A Preliminary Assessment of the Utility of Large-Caliber Processed Nerve Allografts for the Repair of Upper Extremity Nerve Injuries

Jonathan Isaacs¹ and Bauback Safa²

Abstract

Background: Cabled sensory nerve autografts are the historical gold standard for overcoming gaps in larger diameter nerves as repair utilizing large-diameter autograft risks central graft necrosis. Commercially available processed nerve allograft (PNA) is available in diameters up to 5 mm but represents an acellular 3-dimensional matrix as opposed to viable tissue. The purpose of this study is to specifically evaluate whether similar concerns regarding the use of large-caliber PNA are warranted. **Methods:** The RANGER Registry is an active database designed to collect injury, repair, safety, and outcomes data for PNAs (Avance® Nerve Graft; AxoGen, Inc, Alachua, Florida) according to an institutional review board–approved protocol. The database was queried for patients presenting with large-caliber nerve allograft repairs in the upper extremity. Identified patients reporting quantitative outcomes with a minimum of 9-month follow-up were included in the data set. **Results:** The large-caliber PNA subgroup included 13 patients with 15 injuries. The mean $\pm$ SD age was 36 ± 22 years. Large-caliber single-stranded repairs included twelve 4- to 5-mm-diameter grafts. Large-caliber cabled repairs included the combined use of 3- to 4-mm and 4- to 5-mm-diameter nerve allografts in 3 repairs. The mean nerve gap was 33 ± 10 mm with a mean follow-up time of 13 months. Available quantitative data reported meaningful recovery of sensory and motor function in 67% and 85% of the repairs, respectively. **Conclusion:** Although based on a small subset of patients, PNAs of up to 5 mm in diameter appear capable of supporting successful nerve regeneration.

Keywords: acellular nerve allograft, large-diameter nerve graft, nerve repair, nerve repair outcomes, nerve gap

Background

Although autograft is the historical gold standard for bridging gaps in peripheral nerve surgery, processed acellular nerve allograft has been promoted as a potential replacement. A growing body of data strongly supports this application for small-diameter, less than 2 to 3 mm, sensory and digital nerves,^{9,17} though the implementation of processed nerve allograft (PNA) in major peripheral nerve repair is more controversial.⁸ This observation applies to not only whether or not PNA should be used for these types of repairs but also how exactly it should be incorporated.

In general, PNA is used in an analogous fashion to autograft nerve tissue. After appropriate debridement of the recipient site, the remaining gap is measured and an appropriately sized PNA up to 7 cm long is chosen and secured between the in situ nerve stumps most commonly with sutures. However, when fixing a large-diameter nerve with autograft, a thin sensory donor nerve such as the medial antebrachial or sural nerves measuring 2 to 3 mm in diameter is typically used.

The harvested nerve is cut into pieces, and these pieces are then stacked together in a multistranded cable until the entire face of the transected nerve has been covered. The choice of donor nerves is based in part on the limited donor morbidity of sacrificing nonessential sensory nerves. In addition, small-diameter nerve autografts are known to revascularize quickly and predictably¹ as compared with larger diameter autografts (when not applied as a vascularized graft) which are limited by central necrosis.^{3,14,18} This central necrosis is presumably due to delayed and ineffective revascularization. As a result, the graft becomes fibrotic and does not support sufficient axon regeneration.

¹Virginia Commonwealth University, Richmond, VA, USA

²The Buncke Clinic, San Francisco, CA, USA

Corresponding Author:

Jonathan Isaacs, Department of Orthopaedic Surgery, Virginia Commonwealth University Medical Center, 1200 East Broad Street, P.O. Box 980153, Richmond, VA 23235, USA.
Email: jonathan.isaacs@vcuhealth.org

PNA comes in a 2- to 3-mm diameter option, which can be stacked into cables in an analogous fashion to autograft for bridging gaps in large-diameter nerves. However, PNA is also available in diameters up to 4 to 5 mm that can be used as a single graft to bridge a gap in large-diameter nerves, thus eliminating the need for multicable strands. Tang et al compared cable grafting versus single nerve allografts in a rodent model and found that single nerve allografts were superior.¹⁶ However, the diameter of the rat sciatic nerve repaired in this study was only 1.5 mm, so in this case a single nerve allograft would still revascularize quickly. In addition, the assembly and implantation of nerve graft cables small enough to repair the small-diameter rat sciatic nerve represents a significant technical challenge. Whether a thicker diameter PNA would suffer the same fate as thick autograft is not known and is difficult to answer due to lack of appropriate animal models.

A rolling and active multicenter database (referred to as the RANGER Registry) includes patients having undergone nerve repair utilizing 4- to 5-mm PNA. A preliminary analysis of these patients could ascertain if the thicker PNA is detrimental to nerve regeneration.

Materials and Methods

Study Design

The RANGER® Registry is an ongoing industry-supported observational study collecting data on the use and outcomes of PNA (Avance Nerve Graft; AxoGen Inc, Alachua, Florida) in peripheral nerve repair. This investigation and the RANGER® Registry were performed in accordance with all participating centers' institutional review board approvals. All patients at least 18 years old treated with PNA at participating sites were eligible to be in the study. Repairs were performed by experienced plastic or orthopedic surgeons who at a minimum completed a fellowship in hand or hand and microsurgery. Each study center followed its own standard of care for patient treatment, rehabilitation regimen, and follow-up measures. Outcome assessments were performed by either the surgeons or experienced hand therapists. The current registry database was queried for large-caliber (4- to 5-mm-diameter) nerve allograft repairs in the upper extremity. Identified patients reporting quantitative outcomes with a minimum of 9-month follow-up were included in the data set.

Clinical Evaluation

Standardized case report forms were designed to collect general patient demographics, details of the nerve injury, the nerve repair(s) performed, concomitant treatments, follow-up evaluations performed, and the corresponding outcomes. Chart reviews were completed at each participating institution by designated researcher assistants in an observational manner, and data were collected to the extent they were available in the medical records. Preoperative,

Table 1. Summary of Subject and Injury.

Demographics	
Nerve diameter	4-5 mm
Subjects	13
No. of repairs	15
Nerve repaired	
Median/digital ^a	1
Median	7
Ulnar ^b	3
Radial ^c	3
Musculocutaneous ^c	1
Mechanism of injury	
Laceration	7
Amputation/avulsion	1
Blast/gunshot	5
Crush	1
Neuroma resection	1

^aThe proximal processed nerve allograft (PNA) was repaired to the median nerve, whereas the distal PNA was split into components and repaired to digital sensory nerves.

^bOne patient underwent repair of the sensory component of the ulnar nerve.

^cOnly motor data are available.

operative, postoperative follow-up, and physical therapy notes were the main sources of information. In addition, information on intraoperative or postoperative adverse experiences and complications related to the nerve graft was gathered.

Patient demographics, repair demographics, and recovery of function were compared. Follow-up assessments utilized throughout the sites included a variety of quantitative measures for motor and sensory deficits. Although not all sites completed the same battery of assessments following repair, consistencies allowed for analysis of results. The Mackinnon modification of the Medical Research Council (MRC) grading system was used for the evaluation of sensory and motor recovery with meaningful functional recovery defined as S3/M3 or greater. All data including complication rates, and adverse events were entered into a centralized study database.

Results

Thirteen patients identified in the database had undergone large-caliber allograft reconstruction of peripheral nerve defect. This group of patients consisted of 10 males and 3 females with a mean $\pm$ SD (minimum, maximum) age of 36 $\pm$ 22 (18, 77) years. A total of 15 nerves were repaired, including 2 sensory and 13 mixed nerves. Twelve of these repairs were performed with a single 4- to 5-mm-diameter PNA, and 3 repairs required the combined use of a 3- to 4-mm and a 4- to 5-mm-diameter PNA in a 2-strand cable graft construct to match the diameter of the native nerve (2 median nerves and a radial nerve). Table 1 provides a summary of injury demographics. The "median/digital" repair listed in the table was a

Figure 1. Distribution of sensory and motor MRC scores by nerve caliber.

distal median nerve repair in which the proximal coaptation was the unaltered trunk of the large-caliber PNA; however, intraneural dissection allowed distal coaptations with the digital nerves (the terminal branches of the median nerve). One of the mixed nerve repairs was a musculocutaneous nerve, though no sensory assessments (from the lateral antebrachial cutaneous nerve distribution) were collected on this patient. A majority of the injuries were repaired acutely with the median time to repair of 7 days. The mean time to repair was 138 ± 201 days (range, 3–547 days). The mean gap was 33 ± 10 (5, 50) mm. The mean follow-up time was 13 months.

Available quantitative data reported satisfactory (S3/M3 and better) recovery of sensory and motor function in 67% and 85% of the repairs, whereas “desirable recovery” (S3+/M4 and better) was reported following 42% and 54% of the repairs, respectively. Figure 1 demonstrates the distribution of outcomes. Sensory data were not available for 3 mixed nerve repairs (1 musculocutaneous and 2 radial nerves) presumably due to the limited functional importance of the sensory components of these nerves.

Two nerve repairs were reported as no functional recovery. One was a revision reconstruction of the median nerve in the carpal tunnel performed with a 40-mm-long PNA, 491 days postinjury. The allograft was 27 mm long, though the distal 7 mm was split into branches to repair to the digital nerves. Although no functional recovery was regained, substantial relief of neuropathic pain was achieved. The second was an ulnar nerve repair utilizing a 20-mm PNA 7 days postinjury. This patient suffered a blast injury from an improvised explosive device. The nerve injury was associated with an open ulna fracture and ulnar artery rupture.

Discussion

The detailed data behind the widespread and well-accepted practice of avoiding large-diameter nerve autograft are actually quite limited and in many ways, anecdotal. In 1955,

Brooks noted, “in grafts of large diameter, such as those of the sciatic nerve, rapid revascularization rarely occurs.”³ Seddon also reported poor outcomes when using certain larger caliber nerves as nonvascularized autografts and advised against their use. For example, Seddon states, “The common peroneal nerve is too thick, while the radial nerve is not,”¹⁴ though based on reporting practices of the time, few details and no statistical analysis were provided. Anecdotal reports of nerve grafting failure and reports of central autograft necrosis were interpreted as inadequate tissue perfusion¹⁸ and led to the still ongoing debate regarding vascularized versus nonvascularized autograft selection for certain nerve defects.^{1,15} Best et al however did confirm poor axon regeneration and central graft fibrosis in 2-cm-long peroneal nerve graft in a sheep model (compared with rapid revascularization in thinner grafts).² Unfortunately, the caliber of the graft was not reported—only that it was thick.

Clinical scenarios in which the possibility of using a large-diameter autograft are quite rare, to be sure, as larger diameter nerves tend to be functionally significant and are not typically sacrificable. The rare exceptions include using the ulnar nerve in the presence of lower trunk brachial plexus injuries (including C8-T1 avulsions) in which reanimation of ulnar nerve function following proximal repair is statistically very unlikely or with multiple extremity injuries in which nerves from an otherwise unsalvageable and/or amputated limb can be utilized. Transfer as a pedicled or free vascularized graft¹⁹ or splitting the graft into multiple thin strands⁵ can circumvent any perfusion concerns and have all been successfully incorporated into clinical practice.

Acellular nerve allograft, however, can easily be supplied in larger diameters and offers the theoretical advantages of technical efficiency and ease of implantation compared with cable or vascularized nerve grafting in the reconstruction of larger caliber peripheral nerves. When

extrapolating the “rules” for autograft implementation to processed acellular nerve allograft, the exact diameter at which a nerve is considered too thick is not clear. Nutrient diffusion and waste removal (though not oxygenation) appear to be inhibited after about 2 mm, suggesting that around 4 mm diameter should be the absolute cutoff—though, this has been deduced from non-nerve tissue data.⁷ Acellular allograft is a tissue scaffold and does not rely on diffusion for initial survival. Axon regeneration requires capillary ingrowth, which appears to occur by inosculation in both autograft and allograft.¹

Ultimately, the appropriate size parameters of acellular nerve allograft may be best determined utilizing animal models. To date, however, an adequate animal model has not been developed.¹⁰ Analysis of available clinical outcomes included in the multicenter active database (the RANGER Registry) offers the best available information to guide future application of acellular nerve allograft. Although not statistically scrutinized, the rates of meaningful motor (85%) and sensory (67%) recovery associated with 4- to 5-mm-diameter allograft repairs appear, at least from a preliminary standpoint, comparable with the use of PNA across all sizes. Brooks et al reported on 76 injuries across all nerve types (and including all PNA diameters up to 5 mm). Although the majority of repairs were digital nerves, overall satisfactory sensory or motor recovery (M3 or S3 and better) was reported 87% of the time.⁴ When compared with historical autograft data (applied as 2- to 3-mm strands or cabled together for larger nerves), and using the same minimal criteria for “satisfactory outcome,” repair of median, ulnar, and radial nerves was successful in 57% to 78% of cases.^{6,11,12} Using the more stringent criteria of S3+ and M4 or better (to represent “desirable” outcomes), a meta-analysis of 623 conventional median and ulnar nerve repairs reported success rates of 43% (sensory) and 52% (motor).¹³ These success levels are remarkably close to the 42% and 54% rates (based on this higher criteria) noted in our subgroup analysis of large-diameter PNA-assisted repairs.

Two patients had no recovery, which is of course concerning when evaluating new technology. Many similar repairs performed with autograft (the gold standard) also fail. Both failed cases in this series can be adequately explained by factors unrelated to graft choice. The first failure might be explained by the long delay between injury and definitive repair (491 days), whereas the second failure might be related to a persistent zone of injury (a 2-cm graft is remarkably short for a blast injury resulting in a concomitant open ulna fracture). If there was an obvious problem with the allograft related to the diameter size, we would have expected all or most of the repairs to have suffered.

The small sample size of this preliminary report precludes complete endorsement of large-diameter PNA for

peripheral nerve repair. The purpose of the study, however, was to confirm that concerns regarding gross failure of this size graft, as might be seen in similar caliber autograft, were, at this point, unfounded. The overall success rate suggests that the continued incorporation of 4- to 5-mm-diameter allografts into repair algorithms is acceptable and reasonable, though further study is needed to confirm these findings and to define the upper limits of PNA thickness parameters.

Ethical Approval

This study was approved by our institutional review board.

Statement of Human and Animal Rights

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.

Statement of Informed Consent

Informed consent was obtained from all patients being included in the study.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Both Jonathan Isaacs and Bauback Safa have received speaking fees and partial research support from AxoGen, Inc. Jonathan Isaacs has received educational support from AxoGen, Inc. Jonathan Isaacs is a co-principal investigator in an AxoGen, Inc–sponsored study (grant through Jonathan Isaacs’s institution).

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1. Best TJ, Mackinnon SE. Peripheral nerve revascularization: a current literature review. *J Reconstr Microsurg*. 1994;10:193-204.
2. Best TJ, Mackinnon SE, Midha R, Hunter DA, Evans PJ. Revascularization of peripheral nerve autografts and allografts. *Plast Reconstr Surg*. 1999;104:152-160.
3. Brooks D. The place of nerve-grafting in orthopaedic surgery. *J Bone Joint Surg Am*. 1955;37-A:299-305; passim.
4. Brooks DN, Weber RV, Chao JD, et al. Processed nerve allografts for peripheral nerve reconstruction: a multicenter study of utilization and outcomes in sensory, mixed, and motor nerve reconstructions. *Microsurgery*. 2012;32:1-14.
5. Eberhard D, Millesi H. Split nerve grafting. *J Reconstr Microsurg*. 1996;12:71-76.
6. Frykman G, Gramyk K. Results of nerve grafting. In: Gelberman R, ed. *Operative Nerve Repair and Reconstruction*. Philadelphia, PA: JB Lippincott; 1991:553-568.

7. Griffith CK, Miller C, Sainson RC, et al. Diffusion limits of an in vitro thick prevascularized tissue. *Tissue Eng*. 2005;11:257-266.
8. Isaacs J. Major peripheral nerve injuries. *Hand Clin*. 2013;29:371-382.
9. 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 (N Y)*. 2009;4:245-249.
10. Keating T, Isaacs J, Mallu S, Baxi M. Athymic rat model for studying acellular human allograft. *J Neurosci Methods*. 2015;249:92-98.
11. Kim DH, Han K, Tiel RL, Murovic JA, Kline DG. Surgical outcomes of 654 ulnar nerve lesions. *J Neurosurg*. 2003;98:993-1004.
12. 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.
13. 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.
14. Seddon HJ. *Surgical Disorders of the Peripheral Nerves*. 2nd ed. Edinburgh, Scotland: Churchill Livingstone; 1975.
15. Shibata M, Tsai TM, Firrell J, Breidenbach WC. Experimental comparison of vascularized and nonvascularized nerve grafting. *J Hand Surg Am*. 1988;13:358-365.
16. Tang P, Kilic A, Konopka G, Regalbuto R, Akelina Y, Gardner T. Histologic and functional outcomes of nerve defects treated with acellular allograft versus cabled autograft in a rat model. *Microsurgery*. 2013;33:460-467.
17. Taras JS, Amin N, Patel N, McCabe LA. Allograft reconstruction for digital nerve loss. *J Hand Surg Am*. 2013;38(10):1965-1971. doi:10.1016/j.jhsa.2013.07.008.
18. Tarlov IM, Epstein JA. Nerve grafts: the importance of an adequate blood supply. *J Neurosurg*. 1945;2:49-71.
19. Terzis JK, Kostopoulos VK. Vascularized ulnar nerve graft: 151 reconstructions for posttraumatic brachial plexus palsy. *Plast Reconstr Surg*. 2009;123:1276-1291.