A Multicenter Prospective Randomized Comparison of Conduits Versus Decellularized Nerve Allograft for Digital Nerve Repairs

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Purpose While there are advantages and disadvantages to both processed nerve allografts (PNA) and conduits, a large, well-controlled prospective study is needed to compare the efficacy and to delineate how each of these repair tools can be best applied to digital nerve injuries. We hypothesized that PNA digital nerve repairs would achieve superior functional recovery for longer length gaps compared with conduit-based repairs.

Methods Patients (aged 18–69 years) presenting with suspected acute or subacute (less than 24 weeks old) digital nerve injuries were recruited to prticipate at 20 medical centers across the United States. After stratification to short (5-14 mm) and long (15-25 mm) gap subgroups, the patients were randomized (1:1) to repair with either a commercially available PNA or collagen conduit. Baseline and outcomes assessments were obtained either before or immediately after surgery and planned at 3-, 6-, 9-, and 12-months after surgery. All assessors and patients were blinded to the treatment arm.

Results In total, 220 patients were enrolled, and 183 patients completed an acceptable last evaluable visit (at least 6 months and not more than 15 months postrepair). At last follow-up, for the short gap repair groups, average static two-point discrimination was 7.3 ± 2.8 mm for PNA and 7.5 ± 3.1 mm for conduit repairs. For the long gap group, average static two-point discrimination was significantly lower at 6.1 ± 3.3 mm for PNA compared with 7.5 ± 2.4 mm for conduit repairs. Normal sensation (American Society for Surgery of the Hand scale) was achieved in 40% of PNA long gap repairs, which was significantly more than the 18% observed in long conduit patients. Long gap conduits had more clinical failures (lack of protective sensation) than short gap conduits.

Conclusions Although supporting similar levels of nerve regeneration for short gap length digital nerve repairs, PNA was clinically superior to conduits for long gap reconstructions. (*J* Hand Surg Am. 2023;48(9):904–913. Copyright © 2023 by the American Society for Surgery of the Hand. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).)

Type of study/Level of evidence Therapeutic I.

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D IGITAL NERVE REPAIR IS the most common nerve reconstruction surgery performed in the United States. Tissue loss, zone of injury, time elapsed, and nerve retraction often result in substantial gaps. Excessive tension across such repairs may induce intraneural ischemia and compromise axonal regeneration.^{1–3} Therefore, digital nerve gaps must be bridged using one of the following three options: nerve autograft, processed nerve allograft, or conduits.

Collagen conduits are those cleared by the United States Food and Drug Administration and commercially available for nerve defects up to 25 mm. Microsutures placed as horizontal mattresses through the ends of the conduit are used to pull the proximal and distal nerve stumps a couple of millimeters into the lumen. Irrigation of the lumen removes debris and retained intraluminal irrigant supports the formation of a fibrin scaffold.⁴ This scaffold is necessary for Schwann cell migration and subsequent axonal elongation across the conduit. This fibrin clot, however, can become unstable, particularly with increasing conduit lengths.⁵

Processed decellularized nerve allograft (PNA) is a donated human nerve rendered immunotolerant through detergent-based decellularization and cleansing followed by gamma irradiation sterilization. The product must be maintained at subfreezing temperatures until being thawed for implantation. The surgical technique is then analogous to autografting. The preserved native intraneural three-dimensional anatomy provides guidance channels and cues. An additional enzymatic process to remove axon-inhibiting chondroitin sulfate proteoglycans improves regeneration.⁶ Native Schwann cells must migrate into the PNA to create a neurotrophic environment supportive of axon elongation.⁷

While small animal studies support use of PNA over collagen conduits,^{8,9} the contemporary clinical literature is more controversial. In general, approximately 75% of conduit-assisted digital nerve repairs have achieved good or excellent outcomes,^{10,11} although these results have worsened with longer gap lengths.^{12–14} PNA digital nerve repairs have resulted in around 85% good or excellent outcomes in several studies in gaps approaching 3 cm.^{15,16} A

small multicenter, prospective, randomized pilot study with a minimum of 6-month follow-up demonstrated a higher percentage of PNA cases recovering excellent sensibility.¹⁷ With these preliminary findings, a sufficiently powered prospective study was needed to determine comparative efficacy. We hypothesized that conduits would be superior for shorter gaps, whereas PNA would be superior for longer gaps.

MATERIAL AND METHODS

In partnership with AxoGen, the manufacturer and distributer of Avance Nerve Graft (PNA), the lead investigators (J.I. and L.S.L.) formed a consortium of 20 medical centers with a target sample size of 220 digital nerve injuries suitable for repair with either type I bovine collagen conduit (nerve cuff) or PNA. The investigation was designed around key study elements highlighted in the study title acronym RECON—A Multicenter, Prospective, Randomized, Subject, and Evaluator Blinded Comparative Study of Nerve Cuffs and Avance Nerve Graft Evaluating Recovery Outcomes for the Repair of Nerve Discontinuities.

Centers were recruited to participate based on the anticipated patient volume, the historical use of both Avance Nerve Graft and NeuraGen Nerve Guide (Integra LifeSciences) collagen conduits at that institution, adequate clinical research infrastructure, and willingness to randomize treatments. All participating surgeons underwent technique training to encourage surgical consistency with standard clinical practice and manufacturer's instructions for use. Hand therapists and specialized research nurses blinded to repair type performed all assessments.

Appropriate institutional review board approval was obtained for all participating sites, and all subjects provided written consent for participation. The study was HIPAA compliant and conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The study was registered on clinicaltrials.gov under registry number NCT01809002.

Patients presenting with suspected digital nerve lacerations were recruited from emergency rooms, urgent care facilities, and clinics and screened for

TABLE 1. Inclusion/Exclusion Criteria

Inclusion Criteria

- 1. Subjects 18-69 y of age, inclusive;
- 2. Require primary or secondary nerve injury repair with nerve cuff (NeuraGen Nerve Guide a type 1 bovine collagen nerve cuff) or Avance Nerve Graft in at least 1 digital nerve;
- 3. Zone of injury must be resectable;
- 4. Nerve gaps following resection, between 5 and 25 mm, inclusive;
- 5. Undergo tension free end-to-end nerve to nerve coaptation on both the proximal and distal portion of the nerve gap in the Avance Nerve Graft Group or nerve entubulation in the Nerve Cuff group;
- 6. Have an uninjured contralateral or adjacent digit that is suitable to serve as a referenced digit for baseline functional assessments;
- 7. Be willing and able to comply with all aspects of the treatment and evaluation schedule over a 12-mo duration

Exclusion Criteria

- 1. Estimated distance of regeneration of >150 mm (distance from the proximal injury site to the tip of the target digit);
- 2. Injuries distal to the distal interphalangeal joint;
- 3. Extensive soft tissue injury that will impair recovery assessment;
- 4. Incomplete nerve transections;
- 5. Injury requiring replantation of target digit;
- 6. Injuries to the affected nerve proximal to the superficial palmar arch;
- 7. Nerve injuries >24 wk after initial injury;
- 8. End to side nerve repair;
- 9. Injuries with vascular damage resulting in inadequate perfusion despite repair;
- 10. Subjects with type 1 diabetes mellitus or type 2 diabetes mellitus requiring regular insulin therapy;
- 11. Subjects who are undergoing or expected to undergo treatment with chemotherapy, radiation therapy, or other known treatment that affects the growth of neural and/or vascular system;
- 12. Use of bovine collagen-based nerve conduit in a subject with known or suspected bovine sensitivity;
- 13. History of neuropathy, diabetic neuropathy, or any other known neuropathy;
- 14. Currently enrolled in another investigational study;
- 15. Expected use of medication during the study that is known to impact nerve regeneration or cause peripheral neuropathy;
- 16. History of chronic ischemic condition of the upper extremity; and
- 17. Any subject who at the discretion of the Investigator is not suitable for inclusion in the study.

inclusion/exclusion criteria (Table 1). Intrasurgically, injured digital nerves were dissected, and damaged nerve tissues were resected in preparation for nerve repair per standard surgical treatment. With the digit extended, the in-continuity gap and distance from anticipated proximal nerve coaptation to the fingertip were measured to ensure that inclusion/exclusion criteria for at least one nerve were satisfied. The digital nerve with the longest gap was considered the primary target nerve and was stratified into predetermined gap length categories as "short" (5-14)mm) or "long" (15-25 mm). The gap was remeasured after insetting, and this measurement was used for final categorization and analysis. Additional nerve repairs in the same patient were not analyzed. Subjects were then randomized by a single interactive online response system to either PNA or conduit repair in a 1:1 ratio. Repairs were performed under optical magnification (either loupe or surgical microscope) and using microsutures only. Patients and assessors were strictly blinded to the repair technique. Surgeons were asked to complete a VAS-based satisfaction survey following each nerve repair.

Subjects were evaluated, and data were collected at all completed visits from initial presentation (up to 10 days postrepair) and at predetermined postoperative months 1, 3, 6, 9, and 12. Medical history, demographics, and traumatic injury history were all recorded. Sensibility assessments were obtained of affected and contralateral or adjacent digits using static two-point discrimination, moving two-point discrimination, and pressure threshold (Semmes-Weinstein) monofilament testing (SWMF). For patients undergoing a common digital nerve repair, assessors randomly identified one digital nerve branch as the target nerve. These measurements were categorized based on the Medical Research Council Classification rating (Table 2) and the American Society for Surgery of the Hand (ASSH) classification (2PD less than 6 mm is "normal," 6 to 10 mm is "fair," and 11 to 15 mm and protective or anesthetic is "poor").¹⁸ Subjects completing at least 6 months of follow-up (but with the last visit not more than 15 months postrepair) were included in the analysis.

The study database was established and managed by an independent, third-party contract research

TABLE 2. MRCC Classification for the Recovery ofSensory Function

S 0	Absence of sensibility in the autonomous area— SWM "absent"
S 1	Recovery of deep cutaneous pain sensibility within the autonomous area of the nerve—SWM $= 6.65$
S2	Return of some degree of superficial cutaneous pair and tactile sensibility within the autonomous area of the nerve—SWM = 4.56
S 3	Return of superficial cutaneous pain and tactile sensibility throughout the autonomous area, with

- disappearance of any previous over response— SWM = 4.31 S3+ Return of sensibility as in S3; in addition, there is
- some recovery of 2-point discrimination within the autonomous area 7–15 mm
- S4 Complete recovery 2-point discrimination 2–6 mm

organization and associated biostatisticians. Static 2point discrimination (s2PD) was the primary outcome measure for the last evaluable visit and was analyzed as a continuous variable. The study design incorporated a sequential testing procedure to assess noninferiority and superiority across the study populations. If PNA performed as good or better than conduit, superiority could be tested. Study completion of 88 subjects per repair group was required to ensure a study power of >80%. For superiority testing, the shorter gap group had >95%power and the longer gap group had >80% power (further details in Supplement). When comparing between-group means, Wilcoxon Rank Sum or independent t-tests were performed as appropriate for variables exhibiting nonparametric or parametric outcomes, respectively. Fisher's exact tests were used for categorical data analyses to compare proportions. The number and percentage of subjects who recovered s2PD in the target repair (ie, s2PD of 2-15 mm) at the last evaluable visit were summarized by repair type. The last evaluable visit was defined as at least 6-months but not later than 15months (ie, 6-month, 9-month, 12-month visit +3 months window). After observing statistical significance between products for the 15-25 mm gap group, the group was incrementally increased to incorporate smaller gap lengths (eg, 14 mm, 13 mm, etc.) to determine the inflection point where a statistically significant difference between the groups was observed.

Significance was interpreted using $\alpha < 0.05$. The study adhered to the Consolidated Standards Of Reporting Trials (CONSORT) guidelines.

TABLE 3. Demographics

	Conduit	PNA	Overall
Subjects consented, <i>n</i>			372
Subjects screen failed, <i>n</i>			152
Subjects randomized, <i>n</i>	108	112	220
Women (%)	28.7%	30.4%	29.5%
Men (%)	71.3%	69.6%	70.5%
Age, y			
Mean (SD)	39.5 (14.1)	36 (13.6)	38.5 (13.8)
Min, Max	18, 69	18, 68	18, 69

RESULTS

In total, 220 patients were enrolled and 183 completed an acceptable evaluable visit (between 6and 15-months postrepair) and were included in the analysis. Population demographics are included in Table 3. Only primary target nerves were used in this analysis and included 59 conduit and 56 PNA repairs for short gaps (5–14 mm), and 33 conduit and 35 PNA repairs for long gaps (15–25 mm). In total, there were a total of 152 total screen. Of those, 25 patients did not have a full transection, and during surgical exploration, 43 patients did not require repair. The number of subjects treated with primary repair was not collected.

For the short gap groups, the average s2PD for the PNA group was 7.3 \pm 2.8 mm compared with 7.5 \pm 3.1 mm for the conduit group at the last evaluable visit. This difference became statistically significant for gaps greater than 12 mm (one-sided Wilcoxon Rank Sum test; P < .05) (more details in Supplement). The PNA and conduit groups achieved 80.0% and 79.7% S3+ or better, respectively; the PNA group achieved 34.5% S4 compared with 27.1% for the conduit group (Table 4). The short PNA and conduit groups achieved 92.7% and 89.8% return of protective sensation (4.31 monofilament or better), respectively. The PNA and conduit groups achieved 70.9% and 66.1% return of light touch (3.61 monofilament or better), respectively; the PNA group achieved 40.0% normative range of pressure detection (2.83 monofilament) compared with 27.1% for the conduit group (Table 5). The average m2PD for the PNA group was 6.9 \pm 3.2 mm compared with 7.1 \pm 3.0 mm for the conduit group at the last evaluable visit. The PNA and conduit groups achieved m2PD < 8 mmat 64.5% and 51.1%, respectively; the PNA group

TABLE 4. Static 2PD at Last Evaluable Visit				
	Gaps 5–	Gaps 5–14 mm		–25 mm
	Conduit	PNA	Conduit	PNA
Total <i>n</i>	59	56	33	35
Missing	0	1	1	1
Absent s2pd [†]	12	11	12	11
Last evaluable visit n	47	44	21	24
Mean (mm)	7.5	7.3	7.5	6.1*
Median (mm)	7.0	7.0	8.0	5.0
Min (mm)	2	3	5	2
Max (mm)	15	14	14	14
Standard deviation (mm)	3.1	2.8	2.4	3.3
S3+%	52.5%	45.5%	36.4%	28.6%
S4%	27.1%	34.5%	27.3%	40.0%

Means were compared via Wilcoxon rank sum tests. Proportions of categorical data were compared via Fisher's exact tests. *P < .05, one-sided Wilcoxon rank sum test.

†Individuals who did not recover s2PD to 15 mm were not included in calculation of mean s2pd.

TABLE 5. Semmes Weinstein Monofilament Recovery at Last Evaluable Visit

	Gaps 5–14 mm		Gaps 15-25 mm	
	Conduit	PNA	Conduit	PNA
Total <i>n</i>	59	56	33	35
Missing	0	1	0	0
Last evaluable visit <i>n</i>	59	55	33	35
Mean	3.8	4.0	3.3	3.7
Median	4.0	4.0	3.0	4.0
Min	0	2	1	1
Max	5	5	5	5
Standard deviation	1.0	1.0	1.5	1.3
4.31 monofilament %	23.7%	21.8%	21.2%	20.0%
3.61 monofilament %	39.0%	30.9%	18.2%	25.7%
2.83 monofilament %	27.1%	40.0%	30.3%	34.3%
Return of protective Sensation rate	89.8%*	92.7%	69.7%*	80.0%

Means were compared via Wilcoxon rank sum tests. Proportions of categorical data were compared via Fisher's exact tests *P < .05.

achieved 2–3 mm m2PD in 15.6% compared with 12.8% for the conduit group (Table 6). Classification based on the ASSH scale did not reveal any significant differences between PNA and conduits for short gap repairs (Fig. 1).

For the long gap groups, the final average s2PD for the PNA group, 6.1 ± 3.3 mm, was significantly better than the conduit group, 7.5 ± 2.4 mm (P < .05). The PNA and conduit groups achieved 68.6% and 63.6% S3+ or better, respectively; the PNA group achieved 40.0% S4 compared with 27.3% for the conduit group (Table 4). The PNA and conduit groups achieved 80.0% and 69.7% return of protective sensation, respectively. The rate of return of protective sensation in the long conduit group was significantly lower than the short conduit group (P < .05). The PNA and conduit groups achieved 60.0% and 48.5% return of light touch, respectively; the PNA group achieved 34.3% normative range of pressure detection compared with 30.3% for the conduit group (Table 5). The average m2PD for the PNA group was 7.0 \pm 3.1 mm compared with

TABLE 6. Moving 2PD at Last Evaluable Visit					
	Gaps 5–	Gaps 5–14 mm		Gaps 15–25 mm	
	Conduit	PNA	Conduit	PNA	
Total n	59	56	33	35	
Missing	0	1	0	1	
Absent m2pd*	12	10	9	7	
Last evaluable visit n	47	45	24	27	
Mean	7.1	6.9	7.8	7.0	
Median	7.0	7.0	7.0	7.0	
Min	2	2	4	2	
Max	14	13	15	12	
Standard deviation	3.0	3.2	3.4	3.1	
>7 mm	48.9%	35.6%	50.0%	37.0%	
4-7 mm	38.3%	48.9%	50.0%	48.1%	
2-3 mm	12.8%	15.6%	0.0%	14.8%	

Means were compared via Wilcoxon Rank sum tests. Proportions of categorical data were compared via Fisher's exact tests. *Individuals who did not recover s2PD to 15 mm were not included in the calculation of mean m2pd.

7.8 \pm 3.4 mm for the conduit group at the last evaluable visit. The PNA and conduit groups achieved m2PD < 8 mm 62.9% and 50.0%, respectively; the PNA group achieved 2–3 mm m2PD 14.8% compared with 0.0% for the conduit group (Table 6). Additionally, the ASSH classification of "normal" for the PNA group (40.0% normal, 22.9% fair, and 37.1% poor) was significantly better than for the conduit group (18.2% normal, 39.4% fair, and 42.4% poor) (*P* < .05) (Fig. 1).

Twenty-seven complications including infection, wound healing problems, or the need for secondary surgical interventions were reported (17 in the PNA groups and 10 in the conduit groups). One infection required an additional surgery but was deemed unrelated to the nerve repair. One patient in the conduit group required a revision procedure and removal of the device.

Surgeon satisfaction was high with both tools though significantly better for the PNA (Table 7).

DISCUSSION

PNA and conduit performance were similar at shorter gaps based on s2PD and similar percentages (approximately 80%) achieving S3+ or better. No categorical differences were noted based on the ASSH classification system. PNA performance, however, was superior at the top quartile of the shorter gap group, and this difference remained consistent across the longer gap groups as demonstrated by improved 2PD in the PNA group. For long gap repairs, approximately twice as many PNA-treated nerves achieved normal sensation compared with conduit-treated nerves. These results are similar to previous publications for PNA but better than expected for conduits. Taras et al¹⁵ reported a similar restoration of an average of 7 mm 2PD in 18 digital nerve PNA reconstructions with gaps averaging 11 mm (range of 5-30 mm). Although using a slightly different scale, 83% were believed to have good or excellent recovery.¹⁵ Reports generated from an industry-sponsored multicenter registry (RANGER) corroborate these findings-average 2PD of 7 mm and an 84% rate of S3+/S4 recovery for short gap PNA repairs.^{16,19} Gap size subanalysis reported S3 or better recovery in 92% (14 mm and less) and 85% (15-25 mm) of PNA repairs. By contrast, this same study reported 67% (14 mm and less) and 45% (15–25 mm) of a matched patient cohort regaining S3 or better sensibility following conduit repair.²⁰ Conduit repairs across gaps greater than 8 to 12 mm have been associated with poorer results.^{12,13,21} We found that for both short and long gap conduit repairs, patients recovered a mean static 2PD of 7.5 mm, although clinical failure (as defined by lack of protective sensation) occurred three times more commonly in the long gap conduit group. In contrast to our findings, Rinker and Liau¹² reported a mean recovery of 7.4 and 9.5 mm 2PD for short (less than 10 mm) and long (10-25 mm) gaps, respectively. Although we categorized **ASSH Classification**

PNA (normal %) > Conduit (normal %): *p* < 0.05

FIGURE 1: ASSH classification of sensory recovery for conduit and PNA repairs based on the gap length.

TABLE 7. Physician Satisfaction (1–10 With 1Being the Best Score)			
	Conduit	PNA	
	Mean (SD)		
Ease of implantation	2.9 (2.19)	2.6 (1.57)	
Handling properties of implant*	3.0 (2.12)	2.4 (1.57)	
Ability to properly size*	3.5 (2.21)	2.9 (1.96)	
Overall satisfaction*	3.1 (2.34)	2.3 (1.75)	

Means were compared via Wilcoxon rank sum tests *P < .05.

patients not recovering at least 15 mm 2PD as "absent 2PD," Rinker and Liau¹² arbitrarily assigned similar patients a value of 16 mm 2PD. Higher rates of failure (to regain 2PD), therefore, positively skewed our results—ie, the mean 2PD for conduit repairs appears consistent across gap lengths but does not account for a nearly 2-fold incidence of the absence of 2PD in the long versus short gap groups. By contrast, using a default value of 16 mm would imply a level of sensibility that was not achieved.

These results support our hypothesis and appear to reflect superior axon regeneration in PNA compared with conduits for longer gaps. PNA offers an organized internal architecture, guidance cues such as laminin and fibronectin, and some endogenous retention of growth factors.⁸ Conduits rely on the formation of a fibrin-based scaffold within the

conduit lumen to support axon regeneration. Fibronectin has been identified in this matrix early in the process of nerve regeneration, whereas neurotrophic factors secreted by the inserted nerve stumps may accumulate within the lumen as well.^{22,23} In situ Schwann cells must migrate across and populate the fibrin scaffold of the conduit or internal architecture of the PNA to support axonal elongation.^{7,24} At shorter lengths, differences in neurotrophic potential may be less critical, While at longer lengths, as evidenced by in vivo small animal studies, fibrin matrix instability becomes a potential problem.⁵ Axon regeneration clearly decreased in direct correlation with gap size in a rodent sciatic nerve repair model.⁸ Post hoc histological analysis highlighted the poorly organized clustering of axon regeneration in conduits compared with the even distribution noted in PNA. The authors of that study implicated a "lack of endoneurial microstructure" in the conduits.²⁵ With catastrophic fibrin scaffold collapse, no axon regeneration would be expected. Clinical failure in our study, defined by lack of protective sensibility, occurred following approximately 10% of short gap versus 30% of long gap conduit repairs supporting this notion. For longer PNAs, a poorly understood degradation of Schwann cell regenerative support has been cited as a cause of failure.²⁶ This has not been suggested as a problem with the lengths of PNA used in this study, and more importantly, we did not see a degradation of recovery between short and long PNA digital nerve repairs. In fact, for longer length gaps, S4 was obtained in 40% of PNA repairs versus 27% of conduit repairs and moving 2PD of 2-3 mm in 15% of the PNA repairs versus none in conduit repairs.

Some failures occurred in both groups, and in addition to inherent differences between conduits and PNA, technical issues must be considered. Failure to adequately debride damaged nerve tissue,²⁷ inadequate alignments of coaptations, and catastrophic repair rupture could occur, regardless of the technique. Poor size matching of conduits to the target nerve could compromise outcomes as well but may be considered specific to that tool.²⁸ Indeed, the surgeon survey in our study did indicate a greater difficulty in properly sizing conduits compared with PNA.

Although the target follow-up was 12 months from surgery, patients assessed at or greater than 6 months from surgical repair up to 15 months were included in final analysis. Experimental axon regeneration occurs at 1 mm per day.²⁹ Fibrin matrix formation and migration of Schwann cells into both the conduit and the PNA must precede axon elongation. Animal studies suggest that this should occur within weeks.^{7,24} The maximum regeneration length was 150 mm; hence, even by conservative standards, measurable regeneration should have occurred by the 6-month time point. Although the literature suggests continued recovery after 6 months,^{30,31} the exact plateau point is unknown. Six months was considered sufficient for analysis, meaningful, and consistent between groups. Furthermore, as demonstrated by sensitivity analysis, the time-point range for the last evaluable visit did not appear to influence outomes (see Supplement material).

At the time of this study, commercially available conduits (in the United States) are manufactured using bovine collagen, polyglycolic acid (PGA), polycaprolactone (PCL), or processed porcine small intestine submucosa. Differences in these materials including resistance to kinking, permeability, and absorbability could affect nerve regeneration. In one animal study, PGA conduits were inferior to alternative products.³² For this study, to maintain consistency, all conduit repairs used the collagen-based Neuragen Nerve Guide. Because no clinical difference has been demonstrated between conduit options, this collagen conduit is offered as a surrogate to represent all conduit-based digital nerve repairs, although we acknowledge the possibility that an alternative conduit product could have produced different results.

In conclusion, this multicenter, prospective, randomized, double-blinded clinical outcome study comparing conduit and PNA for digital nerve repairs showed that PNA and conduits supported similar recovery of sensibility at shorter lengths. However, PNA was superior to conduits for longer length gaps.

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REFERENCES

- Wood MD, Kemp SW, Weber C, Borschel GH, Gordon T. Outcome measures of peripheral nerve regeneration. *Ann Anat.* 2011;193(4): 321–333.
- Clark WL, Trumble TE, Swiontkowski MF, Tencer AF. Nerve tension and blood flow in a rat model of immediate and delayed repairs. *J Hand Surg Am.* 1992;17(4):677–687.
- 3. Yi C, Dahlin LB. Impaired nerve regeneration and Schwann cell activation after repair with tension. *Neuroreport.* 2010;21(14): 958–962.
- Williams LR, Varon S. Modification of fibrin matrix formation in situ enhances nerve regeneration in silicone chambers. *J Comp Neurol*. 1985;231(2):209–220.
- 5. Lundborg G, Dahlin LB, Danielsen N, et al. Nerve regeneration in silicone chambers: influence of gap length and of distal stump components. *Exp Neurol*. 1982;76(2):361–375.
- 6. Neubauer D, Graham JB, Muir D. Chondroitinase treatment increases the effective length of acellular nerve grafts. *Exp Neurol*. 2007;207(1):163–170.

- Hayashi A, Koob JW, Liu DZ, et al. A double-transgenic mouse used to track migrating Schwann cells and regenerating axons following engraftment of injured nerves. *Exp Neurol.* 2007;207(1):128–138.
- Whitlock EL, Tuffaha SH, Luciano JP, et al. Processed allografts and type I collagen conduits for repair of peripheral nerve gaps. *Muscle Nerve*. 2009;39(6):787–799.
- **9.** Giusti G, Willems WF, Kremer T, Friedrich PF, Bishop AT, Shin AY. Return of motor function after segmental nerve loss in a rat model: comparison of autogenous nerve graft, collagen conduit, and processed allograft (AxoGen). *J Bone Joint Surg Am.* 2012;94(5):410–417.
- Meek MF, Coert JH. Recovery of two-point discrimination function after digital nerve repair in the hand using resorbable FDA- and CEapproved nerve conduits. *J Plast Reconstr Aesthet Surg.* 2013;66(10):1307–1315.
- Taras JS, Jacoby SM, Lincoski CJ. Reconstruction of digital nerves with collagen conduits. J Hand Surg Am. 2011;36(9):1441–1446.
- Rinker B, Liau JY. A prospective randomized study comparing woven polyglycolic acid and autogenous vein conduits for reconstruction of digital nerve gaps. *J Hand Surg Am.* 2011;36(5):775–781.
- Weber RA, Breidenbach WC, Brown RE, Jabaley ME, Mass DP. A randomized prospective study of polyglycolic acid conduits for digital nerve reconstruction in humans. *Plast Reconstr Surg.* 2000;106(5):1036–1045; discussion 1046–1048.
- Battiston B, Geuna S, Ferrero M, Tos P. Nerve repair by means of tubulization: literature review and personal clinical experience comparing biological and synthetic conduits for sensory nerve repair. *Microsurgery*. 2005;25(4):258–267.
- Taras JS, Amin N, Patel N, McCabe LA. Allograft reconstruction for digital nerve loss. J Hand Surg Am. 2013;38(10):1965–1971.
- Rinker BD, Ingari JV, Greenberg JA, Thayer WP, Safa B, Buncke GM. Outcomes of short-gap sensory nerve injuries reconstructed with processed nerve allografts from a multicenter registry study. *J Reconstr Microsurg*. 2015;31(5):384–390.
- 17. Means KR Jr, Rinker BD, Higgins JP, Payne SH Jr, Merrell GA, Wilgis EF. A multicenter, prospective, randomized, pilot study of outcomes for digital nerve repair in the hand using hollow conduit compared with processed allograft nerve. *Hand (N Y)*. 2016;11(2): 144–151.
- Wang Y, Sunitha M, Chung KC. How to measure outcomes of peripheral nerve surgery. *Hand Clin.* 2013;29(3):349–361.
- Safa B, Jain S, Desai MJ, et al. Peripheral nerve repair throughout the body with processed nerve allografts: results from a large multicenter study. *Microsurgery*. 2020;40(5):527–537.

- Leversedge FJ, Zoldos J, Nydick J, et al. A multicenter matched cohort study of processed nerve allograft and conduit in digital nerve reconstruction. J Hand Surg Am. 2020;45(12):1148–1156.
- Lohmeyer JA, Kern Y, Schmauss D, et al. Prospective clinical study on digital nerve repair with collagen nerve conduits and review of literature. J Reconstr Microsurg. 2014;30(4):227–234.
- Longo FM, Manthorpe M, Skaper SD, Lundborg G, Varon S. Neuronotrophic activities accumulate in vivo within silicone nerve regeneration chambers. *Brain Res.* 1983;261(1):109–116.
- 23. Lundborg GA. A 25-year perspective of peripheral nerve surgery: evolving neuroscientific concepts and clinical significance. *J Hand Surg Am.* 2000;25(3):391–414.
- Williams LR, Longo FM, Powell HC, Lundborg G, Varon S. Spatialtemporal progress of peripheral nerve regeneration within a silicone chamber: parameters for a bioassay. *J Comp Neurol.* 1983;218(4): 460–470.
- 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(2):83–90.
- Saheb-Al-Zamani M, Yan Y, Farber SJ, et al. Limited regeneration in long acellular nerve allografts is associated with increased Schwann cell senescence. *Exp Neurol.* 2013;247:165–177.
- Millesi H. The nerve gap. Theory and clinical practice. *Hand Clin*. 1986;2(4):651–663.
- 28. Isaacs J, Mallu S, Yan W, Little B. Consequences of oversizing: nerve-to-nerve tube diameter mismatch. *J Bone Joint Surg Am.* 2014;96(17):1461–1467.
- Flores AJ, Lavernia CJ, Owens PW. Anatomy and physiology of peripheral nerve injury and repair. Am J Orthop (Belle Mead NJ). 2000;29(3):167–173.
- Bulut T, Akgun U, Citlak A, Aslan C, Sener U, Sener M. Prognostic factors in sensory recovery after digital nerve repair. *Acta Orthop Traumatol Turc*. 2016;50(2):157–161.
- Mermans JF, Franssen BB, Serroyen J, Van der Hulst RR. Digital nerve injuries: a review of predictors of sensory recovery after microsurgical digital nerve repair. *Hand* (N Y). 2012;7(3): 233-241.
- 32. Shin RH, Friedrich PF, Crum BA, Bishop AT, Shin AY. Treatment of a segmental nerve defect in the rat with use of bioabsorbable synthetic nerve conduits: a comparison of commercially available conduits. J Bone Joint Surg Am. 2009;91(9):2194– 2204.