrolled diabetes or any other known neuropathy, secondary nerve repair more than 12 weeks following initial injury, patient currently enrolled in another investigational study, expected use of medications during the study that are known to cause peripheral neuropathy, or history of Raynaud's or other disorders known to compromise circulation or sensation in the upper extremity. Participants were randomized to a treatment group intraoperatively, in a 3:2 allograft:conduit distribution, based on randomization codes enclosed in successively numbered envelopes.

Baseline assessments and follow-up assessments of functional recovery and adverse events were performed by qualified personnel blinded to the treatment. Follow-up assessments were performed 1, 3, 6, 9, and 12 months postoperatively. All evaluators completing follow-up sensory assessments were trained to standardized sensory test procedures. The contralateral digit was used as the control for all participants. The primary outcome was the assessment of static 2-point discrimination (s2PD) at 12 months after injury to determine the return of sensitivity (innervation density) in the affected digit. Secondary outcomes were moving 2PD (m2PD); Semmes-Weinstein Monofilament (SWMF) assessment; Medical Research Council Classification (MRCC) of sensory function in the hand; Disability of the Arm, Shoulder and Hand (DASH) scores; thermal discretion via the application of hot and cold object; and pain assessment via a visual analog scale (0-10). Repairs reporting absent sensation after the completion of follow-up assessments were assigned a corresponding score of S0 for MRCC sensory function, 16 mm for static and/or m2PD, and 6.65 for SWMF testing.

An assessment of normality was conducted on all data (including log transformed values) compared using the Shapiro-Wilk test. If the data were not normally distributed, we performed nonparametric testing. A repeated measures mixed linear model with covariates (visit and treatment by visit) was applied to longitudinal data to assess statistical significance. Continuous variables were compared between treatment group participants using the Mann-Whitney $U$ test. Categorical variables expressed as number (percentage) were compared using the Fisher exact test. $P < .05$ was considered significant.

The research team identified patients as they presented to the clinic or emergency room. Between the 5 treatment sites, 42 patients identified with a potential nerve injury in

**Table 1.** Participant Disposition.

| Participants | Processed allograft | Conduit | Total |
|---|---|---|---|
| Screened | — | — | 42 |
| Randomized | | | |
| Participants | 14 | 9 | 23 |
| Repaired nerves | 18 | 13[a] | 31 |
| Safety population (participants) | 14 | 9 | 23 |
| Adverse experience | 1 | 2 | 3 |
| Related to product | 0 | 2 | 2 |
| Completed at least 6 months | | | |
| Participants | 7 | 9 | 16 |
| Repaired nerves | 8 | 12[a] | 20 |
| Completed 12 months | | | |
| Participants | 5 | 7 | 12 |
| Repaired nerves | 6 | 9 | 15 |

[a]Two repairs had one target digit at the small finger but was assessed as a single repair during follow-up. This participant did not complete the 12-month visit.

the hand were screened for inclusion; 19 did not meet study criteria whereas 23 participants met criteria and agreed to participate. These 23 patients with 31 digital nerve injuries were randomized to treatment with a processed nerve allograft or hollow conduit. Fourteen participants requiring 18 repairs were randomized to the processed allograft group, whereas 9 participants requiring 13 repairs were randomized to the hollow conduit group; these comprised the intent-to-treat (ITT) population. Subsequent to treatment, 16 participants totaling 20 nerve repairs returned for at least 6 months of follow-up visit with 12 of those participants completing the final visit at 12 months; these comprised the modified ITT population (mITT). See Table 1 for a disposition of participants randomized to the study.

### *Surgical Technique*

All surgeons participating in the study completed hand and/or microsurgical fellowship training. Surgeons were instructed on how to perform the study procedures with regard to gap measurement with a ruler and allograft or conduit implantation according to the manufacturer's instructions. Preoperative preparation and injury site dissection and repair of concomitant injuries were completed based on each institution's standard of care. The distance between the debrided nerve ends was measured with the hand and digits extended. Nerve gaps of 5 to 20 mm meeting all other inclusion/exclusion criteria were randomized to a treatment group. If more than one nerve was being repaired in the affected hand during randomization, the same treatment was used for all repairs meeting the inclusion/exclusion criteria. Placement of processed allograft or hollow conduit was completed per the instructions for use for each product. Product information, suture placement, and magnification used were recorded. All repairs were performed under magnification with a surgical microscope or loupes using either 8-0 or 9-0 suture per surgeon preference. Coaptation to the proximal and distal nerve stumps was achieved using an average of 3 sutures for processed nerve allograft and 2 sutures for the hollow conduit. Wound closure and immobilization for each participant was based on the institution's standard of care.

## Results

Participant demographics and baseline characteristics including race, occupation, smoking history, hand dominance, and gender were compared (Table 2). No statistically significant differences in demographics were detected. Participants most commonly reported occupations of manual labor (>50%). Concomitant injuries involving bone, tendon, and vascular artery were similar in both groups, and were not a statistically significant factor. Note that one participant with multiple repairs in the processed allograft group had one injury with a gap of 23 mm, which was beyond the established inclusion criteria, but was allowed as a protocol exception because the participant had other injuries that qualified and were enrolled. This participant was lost to follow-up 3 months post repair and thus was not included in the outcomes analysis.

Subsequent to treatment, 16 participants totaling 20 nerve reconstructions returned for at least 6 months of follow-up visit with 15 nerve reconstructions completing the final visit at 12 months (Table 3). When looking at s2PD, treatment groups showed a statistically significant difference ($P < .05$) at month 12, with greater recovery for participants in the processed allograft treatment group. The mean s2PD at 12 months for processed allograft was 5 ± 1 mm and 8 ± 5 mm for the conduit group (Figure 1). This represents a 66 ± 6% and 38 ± 11% improvement from baseline for the allograft and conduit groups, respectively. For the m2PD assessment, the allograft group had a mean of 5 ± 1 mm, whereas the conduit group had a mean of 7 ± 5 mm ($P > .05$; Figure 2).

When looking at participants reporting a minimum of 6-month follow-up, return to S3+ was reported in all of the processed allograft participants (8 of 8 digits) as compared with 75% (9 of 12 digits) in the conduit group. Return to S4 was reported in 83% of processed allograft repairs and 50% of hollow conduit repairs, although this difference was not statistically significant.

For SWMF testing, the processed allograft group had a mean of 3.6 ± 0.7 whereas the conduit group had a mean of 4.4 ± 1.4 at month 12. Comparisons between the treatment groups showed a statistically significant difference ($P < .05$) at month 12. In addition, recovery of protective sensation (SWMF score of 4.31 or better) was reported in 100%

**Table 2.** Participant Demographics.

| | Processed allograft | Conduit |
|---|---|---|
| Participants randomized | 14 | 9 |
| Digital nerve repairs | 18 | 13 |
| Male/female | 12/2 | 6/3 |
| Smokers | 57% | 44% |
| Participants with relevant medical history | 43% | 22% |
| Average age (range) | 42 ± 13 (21, 63) | 38 ± 12 (20, 53) |
| Average gap length (mm; range) | 12.8 ± 4.6 (5, 23) | 12.2 ± 4.5 (5, 20) |

and 75% of digits in the processed allograft and conduit groups, respectively.

Statistical comparisons between treatment groups for DASH questionnaire, thermal discretion, and pain assessment scores at month 12 demonstrated positive outcomes for both groups and found no statistical significance between treatments (Table 4). We did not find any associations between age or gap length and sensory recovery. Given the sample size, we were unable to determine whether there was any significant difference in outcomes between the two groups with respect to gap size.

The safety population for the study included all participants randomized to treatment. When surgeons determined that an adverse event necessitating graft explant could be related to the product, the participant was included in the data analysis as a failure and assigned a corresponding score representing absent sensation. One adverse event was reported in the processed allograft group resulting from a severe skin infection at the injury site that required hospitalization and antibiotics before resolution. This was determined to be unrelated to the treatment as multiple culture results from additional stab wounds other than the grafted wound provided positive cultures. The conduit group had 2 possibly product-related adverse events: (1) persistent pain at the repair site, which was considered of minimal severity and was treated and resolved with ibuprofen; (2) tube extrusion, osteomyelitis, and fungal infection of the hand, considered serious and requiring hospitalization, which was resolved following amputation of the affected digit.

## Discussion

Alternatives to primary peripheral nerve repairs have been researched for over 2 centuries.[1,6] As microsurgery progressed in the second half of the 20th century, autografts became the standard of care to bridge nerve gaps. Use of nerve autograft creates a new sensory deficit in one area to repair another and can cause other complications such that their benefits may not outweigh the risks, thus creating a desire for a viable alternative. We sought to compare 2 off-the-shelf alternatives to determine their viability in a standardized digital nerve injury model for gaps of 5 to 20 mm.

In this study, we evaluated 20 digital nerve injuries randomized to either processed nerve allograft or hollow tube conduit. Both groups reported a lack of pain suggesting that either technique is successful in preventing significant symptomatic neuroma formation, and though both groups reported improvements in s2PD, m2PD, and SWMF assessments, outcomes for processed nerve allografts were more consistent with marked increases in sensory function at the 12-month point. As expected, based on the nerve gap lengths and distances for reinnervation, little difference was seen between the groups prior to the 6-month assessments. However, assessments showed modest improvements from baseline prior to the 6-month time point in both groups. By the 12-month time point, we found statistically significant differences between groups for s2PD and SWMF testing, which are largely the standard for peripheral nerve regenerative sensory assessment. In the processed allograft group, all 8 digits had return of 2PD discrimination as compared with 9 of 12 in the conduit group. Considering this, we suggest that processed nerve allograft performs as well as or better than conduit for digital nerve repairs but reserve final judgment as to which, if any, technique is superior until further comparative studies have been completed to validate the improved outcomes that we found in this initial study.

Limitations of the study include small sample size and relatively high attrition rate, with more patients lost to follow-up in the allograft group. Due to the small sample, the study was not sufficiently powered to support claims of superiority. Granting this, statistically significant differences between the groups were reported. We found that the attrition rate was related to the distance patients were required to travel and noncompliance with the follow-up schedule. We found no reason for a higher attrition rate in the allograft group. Another potential limitation for the study is the multicenter, multisurgeon nature of study. With different surgeons and outcome assessors, there is a possibility that variations in surgical and/or assessment techniques could have influenced results in ways that could not be accounted for or controlled. We attempted to mitigate this potential bias by educating surgeons and assessors on standardized techniques for each portion of the study in which they participated.

**Table 3.** Demographics and Functional Sensory Assessment Outcomes Completing at Least 6 Months of Follow-Up.

| Group[a]/ participant | Demographics/repair | | | | | Static 2PD | | | Moving 2PD | | | Semmes-Weinstein monofilament | | | MRCC sensory |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Gender[b] | Age[b] | Location of injury[c] | Gap length | Adverse event | 6 months | 9 months | 12 months* | 6 months | 9 months | 12 months | 6 months | 9 months | 12 months* | Final score[d] |
| A-1 | Male | 46 | PA 2RDN | 9 | No | 7 | LFU | LFU | 6 | LFU | LFU | 4.31 | LFU | LFU | S4 |
| A-2 | Male | 41 | 1RDN | 10 | No | 6 | LFU | LFU | 7 | LFU | LFU | 3.61 | LFU | LFU | S3+ |
| A-3 | Male | 52 | PA 2RDN | 12 | No | 10 | 12 | 7 | 9 | 10 | 7 | 3.61 | 3.61 | 3.61 | S3+ |
| A-4 | Male | 48 | 5UDN | 12 | No | 10 | 7 | 5 | 10 | 5 | 5 | 4.31 | 3.61 | 2.83 | S4 |
| A-5 | Male | 41 | 1UDN | 12 | No | 6 | 7 | 4 | 4 | 6 | 4 | 3.61 | 3.61 | 3.61 | S4 |
| A-6 | Male | 43 | 2RDN | 10 | No | 6 | 5 | 6 | 5 | 4 | 6 | 3.61 | 3.61 | 2.83 | S4 |
| A-7 | Male | 63 | 2RDN | 20 | No | 7 | 6 | 4 | 16 | 8 | 5 | 4.31 | 4.31 | 4.31 | S4 |
| A-7 | — | — | 3RDN | 9 | No | 8 | 4 | 3 | 16 | 7 | 5 | 4.31 | 4.31 | 4.31 | S4 |
| C-1 | Male | 52 | 2UDN | 13 | No | ND | 4 | 5 | ND | 4 | 4 | ND | 4.31 | 4.31 | S4 |
| C-1 | — | — | 3RDN | 20 | No | ND | 5 | 5 | ND | 4 | 4 | ND | 4.56 | 4.31 | S4 |
| C-2 | Female | 47 | 5RDN | 5 | No | 16 | 16 | LFU | 16 | 16 | LFU | 6.65 | 6.65 | LFU | S0 |
| | — | — | 5UDN | 9 | No | | | | | | | | | | |
| C-3 | Male | 31 | 2UDN | 18 | No | 15 | 10 | LFU | 8 | 7 | LFU | 2.83 | 2.83 | LFU | S3+ |
| C-3 | — | — | 3RDN | 17 | No | 13 | 10 | LFU | 6 | 8 | LFU | 2.83 | 2.83 | LFU | S3+ |
| C-4 | Female | 42 | 3RDN | 9 | No | 7 | 4 | 5 | 5 | 4 | 4 | 4.31 | 3.61 | 3.61 | S4 |
| C-5 | Male | 29 | 5UDN | 11 | Yes | 10 | 6 | 8 | 10 | 5 | 8 | 3.61 | 3.61 | 3.61 | S3+ |
| C-6 | Female | 20 | 1RDN | 7 | No | 6 | 6 | 5 | 4 | 5 | 5 | 4.31 | 3.61 | 3.61 | S4 |
| C-7 | Male | 26 | 2RDN | 15 | No | 6 | 6 | 4 | 6 | 6 | 4 | 3.61 | 3.61 | 3.61 | S4 |
| C-8 | Male | 53 | 4RDN | 12 | No | 8 | 5 | 6 | 7 | 6 | 5 | 4.31 | 3.61 | 3.61 | S4 |
| C-9 | Male | 39 | 2UDN | 13 | Yes | 16 | 16 | 16 | 16 | 16 | 16 | 6.65 | 6.65 | 6.65 | S0 |
| C-9 | — | — | 3RDN | 9 | Yes | 16 | 16 | 16 | 16 | 16 | 16 | 6.65 | 6.65 | 6.65 | S0 |

*Note*. PD, point discrimination; MRCC, Medical Research Council Classification; RDN, radial digital nerve; UDN, ulnar digital; PA, palmar aspect; ND, no data due to missed follow-up visit; LFU, participant lost to follow-up.
[a]Group designation: A = processed allograft; C = hollow tube conduit.
[b]Gender and age for participants with multiple nerve repairs were only reported once in the table. See corresponding participant number in the first column for each respective data point.
[c]Location of injury: 1 = thumb, 2 = index, 3 = middle; 4 = ring; 5 = small.
[d]Final score was assigned using the MRCC Scale for Sensory Recovery for participants reporting a minimum of 6-month follow-up.
*Statistically significant difference between treatment groups ($P < .05$).

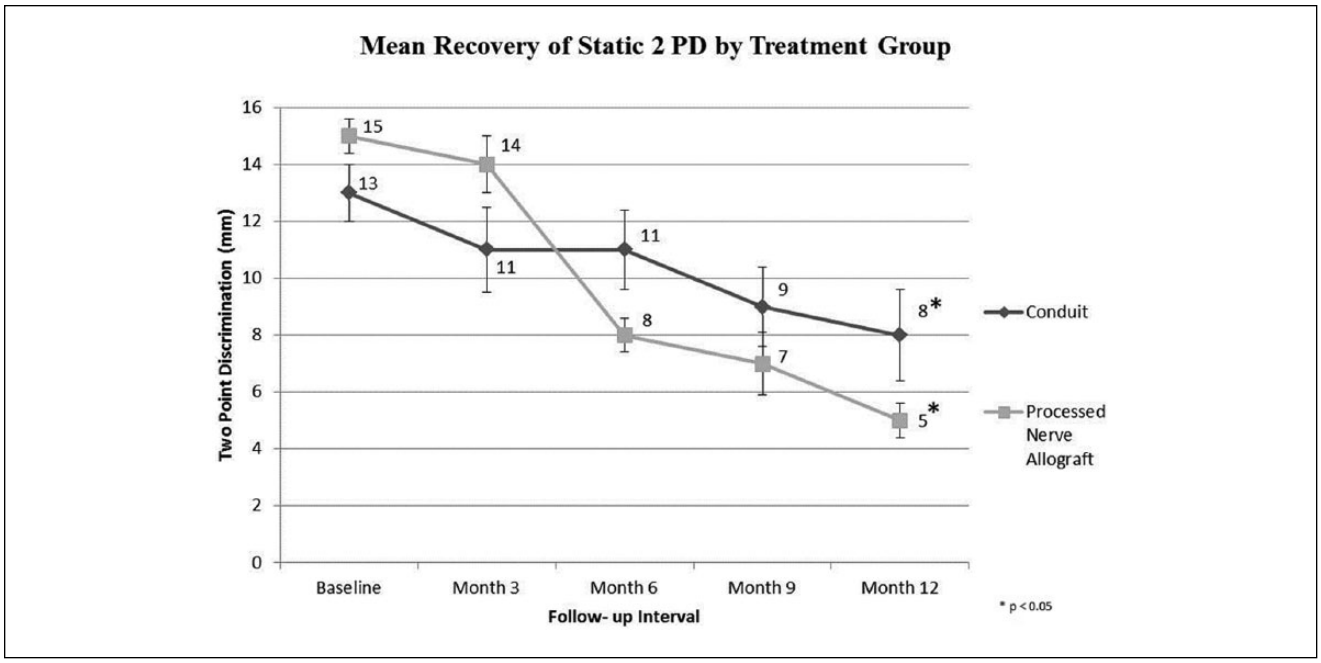


**Figure 1.** Mean change and standard error of s2PD discrimination by treatment over time for participants in the mITT population.
*Note.* s2PD, static 2-point discrimination; mITT, modified intent-to-treat population.

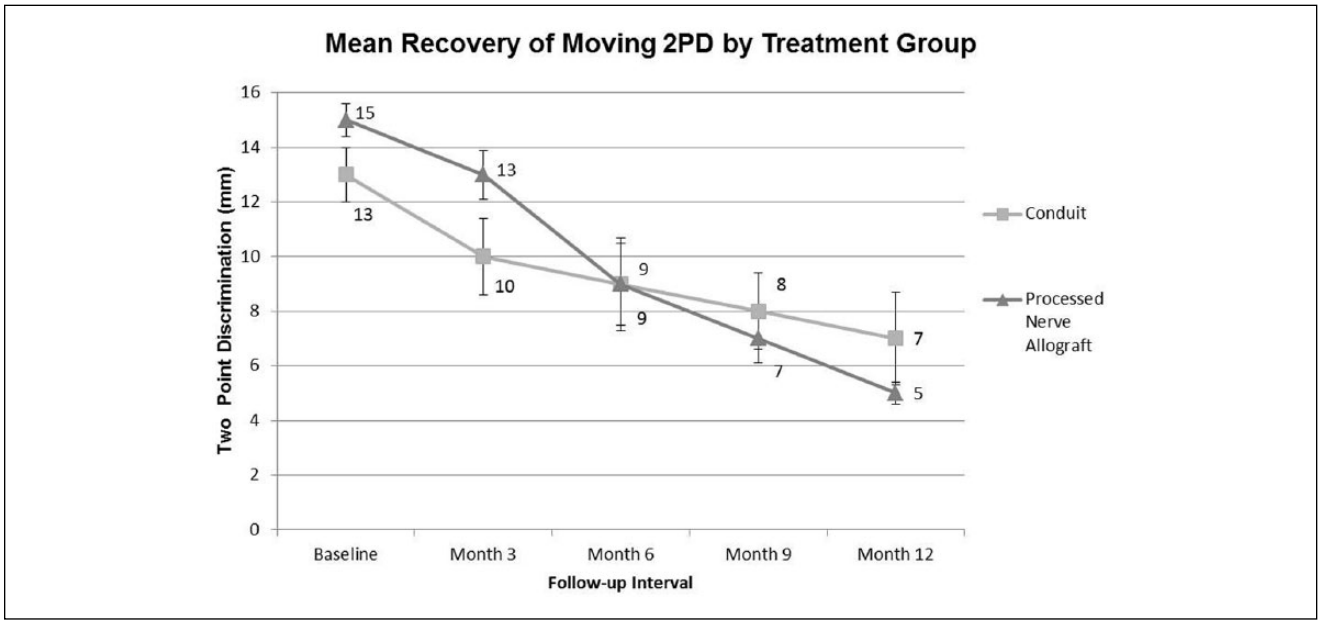


**Figure 2.** Mean change and standard error of m2PD discrimination by treatment over time for participants in the mITT population.
*Note.* m2PD, moving 2-point discrimination; mITT, modified intent-to-treat population.

Given these limitations to our study, comparisons of each treatment group with outcomes reported in the literature are warranted. Available clinical data for processed nerve allograft are comparative with our findings. A study from the Mayo Clinic on repairs of sensory nerves up to 30 mm found all participants recovered 2-point discrimination of 6 mm or better.[13] Other investigator-initiated single-center studies reported similar outcomes. Guo et al reported on 6 digital injuries with a mean gap of 23 mm that returned a mean 2PD of 6 mm. Taras et al reported on outcomes in 18 digital nerve repairs with a mean gap of 11 mm (5-30 mm) where 83% of repairs reported good to excellent static or

**Table 4.** DASH, Thermal Discretion, and Pain Intensity Results at Baseline Compared With 12 Months.

| | Baseline | | | 12 months | | |
|---|---|---|---|---|---|---|
| | Processed allograft | Conduit | *P* value | Processed allograft | Conduit | *P* value |
| DASH | | | | | | |
| Mean (SD) | 49 (20.6) | 42 (28.3) | .5585 | 5 (6.5) | 8 (6.3) | .3182 |
| Thermal | | | | | | |
| Yes | 1 (8.3%) | 3 (30.0%) | ND | 6 (100.0%) | 7 (100.0%) | ND |
| No | 11 (91.6%) | 7 (70.0%) | | 0 (0.0%) | 0 (0.0%) | |
| Pain intensity | | | | | | |
| Mean (SD) | 4.7 (3.4) | 4.4 (2.1) | .9896 | 0.5 (0.6) | 0.9 (1.0) | .4316 |

*Note.* DASH, Disability of the Arm, Shoulder and Hand; ND, no data due to missed follow-up visit.

moving 2PD of at least 7 mm.[7,23] Furthermore, Cho et al used a multicenter registry on nerve allograft to report on 35 digital nerve repairs with a mean gap of 19 mm where 89% returned to S3 or and greater.[4]

Outcomes reported in the literature for digital nerve repairs with conduits have varied widely. Investigator initiated studies with collagen conduits report positive outcomes as high as 89% to as low as 40%.[3,8,14,24] In a prospective study comparing conduits with direct repair and autograft, Weber et al reported positive results in 66% of digital repairs greater than 5 mm.[25] In a recent analysis of the literature, Isaacs et al concluded that as the gap size increases, the outcome of the repair becomes less predictable, which may help explain the large variation in outcomes with conduit repairs.[11]

Although this pilot was intentionally limited to a small sample size, we utilized a well-defined randomized controlled blinded study design to provide a higher level of clinical evidence to determine the differences in functional recovery outcomes. Our study design and data should be considered when powering and determining minimum follow-up periods for future larger randomized controlled studies. Even with the small sample size, we found statistically and clinically significant differences between groups: Processed nerve allograft reconstruction resulted in improved sensory outcomes compared with reconstruction with hollow conduits.

## Ethical Approval

This study was approved by our institutional review board.

## Statement of Human and Animal Rights

This IRB-approved study was conducted 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.

## Statement of Informed Consent

This study was conducted in accordance with an institutional review board approved protocol. Informed consent, as well as any necessary Health Insurance Portability and Accountability Act consent, was obtained in accordance with the IRB approvals.

## Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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