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A Retrospective Case Series of Peripheral Mixed Nerve Reconstruction Failures Using Processed Nerve Allografts

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Background: Favorable rates of meaningful recovery (≥M3/S3) of processed nerve allografts (PNAs) for mixed and motor nerve injuries have been reported, but there are few reports of patients having complete PNA failure (M0/S0). The purpose of this study was to describe the outcomes, including rate of complete failures, in a case series of patients who underwent PNA for peripheral mixed nerve reconstructions.
Methods: A retrospective review of outcomes between May 2018 to September 2020 was performed. Consecutive patients who underwent nerve reconstruction (>15 mm) with PNA for a peripheral mixed nerve injury of the upper or lower extremity were eligible. Those who returned to clinic for a 10-month postoperative visit were included in this study. The primary outcome was whether the patient was defined as having a complete failure (M0/S0).
Results: A total of 22 patients underwent a PNA during the time period; 14 patients participated in follow-up and were included (average age: 34.7 years) with a mean follow-up of 11.9 months. The average gap length was 46.4 mm (range 15–110 mm). At their 10-month postoperative visit, no patients had any motor or sensory improvement; all patients were deemed as having complete failure. Four patients underwent or were planned for subsequent revision surgery.
Conclusions: In this study, we demonstrated a high number of complete failures, with all 14 included patients sustaining a complete failure (100% failure rate) at a minimum 10-month follow-up visit. Failure in this case series was not observed to affect one nerve type, location, or be related to preoperative injury size. *(Plast Reconstr Surg Glob Open 2021;9:e3983; doi: 10.1097/GOX.0000000000003983; Published online 7 December 2021.)*

INTRODUCTION

Processed nerve allografts (PNAs) are decellurized nerve allografts that theoretically provide a three-dimensional, nonimmunogenic scaffold to support axonal growth in patients with segmental nerve defects. Currently, PNAs are being used clinically for sensory, motor, and mixed nerve reconstructions for defects between 5 and 50 mm often in place of when nerve autografts, the gold standard for nerve reconstruction, would be historically used.[1,2] In contrast to conventional nerve autografts, PNAs are attractive, as they are not limited based on the amount of donor tissue available and their use prevents an additional secondary surgical site, which can result in donor-site morbidity, pain, and complications.

Despite the benefits associated with PNAs, studies in animal models have provided mixed results as to whether PNAs provide outcomes comparable to autografts, especially for larger segmental nerve defects.[3–5] Some prior studies have demonstrated that they may be superior to conduit-style nerve guides and may provide similar histomorphometric findings and functional outcomes to autografts at mid-term time points (12–17 weeks) for 10–14 mm defects, but there is scant basic science literature

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supporting similar outcome properties of allografts used for larger defects (eg, 28 mm).[6–8] Furthermore, other studies have suggested that PNAs may not provide as robust motor recovery even for smaller defects.[5] Differences in PNAs and autografts may be in part attributed to differences in vascular perfusion patterns, and greater vascular fraction and microvessel growth rate in autografts, especially at early time points.[5,9]

In contrast to the mixed results observed in animal models, clinical literature has demonstrated generally favorable outcomes after PNA for peripheral nerve injuries in a wide range of settings, although these outcomes may be dependent on nerve type and defect size.[3,10–17] For example, in a large cohort of sensory, mixed, and motor nerve reconstructions, Safa et al reported an 82% meaningful recovery rate (≥M3/S3); however, this rate may be inflated by the inclusion of digital sensory nerves.[12] In a case series focusing on outcomes of mixed or motor nerve reconstructions with PNA to the face or upper extremity, Safa et al reported a 73% of meaningful motor recovery (≥M3).[3] Other studies, however, have reported significantly inferior meaningful recovery rates. For example, in a case series, Dunn et al reported only a 27.3% meaningful recovery rate.[18]

The current literature focuses on reporting meaningful recovery rates (often reported as ≥M3 and/or ≥S3) with few studies reporting on a breakdown of outcomes based on MRC. Two prior case series have been published focusing on PNA failure, one of which reported complete failure (M0/S0) in three cases.[19] However, this case series included a range of PNA settings, including a digital PNA, one for a tibial nerve injury, and a neonatal upper trunk brachial plexus reconstruction. Given the scant literature on complete failures after using PNA for peripheral mixed nerve injuries greater than 15 mm, the purpose of this study was to describe the outcomes, including rate of complete failures, in a case series of patients who underwent PNA for peripheral mixed nerve reconstructions.

Takeaways

Question: The purpose of this study was to describe the outcomes, including rate of complete failures, in a case series of patients who underwent peripheral nerve allograft for peripheral mixed nerve reconstructions.

Findings: In this study, we demonstrated a high number of complete failures of allograft, with all 14 included patients sustaining a complete failure (100% failure rate) at the 10-month follow-up visit.

Meaning: We argue that peripheral nerve allograft may not be a strong replacement for an autograft for mixed and motor nerve injuries, and instead may be a comparable product to a conduit.

METHODS

This study received institutional review board approval at both medical centers (SUNY Downstate Medical Center and Kings County Hospital Center). The surgical log of the principal investigator (SMK) was reviewed for patients who underwent a peripheral PNA using an Axogen Avance (Axogen, Alachua, Fla.) nerve graft from May 1, 2018 to September 30, 2020. The principal investigator is a fellowship-trained hand and microsurgeon who specializes in peripheral nerves. He performs more than 100 peripheral nerve repair/reconstructive surgeries a year, excluding neuroplasties, and has participated in multiple industry sponsored PNA training sessions.

Identified patients underwent chart review to (1) confirm that the patient underwent a peripheral PNA to a mixed motor/sensory nerve and (2) check if they returned for a 10-month or later postoperative clinical visit. The 10-month postoperative visit was selected based on a similar study on peripheral nerve outcomes after allograft reconstruction performed by Dunn et al, which evaluated patients with a minimum of a 6-month follow-up vist.[18] Since at the 6-month visit, we would expect some sensory and motor recovery (at least M1/S1), the 10-month visit was a reasonable time point to capture some evidence of recovery. Thus, if the patient was M0/S0 at their 10-month postoperative visit, they were deemed as having a failure. The Mackinnon-Dellon Modification of the Medical Research Council Classification sensory and motor scales were used to evaluate sensory and motor recovery.

Patients who met these two selection criteria were then screened to ensure that they met all inclusion criteria. Inclusion criteria were patients who met the following: had undergone nerve reconstruction with PNA and completed their 10-months postoperative clinic visit. Exclusion criteria included the following: patients younger than 18 years, patients who underwent digital nerve reconstruction with PNA, and patients who were lost to follow-up. The final patients that met our inclusion criteria underwent full data extraction. Data extracted from patients' charts included sex, age, body mass index, previous medical history, previous surgical history, comorbidities, medications, smoking status, diagnosis, patient presentation details, pre- and postoperative two-point discrimination measurements, X-ray imaging, MRI imaging, ultrasound imaging, operative treatment, follow-up period duration, outcomes, and additional or planned surgical procedures after PNA failure.

RESULTS

A total of 22 patients underwent peripheral mixed nerve PNA; of these, 14 met our inclusion criteria and were included in analysis (63% compliance) (age: 34.7, median 30, range 18–67 years, 10 women/four men) with a mean follow-up of 11.9 months (median 12, range 10–16 months) (Fig. 1, Table 1). Four patients underwent PNA to the median nerve, eight to the ulnar nerve, and two to the common peroneal nerve. There was a range of indications for the PNA: three patients were indicated for PNA due to the presence of a neuroma in continuity (due to a subacute laceration confirmed on MRI and/or US (<1 month from injury in all cases), seven had a laceration with a gap, three sustained injuries due to a fracture, and one sustained iatrogenic injury from a carpal tunnel

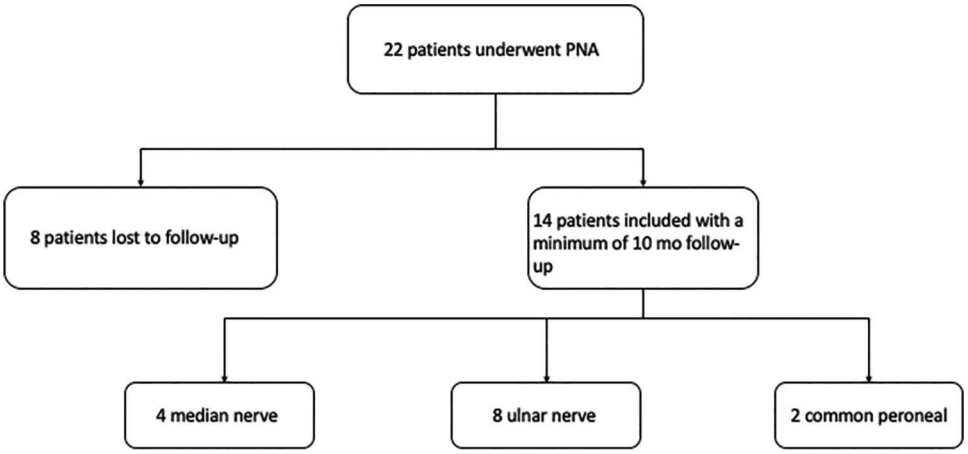

Fig. 1. Flowchart of included patients.

release. The average gap length was 46.42 mm (range 15–110 mm).

At the 10-month follow-up visit, no patients had any motor or sensory improvement; all patients were deemed as having complete functional failure (M0/S0) (Table 2). In addition, nine patients completed their 1-year follow-up visit and demonstrated no improvement. At the last clinical visit, all patients reported continued numbness, while two patients reported persistent pain and five demonstrated clawing on physical examination. Two-point discrimination testing was performed on 12 individuals and demonstrated a greater than 15 mm discrimination distance. Eight patients had planned or underwent subsequent revision reconstruction surgery: one autograft reconstruction, one distal nerve transfer and claw hand correction, one tendon transfer for foot drop, one neuroma excision with targeted muscle reinnervation, and four claw hand corrections. Intraoperatively, a large neuroma was observed in the two patients who have undergone revision surgery (Fig. 2).

DISCUSSION

This study reported a total of 14 patients who demonstrated complete failure (M0/S0) after peripheral mixed nerve reconstruction, using a PNA (100% failure rate). Complete failure of peripheral mixed nerve allografts has been sparsely reported in the literature, and this case series highlights that PNA may not, in fact, be efficacious for the management of peripheral mixed nerve lesions. Furthermore, although analysis of demographic and intraoperative variables could not be performed due to the small sample size, our heterogeneous cohort involving three different nerve locations, a range of lengths, and a variety of surgical indications, suggests that PNA failure may be widespread and not limited by nerve type or graft length.

Prior studies on outcomes after PNA have been generally favorable. In one of the largest cohort studies on the topic, Safa et al reported on the success of PNAs using data from the RANGER Registry.[12] In 624 nerve reconstructions, there was an overall meaningful recovery of 82% (≥M3/S3). The authors also observed significant differences in outcome based on mechanism of injury and gap length (<15 mm versus 50–70 mm). These results are not directly comparable to our findings; however, the included injuries were heterogenous (eg, included sensory only nerves, head and neck nerve reconstructions, and digital nerve reconstructions) and the authors did not report on complete failure. In addition, Cho et al reported favorable outcomes in a heterogeneous cohort of patients who underwent sensory, motor, or mixed PNA to the upper extremity also from the RANGER Registry.[4] Specifically, in 51 patients (mean gap length of 23 ± 12 mm), the authors reported 86% of patients achieved S4 or M4 and above. In an additional study using the RANGER data, Safa et al reported meaningful motor recovery (≥M3) in 73%, specifically in patients undergoing peripheral mixed and motor nerve reconstructions.[3] In the 19 included nerve reconstructions, 50% of patients reported M4 or greater, with a complete failure rate of 9% at a mean follow-up of 779 ± 480 days. In this study, the mean age of the subjects was 38 ± 19 years and the mean graft length was 33 ± 17 mm (10–70 mm). Of note, achievement of M3 or greater motor function was not significantly related to gap length, nerve, age, comorbidities, or smoking status. These variables were all included in our case series and a range of gap lengths, nerves, ages, comorbidities, and smoking status were observed in this case series of failed PNAs.

Other studies, however, have suggested inferior outcomes after PNA. For example, Leckenby et al reported on 171 heterogeneous peripheral nerve grafts in 129 patients.[20] In their cohort with a mean allograft length of 27 mm (8–100 mm), the authors reported that 77% of patients achieved S3 or greater but only 36% achieved a score of M3 or above. In addition, longer graft length and increased graft diameter was significantly associated with poorer outcomes. Notably, lower limb nerve reconstructions yielded inferior results. Again, while this study was not able to assess risk factors of failure, a mix of graft lengths and locations were also observed in our failed PNA cohort. In addition, similar inferior outcomes were reported by

Table 1. Demographic and Treatment Information

Patient	Gender	Age	BMI	PMH	PSH	Medications	Current Smoker	Diagnosis	Patient Presentation	Preoperative Imaging	Time from Injury to Operation	Operative Treatment
1	Woman	55	45.2	None	R ankle surgery (x2) and tibial intramedullary nailing	None	No	1. Right superficial peroneal neuropathy and foot drop	Decreased sensation in superficial peroneal distribution after first surgery. Underwent second surgery 1 year later. Experienced significant postoperative pain in her superficial peroneal distribution. Persistent foot drop since second surgery.	US performed suggestive of peroneal neuroma	2 months	R common peroneal nerve allograft (15 mm)
2	Woman	35	20.2	None	None	None	No	1. R median nerve forearm laceration 2. R zone V flexor tendon lacerations 3. R deep forearm foreign body	Patient was trying to catch falling glass and sustained a laceration on her R distal volar forearm. Complains of dense numbness in R IF and MF. Unable to flex her R MF.	X-rays demonstrated no fracture or dislocation. Foreign object at the center of volar wrist, proximal to carpal tunnel at level of pronator quadratus.	1 week	1. R median nerve allograft (35 mm) 2. R zone V flexor tendon repair 3. R forearm deep foreign body excision
3	Woman	67	27.4	Asthma, high cholesterol, hypertension, hypothyroidism	Suicide attempt with cutting wrists	Antipsychotics, antidepressants, synthroid	Yes	1. L median nerve injury 2. Peripheral neuropathic pain	Patient presented with severe hand pain and weakness	N/A	3 months	L median nerve allograft (70 mm)
4	Woman	48	30.7	High cholesterol, hypertension, stroke, diabetes, HTN, HLD, keloids, CVA (right side deficit)	None	Atorvastatin (20 mg), Enalapril maleate (10 mg), Metformin (1000mg), Tramadol (50mg)	No	1. L zone V flexor tendon laceration 2. L ulnar nerve laceration	Patient sustained a hand injury working at daycare. Tripped and her left hand went through a window. She has been unable to flex her pinky and ring fingers and has only been able to partially flex her L MF and IF. Additionally, she is unable to flex her wrist and has diminished sensation in the fourth and fifth digits.	N/A	1 week	1. L ulnar nerve allograft (40 mm) 2. L zone V flexor tendon repair

(*Continued*)

Table 1. (*Continued*)

Patient	Gender	Age	BMI	PMH	PSH	Medications	Current Smoker	Diagnosis	Patient Presentation	Preoperative Imaging	Time from Injury to Operation	Operative Treatment
5	Woman	61	25.2	Asthma, heart attack	Carpal tunnel surgery L hand.	Aspirin	No	1. B/l carpal tunnel syndrome s/p L CTR with concern for nerve injury v. incomplete release – found to be lacerated on exploration 2. B/l pronator syndrome	Patient presented with b/l hand numbness and tingling. Worse in left hand for the past 3 months after CT release. Before surgery, she had numbness and tingling for 1 year.	MRI of L wrist demonstrating median nerve with possible neuroma in continuity	3 months	1. L revision CTR with hypothenar fat flap 2. L median nerve allograft (20 mm) 3. L pronator release
6	Man	18	Not recorded	Asthma	None	None	No	1. Grade 1 open fracture of the right radial shaft due to fall 2. Laceration R median nerve	Acute trauma	N/A	Same day	1. Open reduction and internal fixation of right grade 1 open radius fracture 2. R median nerve allograft (50 mm)
7	Woman	35	Not recorded	None	Exploratory surgery (done by general surgery) resulting in a postop foot drop and numbness and tingling in peroneal distribution.	None	No	1. L common peroneal nerve transection	Iatrogenic	N/A	1 day	L common peroneal nerve allograft (45 mm)
8	Man	39	Not documented	GERD	None	Protonix	No	1. Right ulnar nerve laceration at elbow	Stab wound to L upper arm	N/A	1 day	1. R ulnar nerve anterior transposition and allograft (11 cm, daisy-chain) 2. Reverse end-to-side AIN to deep ulnar motor
9	Woman	23	26.6	Schizophrenia, second degree heart block (Type 1)	None	None	No	1. L ulnar nerve laceration	Stab wound to L hand	CTA, X-rays were unremarkable	1 month	L ulnar nerve allograft (33 mm)

(*Continued*)

Table 1. (*Continued*)

Patient	Gender	Age	BMI	PMH	PSH	Medications	Current Smoker	Diagnosis	Patient Presentation	Preoperative Imaging	Time from Injury to Operation	Operative Treatment
10	Man	18	27.5	None	None	None	No	1. R ulnar nerve laceration at high forearm	Stab wound to R forearm	N/A	3 days	1. R ulnar nerve allograft (50 mm) 2. Reverse end-to-side AIN to deep ulnar motor
11	Man	21	30.4	None	None	None	No	1. R ulnar nerve laceration at elbow	Stab wound to R arm	N/A	2 days	1. R ulnar nerve transposition and allograft (47 mm) 2. Reverse end-to-side AIN to deep ulnar motor
12	Woman	25	30.1	Asthma	None	Albuterol	No	1. L ulnar nerve laceration at distal forearm	Stab wound to L forearm	N/A	1 day	L ulnar nerve allograft (40 mm)
13	Woman	18	26.8	None	None	None	No	1. L ulna nerve laceration at high forearm 2. L proximal forearm both bone fracture	Gunshot to L forearm	X-rays demonstrated proximal radius and ulna fracture with bone loss	2 days	1. L ulnar nerve allograft (45 mm) 2. L radius and ulnar ORIF 3. Reverse end-to-side AIN to deep ulnar motor
14	Woman	23	21.2	None	None	None	No	1. L ulnar nerve laceration at distal forearm 2. L zone V flexor tendon laceration	Stab wound to L forearm	N/A	3 weeks	1. L ulnar nerve allograft (50 mm) 2. L zone V flexor tendon repair

AIN, anterior interosseous nerve; ADL, activities of daily living; APB, abductor pollicis brevis; b/l, bilateral; CTR, carpal tunnel release; FCR, flexor carpi radialis; FCU , flexor carpi ulnaris; FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis; IF, index finger; MF, middle finger; PL, palmaris longus; RF, ring finger; SF, small finger; SLIL, scapholunate interosseous ligament; TFCC, triangular fibrocartilage complex; US, ultrasound.

Table 2. Postoperative Outcomes

Patient	Follow-up Duration	Outcomes	Two-point Discrimination	Additional or Planned Surgery
1	12 months	Numbness and tingling in foot. No significant improvement. S0.	N/A	N/A
2	12 months	Lacking sensation over dorsal thumb, IF, and MF. Formation of large neuroma. S0. M0.	Thumb: >15mm IF: >15mm MF: >15mm RF: 4mm SF: 4mm	Plan for autograft revision
3	16 months	New numbness in the SF that is worsening. No improvement. S0. Significant pain.	Thumb: >15mm IF: >15mm MF: >15mm RF: 3mm SF: 3mm	Plan for L median nerve neuroma excision and targeted muscle reinnervation
4	10 months	No improvement. S0. M0. Clawing.	Thumb: 5mm IF: 5mm MF: 4mm RF: 8mm SF: >15mm	1. Left forearm flexor pronator slide, FPL lengthening and AIN to DUMN ETE nerve transfer (8 mo postsurgery) 2. L SF and RF claw hand correction (8 mo postsurgery)
5	16 months	No improvement. S0. M0.	Thumb: 12mm IF: 15mm MF: >15mm RF: 10mm SF: 4 mm	N/A
6	10 months	No improvement.	Thumb: >15mm IF: >15mm MF: 15mm RF: 10mm SF: 4 mm	N/A
7	10 months	Persistent pain in LLE worse with ambulation; decreased sensation along DP/SP nerves. Unable to fire EHL. Decreased eversion strength (1/5) Decreased dorsiflexion/tib ant strength	N/A	Tendon transfer for foot drop
8	12 months	No improvement. S0. M0. Clawing.	Thumb: 3mm IF: 3mm MF: 4mm RF: >15mm SF: >15mm	Claw hand correction
9	10 months	No improvement. S0. M0. Clawing.	Thumb: 5mm IF: 4mm MF: 4mm RF: 12mm SF: >15 mm	Claw hand correction
10	10 months	No improvement. S0. M0.	Thumb: 3mm IF: 3mm MF: 4mm RF: 10mm SF: >15 mm	N/A
11	12 months	No improvement. S0. M0.	Thumb: 4mm IF: 4mm MF: 3mm RF: 15mm SF: >15 mm	N/A
12	12 months	No improvement. S0. M0. Clawing.	Thumb: 4mm IF: 5mm MF: 4mm RF: >15mm SF: >15 mm	Claw hand correction
13	12 months	No improvement. S0. M0.	Thumb: 4mm IF: 5mm MF: 5mm RF: 14mm SF: >15 mm	N/A
14	12 months	No improvement. S0. M0. Clawing.	Thumb: 3mm IF: 3mm MF: 3mm RF: 4mm SF: >15 mm	Claw hand correction

AIN, anterior interosseous nerve; DP, deep peroneal; DUMN, deep ulnar motor nerve; ETE, end-to-end; EHL, extensor hallicus longus; FPL, flexor pollicis longus; IF, index finger; LLE, left lower extremity; MCP, metacarpophalangeal; MF, middle finger; PIP, proximal interphalangeal; RF, ring finger; SF, small finger; SP, superficial peroneal.

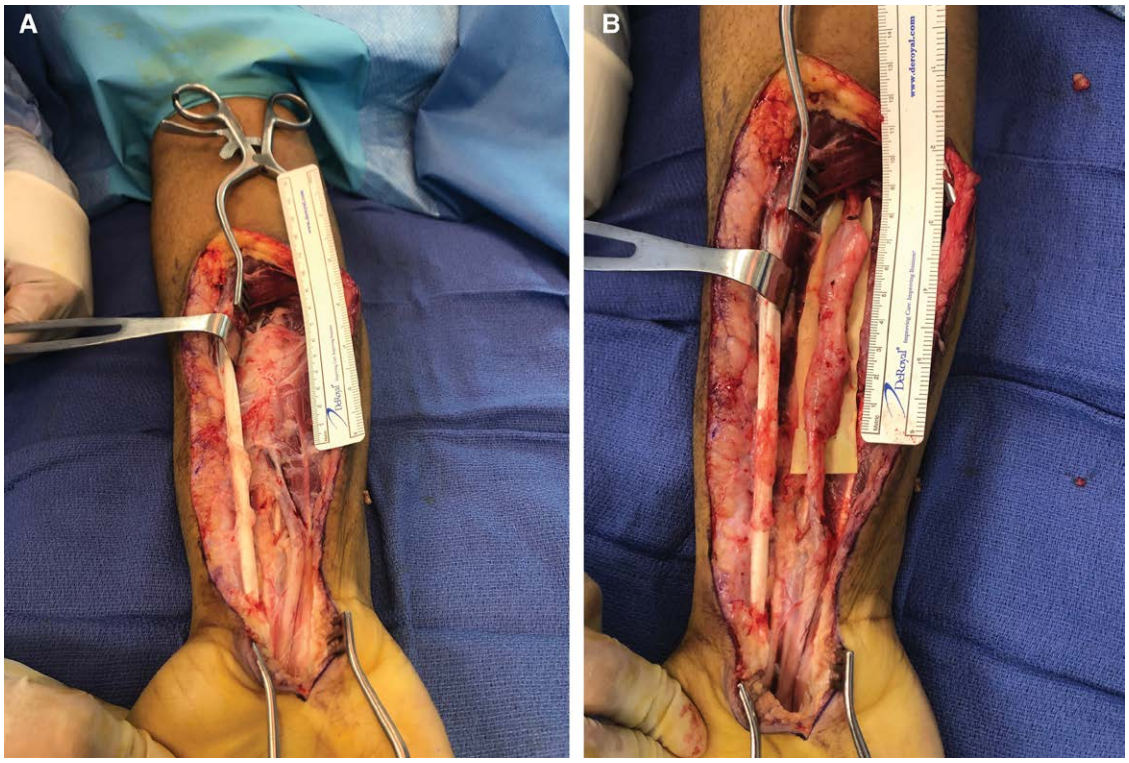

Fig. 2. Intraoperative photographs from an 18-year-old male patient who developed (A) significant adhesions and (B) an 8 cm neuroma of the median nerve 10 months after undergoing a PNA nerve reconstruction. The patient subsequently underwent a neuroma resection and cabled sural nerve autograft reconstructions. A significant neuroma was observed in both patients who underwent revision surgery after failed PNA.

Dunn et al. In a military cohort of 23 service members with 25 motor or mixed peripheral nervous injuries, the authors reported only a 27.3% meaningful recovery rate of mixed nerve injuries at a mean of 393 days follow-up with an average defect size of 77 mm.[18] Furthermore, the authors reported that 56% of subjects were S0 and 41% were M0 at final-follow-up. Although these nerve lesions may have more often been secondary to significant trauma (ie, blast injuries) and larger in size than other studies and the present study, these findings align with our results and together suggest significant limitations of PNA.

A study by Peters et al may provide some insight into the basic science mechanism underlying these allograft failures.[21] In a case series of five patients who failed Axogen PNAs to the median or ulnar nerve and underwent revision surgery, the nerve allograft was collected and used for histological analysis. As in this study, in four of the revision cases the authors reported observing significant neuromas intraoperatively. Histological analysis demonstrated termination of axonal regeneration in three of the five cases, while there was a failure of axons to regenerate into the allograft in the remaining cases. Notably, the PNAs included in this study were 6–11 cm in length. These findings align with other basic science studies, which have demonstrated the limited ability of PNAs to support axonal regeneration at longer graft lengths and the delay in facilitating axonal regeneration (2 weeks versus 2 days) likely due to the acellular nature of PNAs.[22–24]

Additionally, we hypothesize that the location of the nerve allograft significantly contributes to the poor regenerative capacities observed. The upper extremity "neural perforasomes" have been previously mapped with the extrinsic perfusion of peripheral nerves being highly segmental.[25] Maps of the perforasomes have demonstrated notable areas of diminished perfusion in upper extremity nerves. Placement of grafts in these regions may create a more "hostile" environment for allograft revascularization. Already, it has been reported that long acellular nerve allografts require greater time for vascularization, exposing the tissue to prolonged ischemia time.[26] It is possible that an under-explored explanation for the poor regenerative outcomes in acellular nerve allografts could be poor vascularization due to the anatomic location of the grafts in addition to length, leading to ischemia and regenerative failure.

Overall, the findings in this case series question the favorable outcomes reported in prior studies and the use of PNAs for mixed nerve lesions. Furthermore, our findings have caused us to reexamine the current PNA literature, where we have observed numerous limitations. For example, multiple prior reports that demonstrated positive outcomes after PNAs used the same RANGER database, which does not necessarily separate outcomes for digital nerve PNA versus upper extremity PNA.[4,13] This is a clinically important difference, as digital nerve PNA has shown greater success than that of larger motor or mixed motor studies,[15,27] and when grouped together,

could artificially inflate the success of the motor or mixed motor PNA data. In addition, it is unclear from these studies whether the same patients are being used in multiple studies, which could inflate the conclusions of positive outcomes after PNA.

Moreover, although the studies using the RANGER data are promising and offer hope for patients with peripheral nerve lesions, further examination of the intricacies of these studies raises questions of the role of conflict of interest. For example, in the studies by Safa et al,[12], the first author reported receiving payments from Axogen, the lead supplier of PNA on the market. In addition, in the study by Cho et al, the first author disclosed receiving research support from Axogen.[4] Similarly, the first author of a multicenter study (Brook et al) investigating outcomes of PNAs disclosed research support and being a paid presenter or speaker for Axogen.[16] Although we believe these conflicts were adequately disclosed, it represents a significant limitation for both the validity of these studies in addition to all studies reporting on data from the RANGER registry.

An additional concern is the FDA clearance surrounding PNA. To our knowledge, there are no studies investigating the efficacy of PNA itself before FDA approval with all of the RANGER studies performed as post-market surveillance studies. Originally, the FDA 510k clearance for the Axogen was approved for a conduit, rather than the PNA biologic. Axogen used this clearance for the conduit to advertise its safety and efficacy as a medical device company when advertising the PNA. Per Axogen legal notices, it did not pursue pre-market surveillance for the PNA nor did it receive a 510k for the PNA. Instead, Axogen has been granted clearance to proceed with the RECON study for its PNA (NCT01809002), which is a study that is still ongoing and has not published data to date. Additionally, that study is specifically evaluating digital nerve lesions, which, as expanded upon above, should not be generalized to all peripheral nerve lesions.

Given these substantial concerns regarding the validity of studies reporting favorable outcomes of Axogen's PNAs for motor and mixed nerve lesions, we emphatically suggest that there needs to be independent investigations into the use of Axogen's PNAs in larger trials with clinical investigators who are not financially implicated by the company. Our study is one of the few examples of a negative study for the product. Our results come from a high-volume nerve specialist, who has participated in Axogen-led training and who has had excellent successes with nerve autograft and nerve transfers. We urge peripheral surgeons to critically consider the use of allograft in peripheral motor and mixed nerve lesions given the results of our study and the significant limitations of the current literature. We support the use of PNA in digital and sensory nerves, but we believe that there may be nerve caliber limits, nerve gap limits, nerve type limits (ie, motor or mixed nerves), and nerve locations (ie, lower versus upper extremity), which reduce the success of PNA in such circumstances.[20] In light of these findings and limitations, we argue that PNA may not be a strong replacement for an autograft for mixed and motor nerve injuries, and instead may be a superior product to a conduit, but inferior to autograft.

Limitations

The major limitations of our study include the limited number of subjects and the use of a single surgeon. Our study only included 14 subjects and did not include any nonfailures; therefore, we were unable to perform any statistical analysis of risk factors such as gap length or nerve location. Use of a single surgeon's data does raise concern about whether our surgeon's technique is the cause of PNA failure; however, given that our surgeon has had excellent success with other nerve procedures, including nerve autograft and nerve transfers, we believe this is of limited concern. In addition, only 14 patients were available for short-term follow-up out of the 22 peripheral nerve PNAs performed during the study time period. This may have resulted in a sampling bias in the patients included in the case series. However, even if the remaining eight patients did not have complete failure, the 10-month survivorship would be 36%—one of the highest failure rates reported. This study was also limited by its retrospective nature. No patient underwent an accompanying nerve conduction/EMG study at final follow-up. However, all patients were individually assessed by the senior author and deemed as having complete failure using consistent assessments. An additional limitation was our lack of mid to long-term follow-up. Although additional, long-term data are needed to support our findings, this preliminary study of short-term outcomes suggests significant limitations of the Axogen nerve allograft for treating peripheral mixed nerve injuries.

In this study, we demonstrated a high number of complete failures (n = 14) at the 10-month postoperative visit. Failure in this case series was not observed to affect one nerve type or location, or be related to preoperative injury size. This study highlights the need for critical evaluation of the efficacy of PNA in motor and mixed nerve lesions, by independent clinical investigators without financial interest in medical device companies.

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