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Review Article

Nerve Autografts Versus Allografts for Mixed Motor/Sensory Nerve Reconstruction

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Reconstruction of peripheral mixed motor/sensory nerves using autografts has remained the gold standard. Inconsistent and nonphysiologic results across nerve allograft studies, including successful and failed motor reinnervation, have limited the current clinical application of nerve allografts to noncritical small-diameter sensory nerve defects less than 3 cm. This scoping review aimed to compare outcomes in both basic science and clinical applications of autograft and allograft nerve reconstruction for mixed motor/sensory nerves.

Peripheral nerve injuries can result in persistent disabilities and loss of motor function, compromising patients' quality of life with an associated socioeconomic burden.[1] Following nerve trauma, a series of cellular processes occurs, resulting in nerve and muscle degeneration. The degradation of myelin by Schwann cells and macrophages results in distal Wallerian degeneration with proximal degeneration extending to the first node of Ranvier. Axonal neurite regeneration commences from the proximal stump down endoneurial tubes toward the distal target muscle at an average rate of 1 mm per day.[2,3] Insufficient target reinnervation in a timely manner may result in loss of function or maladaptive changes, including neuropathic pain, hyperreflexia, and dystonia.[3] Surgical treatment is often necessary, and when possible, tension-free, end-to-end nerve repair of healthy fascicles is imperative for restoration of function.[4] When resection of damaged nerve ends precludes direct repair, an interposition nerve graft is required to bridge the gap. The gold standard for reconstructing mixed motor/sensory peripheral nerve defect has remained autologous cable nerve grafting over the history of nerve reconstruction. However, this requires harvesting expendable healthy sensory or motor nerves and is associated with donor-site sensation or motor loss, and potential donor-site pain in up to one-third of patients, neuroma formation, and infection. The mismatch in the diameter of the nerve graft to the injured nerve necessitates cabling, and often, there is not enough autograft nerve to reconstruct extensive complex injuries.[1,2,4] Donor sites of autografts commonly involve sensory nerves, each associated with a unique length availability-associated hypesthesia region.[5] The restoration of motor and mixed nerves poses distinct challenges because motor pathways preferentially support motor neuron regeneration, whereas sensory pathways prefer sensory axons in lieu of motor axons.[1,3] Consequently, when reconstructing a mixed motor/sensory nerve defect, employing a motor nerve graft will yield superior functional motor outcomes, and similarly, employing a sensory nerve graft will yield superior sensory outcomes.[1,3] The first human nerve allograft transplantation was reported in 1878, with early reports highlighting rejection as a prominent and substantial adverse effect, necessitating the administration of immunosuppressive medications, which had their own severe side effects.[1] Processed nerve allografts or synthetic nerve conduits were developed to serve as a potential alternative to autografts and are commercially available in the United States. Chemical decellularization removes the myelin and Schwann cells, eliminating the need for systemic immunosuppression while preserving the structural architecture of the nerve. Clinical data comparing outcomes of mixed motor/sensory nerve defects reconstructed with autografts with allografts remain limited and are contaminated with commercial bias and wide discrepancies.[1] Inconsistent and nonphysiologic results across

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studies, including both successful and failed motor reinnervation using nerve allografts, have limited the current clinical application of nerve allografts to noncritical small-diameter sensory nerve defects of less than 3 cm.[1] This scoping review aimed to provide an in-depth comparison of outcomes of basic science and clinical applications of autograft and allograft nerves for mixed motor/sensory nerve reconstruction.

Basic Science Applications

Peripheral nerve regeneration following reconstruction with autografts and allografts continues to be extensively studied through basic science research using animal models, aiming to objectively and accurately measure outcomes.[6] Boriani et al[7] systematically reviewed rodent peripheral mixed nerve defect models (eg, common peroneal nerve, common femoral nerve, or sciatic nerve), reconstructed with autografts, allografts, and allografts with noncellular modification. Despite variations in study design encompassing outcome measures and temporal points of assessment (ranging between 5 days and 16 weeks) across all studies, autograft reconstruction consistently demonstrated superior outcomes compared with allograft reconstruction. Noncellular enrichment of allografts was needed to approach the outcomes of autografts (eg, treatment with growth factors [nerve growth factor, vascular endothelial growth factor, ciliary neurotrophic factor, hepatocyte growth factor, and glial-cell derived neurotrophic factor], laser, wave or electrical stimulation therapy, platelet-rich plasma, or other factors [ginkgo biloba extract, Kruppel-like factor, etifoxine, and graphene oxide]).[7] Large animal peripheral nerve reconstruction models are limited because of their high costs and limited range of outcome measures. However, sheep provide regeneration rates and distances similar to those in humans facilitating clinical translation. Strasberg et al[8] compared the outcomes of fresh nerve autografts with that of fresh allografts, cold-preserved nerve autografts, and cold-preserved nerve allografts in a long-segment (8 cm) median nerve sheep model. At short and long follow-up time points, fresh autografts were proven superior to all other treatment groups.[8] The microenvironment of the nerve regeneration sites increases the specificity and accuracy of the regenerating neurites to return to their end organ target, which is influenced by upregulated factors in motor versus sensory pathways. The accelerated rate of regeneration observed in mixed and motor nerve grafts may be attributed to the presence of motor elements. Motor grafts contain sensory axons in the form of motor afferent fibers, which likely provide trophic support to regenerating motor neurites. In contrast, motor neurites in a pure sensory environment lack these motor-specific factors and may experience slower growth.[3] These findings imply that peripheral nerve injuries involving motor or mixed motor/sensory nerves should be reconstructed with motor nerve grafts.[3] Because the availability of expendable motor autograft sites is limited in the human body, it would be desirable to augment decellularized nerve allografts with a combination of cellular and noncellular treatment to attain comparable outcomes to autografts.[3] Despite decades of basic science research, clinical translation of nerve allograft augmentation therapies remains impeded by safety limitations, including technical difficulties, risk of tumorigenesis, cellular instability, and rejection.[9] Rodent models are commonly used as a bioassay for the evaluation of novel treatments in preclinical basic science research, prior to translation to larger animal models. Translation from rat models to humans may be complicated because of their small gap size, short regeneration distance, and their superlative neuroregenerative capacity. Moreover, the implication of peripheral nerve basic science research depends on the design of the study, selected outcome measures, and time of regeneration per specific animal models. The reviewed studies are limited by including a range of outcome measures assessed at different time points. It is imperative to note that incongruence in these selected parameters often precludes valid interstudy comparisons.[6] However, the findings across all basic science studies conclude that autografts outperformed allograft in mixed nerve reconstructions in studies that adequately assess function in a physiologic time period. A finite time period exists to assess nerve regeneration accurately after treatment. The blow-through theory in rodents explains the effect in which any experimental nerve defect can be bridged given sufficient time, rendering control and experimental groups indistinguishable at later time points. Outcomes that are interpreted outside this window of time, either before axonal regeneration can occur or after the plateau phase, may not be translatable to larger animal models or humans.[6]

Clinical studies

Table 1 provides a comprehensive overview of clinical outcomes following the reconstruction of mixed motor/sensory nerves with allografts or autografts.[5,10,12–19]

Cryopreserved allografts

Mackinnon et al[10] reported one of the first large mixed nerve allograft reconstructions in a single case study. The 23-cm proximal sciatic nerve injury was repaired by a 10-cable cold-preserved nerve allograft with systemic immunosuppression. Protective sensibility was reported after 18 months; however, no motor recovery was reported.[10] In 2001, the same authors described seven cases of mixed nerve injuries reconstructed with cold-preserved cadaveric nerve allografts with systemic immunosuppression. The repaired defects, with a mean defect length of 22 cm, resulted in rejection in one patient and regained motor function in 3.[1,20]

Decellularized allografts

The Axogen Avance (AxoGen Inc) nerve graft is the only Food and Drug Administration–approved cadaveric decellularized nerve graft available for clinical use at the time of this publication. The “Registry of Avance Nerve Graft’s Utilization and Recovery Outcomes Post Peripheral Nerve Reconstruction” study, supported by Axogen, serves as the official registration study for assessing their efficacy. It has resulted in several publications of outcomes of sensory, motor, and mixed nerve defects with lengths up to 7 cm.[20] Brooks et al[12] reported on 76 repairs performed by 25 surgeons, including 18 mixed nerves, with a mean preoperative interval of 170 ± 234 days, a follow-up of 205 ±115 days, and a mean gap length of 29 ± 12 mm. A meaningful motor recovery (M3–M5) and sensory function (S3–S4) on the British Medical Research Council Classification (BMRC; Table 2) scale was reported in 77% of the mixed nerve injuries.[12] Cho et al[13] reported results of 53 nerve defects, including 13 mixed nerves, reconstructed with the Axogen Avance allografts in a subsequent study. Overall recovery of mixed nerve defects (S3–S4 or M3–M5) was reported in 54% of the patients. However, it is noteworthy that the specific details regarding graft length, follow-up time period, and distribution of the BMRC for mixed nerves were not reported but contributed to the overall outcomes of all nerve injuries.[13] In 2017, Isaacs et al[14] evaluated the effect of large graft diameter after reconstruction of 15 nerve defects, including 13 mixed nerves, with Axogen Avance allografts (4–5 mm diameter). The mean gap size was 33 ± 10 mm, with a mean follow-up of 13 months, and resulted in meaningful recovery of sensory and motor function (S3–S4 or M3–M5) in 67% and 85% of the repairs, respectively.[14] In 2020, Safa et al[15] reported results after reconstruction of 624 nerve defects with Axogen Avance allografts, including 61 mixed nerves in the upper extremity and 16 in the lower extremity. Upper extremity mixed nerves with a mean gap length of 35 ± 16 mm resulted in 79%

Table 1
Clinical Application of Nerve Grafts for the Reconstruction of Mixed Motor/Sensory Nerve Defects

Author (y)	Title	Donor Nerve Type	Number of Centers	Location Reconstructed Nerves	*N*	Preoperative Interval (mo, Mean ± SD)	Gap Length (mm, Mean ± SD)	Meaningful Recovery	Follow-Up Time (mo, Mean ± SD)
Mackinnon et al[10] (1992)	Clinical application of peripheral nerve transplantation	Cold-preserved cadaveric nerve allograft, with immune suppression	1	Lower extremity	1	-	230 mm	Protective sensibility, no motor recovery	18 mo
Mackinnon et al[11] (2001)	Clinical outcome following Nerve Allograft Transplantation	Cold-preserved cadaveric nerve allograft with immune- suppression	1	Upper extremity and lower extremity	7	4.4 ± 1.8 months	220 mm[†]	Rejection in one patient and regained motor function in three	30.3 ± 10.8 mo
Brooks et al[12] (2012)	Processed nerve allografts for peripheral nerve reconstruction: a multicenter study of utilization and outcomes in sensory, mixed, and motor nerve reconstructions	Axogen Avance nerve graft[*]	12	Upper extremity and lower extremity	18	5.6 ± 7.7 mo	29 ± 12 mm	77% S3–S4 or M3–M5 on the BMRC scale	6.7 ± 3.8 mo
Cho et al[13] (2012)	Functional outcome following nerve repair in the upper extremity using processed nerve allograft.	Axogen Avance nerve graft[*]	12	Upper extremity	13	-	5–14 mm ($N = 1$) 15–29 mm ($N = 2$) 30–50 mm ($N = 10$)	54% S3–S4 or M3–M5 on the BMRC scale	-
Isaacs et al[14] (2017)	A preliminary assessment of the utility of large-caliber processed nerve allografts for the repair of upper extremity nerve injuries	Axogen Avance nerve graft[*]	12	Upper extremity	13	4.5 ± 6.6 mo[‡]	33 ± 10 mm[‡]	67% S3–S4 and 85% M3–M5 on the BMRC scale	13 mo[†]
Safa et al[15] (2020)	Peripheral nerve repair throughout the body with processed nerve allografts: Results from a large multicenter study	Axogen Avance nerve graft[*]	31	Upper extremity and lower extremity	61 upper extremity 16 lower extremity	5.2 ± 19.6 mo 10.1 ± 21.7 mo	35 ± 16 mm 55 ± 15 mm	79% S3–S4 or M4–M5 on the BMRC scale 44% S3–S4 or M4–M5 on the BMRC scale	At least 18 mo[†]
Leckenby et al[16] (2019)	A retrospective case series reporting the outcomes of avance nerve allografts in the treatment of peripheral nerve injuries	Axogen Avance nerve graft	1	Upper extremity and lower extremity	25	-	41 (15–70) mm[†]	44% S3–S4 and 36% M3–M5 on the BMRC scale	13.7 ± 7.0 mo[‡]
Carlson et al[17] (2018)	Single center's experience in a variety of peripheral nerve injuries	Axogen Avance nerve graft	1	Upper extremity and lower extremity	3	-	65 ± 45 mm[‡]	33% S3–S4 or M4–M5 on the BMRC scale	15 ± 5 mo

Peters et al[5] (2023)	Acellular nerve allografts in major peripheral nerve repairs: an analysis of cases presenting with limited recovery	Axogen Avance nerve graft	1	Upper extremity	5	-	81 ± 21 mm	No clinical or electrophysiological evidence of recovery	16 ± 5.4 mo
Sallam et al[18] (2017)	Nerve transfer versus nerve graft for reconstruction of high ulnar nerve injuries	Autograft, cabled sural nerve	1	Upper extremity	28	7.8 (7–16) mo[†]	30–50 mm[†]	53.6% S3–S4 and 57.1% M3–M5 on the BMRC scale	26.8 (24–36) mo[†]
George et al[19] (2014)	An evidence-based structured review to assess the results of common peroneal nerve repair	Autograft, cabled sural nerve	Review of 28 studies	Lower extremity	431	-	<60 mm 60–120 mm >120 mm	64% M4 and greater 29% M4 and greater 11% M4 and greater	31.8 (9.6–140.4) mo[†]

SD, Standard Deviation.
[*] Industry-sponsored studies.
[†] Mean ± SD values of data were not provided in the original study.
[‡] Mean value of the entire cohort of the original study, including pure motor, pure sensory and mixed motor and sensory nerves. Results were not stratified for mixed motor and sensory nerve reconstructions.

meaningful response, S3 or M4 and above, compared with a mean gap length of 55 ± 15 mm in the lower extremity with a significantly inferior meaningful response of 44%.[15] Although the Registry of Avance Nerve Graft's Utilization and Recovery Outcomes Post Peripheral Nerve Reconstruction studies have vast numbers of patients, their inherent commercial bias is limiting. Studies that were independent of commercial bias and evaluated the Axogen Avance allografts are limited. Leckenby et al[16] included a retrospective chart analysis of 207 nerve defects, including 25 mixed nerves, reconstructed with Axogen Avance allografts. The average diameter measured 3.8 (1–5) mm, whereas the mean length was 41 (15–70) mm. Forty-four percent achieved a significant sensory recovery (S3–S4), and 36% achieved a substantial motor recovery (M3–M5). Poorer results were seen with increasing graft size, prompting the conclusion to advise against the use of nerve allografts for bridging mixed nerves larger than 5 cm. Similarly, poorer results were noted with increasing diameter size.[16] Carlson et al[17] reported single center results of 15 nerve defects, including 3 mixed nerves, with Axogen Avance allografts. Overall recovery of mixed nerve defects, defined as S3 or M4 and above, was reported in 33% of the patients. Mean gap length (65 ± 45 mm), follow-up time (15 ± 5 months), and distribution of BMRC scores were solely provided for the entire cohort, without specific categorization.[17] Peters et al[5] reported on five patients with iatrogenic injuries to the median or ulnar nerve reconstructed prior with an AxoGen AVANCE nerve allograft at an outside institution, necessitating allograft excision followed by autograft reconstruction. The patients had no clinical or electrophysiologic evidence of recovery at presentation, and a mean gap length of 8.1 (6–11) cm. In four cases, large neuromas were found proximal to the allograft upon exploration. Histology of harvested allograft specimens demonstrated myelinated axons present in all proximal native nerve specimens, with failure to regenerate into the allograft in two cases, and diminished or terminated axonal regeneration within the allograft in three cases. This study emphasizes that in long-length, large-diameter nerves, the use of allografts should be carefully considered.[5] Interestingly, the outcomes of the noncommerically supported studies were much poorer than the commercially funded studies.

Autograft

Sallam et al[18] reported results after the reconstruction of complete, isolated high ulnar nerve injuries with sural nerve grafting compared with distal anterior interosseous nerve transfers.

Twenty-eight defects were reconstructed with a sural nerve graft, with a preoperative interval of 7.8 (7–16) months. Gap length averaged between 3 and 5 cm, and defects were reconstructed with 4 reversed cables. Patients were followed up for a mean period of 26.8 (24–36) months. Of 28 patients, 16 patients (57.1%) achieved substantial motor recovery, and 15 patients achieved substantial sensory recovery (53.6%). Meaningful motor recovery was significantly higher after nerve transfers (20 of 24 patients); however, meaningful sensory recovery was comparable.[18] George et al[19] systematically reviewed 28 studies reporting on 431 peroneal nerve injuries reconstructed with autografts. In grafts shorter than 6 cm, 64% of repairs achieved good outcomes (M4 and greater), 29% in grafts between 6 and 12 cm, and only 11% in grafts exceeding 12 cm.[19]

Comparison of autografts and allografts

Few, if any, prospective randomized studies comparing allograft with autograft in human-mixed motor/sensory nerves exist. Lans et al[2] systematically reviewed literature including 1,559 nerve repair outcomes, of which 670 were autograft repairs and 711 were allograft repairs, resulting in comparable meaningful recovery outcomes regardless of gap length or nerve type and comparable complication rates. Mixed nerves were counted as separate nerves

Table 2
BMRC Sensory and Motor Function Scale*

Level of Recovery		Sensory		Motor
Not meaningful recovery	S0	Absence of sensibility in the autonomous area	M0	No contraction
Not meaningful recovery	S1	Recovery of deep cutaneous pain sensibility within the autonomous area of the nerve	M1	Flicker/trace contraction
Not meaningful recovery	S2	Return of some degree of superficial cutaneous pain and tactile sensibility within the autonomous area of the nerve	M2	Active movement with gravity eliminated
Meaningful recovery	S3	Return of superficial cutaneous pain and tactile sensibility throughout the autonomous area, with disappearance of any pervious over response	M3	Active movement against resistance
Meaningful recovery	S3+	Return of sensibility as in S3; in addition, there is some recovery of two-point discrimination within the autonomous area (7–15 mm)	M4	Moderate movement against resistance
Meaningful recovery	S4	Complete recovery (two-point discrimination, 2–6 mm)	M5	Normal/full power

* The British Medical Research Council muscular function grading system includes M4-, slight movement against resistance; M4, moderate movement against resistance; and M4+, strong movement against resistance.[2]

for sensory and motor results, limiting the extraction of meaningful recovery data from mixed nerves. Cost analysis demonstrated that total costs for allograft repair were less than autograft total costs in the inpatient setting, and comparable in the outpatient setting.[2] The limitations of systematic reviews should be considered when interpreting their findings.

Discussion

When faced with the need to reconstruct a segmental mixed motor/sensory nerve defect, the surgeon must balance what type of nerve graft (autologous versus allograft), its diameter (multiple cabled small diameter or single large diameter), and patient preference for the potential outcome of the reconstruction.[4] Peripheral nerve basic science research has guided some of our understanding and has consistently demonstrated the superiority of autograft over allograft nerve reconstructions,[3,6,7] but larger animal models are needed to adequately compare autografts and allografts in mixed motor/sensory reconstructions that enable direct clinical translation.[9] Although there was an observed enhancement in outcomes with the use of cold-preserved human allograft with systemic immunosuppression, the adverse effects of systemic immunosuppression did not outweigh the benefits when compared with autograft reconstructions. Cadaveric commercially processed nerve allografts were introduced to overcome donor-site morbidity with an infinite supply and have been evaluated in more than 8,500 published articles. Clinical guidelines currently recommend use in sensory defects smaller than 3 cm because of insufficient data.[1] Consequently, a myriad of clinical studies have been performed over the past two decades, evaluating reconstruction with the Axogen Avance in longer gaps and larger diameter mixed sensory/motor nerves. Although many industry-sponsored studies have included a large number of patients, only a small portion had mixed motor/sensory nerve defects. Subgroup analyses regarding nerve gap length, age, preoperative interval, and follow-up duration with regards to meaningful response were commonly reported for the entire patient cohort rather than specific to nerve type.[2,4,12–17,20] Meaningful response after reconstruction of mixed nerves with Axogen Avance allografts varied between 44% and 85%, with a mean gap length varying between 17 and 51 mm, in industry-sponsored studies. Poorer outcomes were reported in nonindustry-sponsored studies, with a meaningful response between 33% and 36% and a mean gap length varying between 15 and 110 mm. As meaningful response diminishes proportionally with an increasing gap length, Leckenby et al[16] recommended limiting the reconstruction of mixed nerve defects to a maximum of 5 cm with processed allograft nerves. The outcomes of studies were compared with historical, published data of reconstruction with nerve autografts, which commonly also did not distinguish outcomes based on nerve type.[2,4,12–17,20] Although autograft reconstruction has been performed for decades, recent and detailed data are limited on mixed nerve reconstruction outcomes.[18,19] Moreover, larger nerve defects are commonly reconstructed in autograft studies, resulting in relatively low-recovery rates, as the regenerative function of autografts also decreases in long nerve gaps.[5,18,19] We are cognizant of the limitations of the reviewed studies, which include commercial bias, small mixed nerve sample sizes, retrospective design, differences in outcome measures included, self-reporting of outcomes by the operating surgeon rather than an independent observer, and lack of adequate preoperative studies (electrodiagnostic) and follow-up with missing long-term data. Most importantly, the absence of control groups and lack of blinding result in a large risk of bias. Numerous studies reported BMRC grade 5 outcomes, known to be challenging to obtain, if not impossible after major nerve reconstruction.[1] The utilization of the BMRC grading system, although prevalent, is associated with significant deficiencies and substantial inconsistencies across institutions.[1,21] The lack of comparison of the strength to the contralateral side and inherent inconsistencies to accurately grade manual muscle testing, even when performed by experienced clinicians, introduce a significant source of interpretation bias in data analysis.[1,21] Moreover, motor strength cannot solely be attributed to the reconstructed nerve, as adjacent muscles can influence complex muscle movements. Preoperative clinical examinations and nerve conduction testing are needed to evaluate for anomalous innervations (eg, Martin Gruber or Riche Cannieu anastomosis) when reporting outcomes of median nerve reconstructions.[1] Given the substantial risk of publication bias, in which studies with positive results tend to be more readily published than those with negative findings, interpretation of these studies may be challenging.[4] These discrepancies highlight the need for a prospective, randomized, nonindustry-sponsored study to evaluate outcomes of autografts versus processed nerve allografts after reconstruction of long mixed nerve defects. Although the ease of off-the-shelf products and avoidance of secondary donor-site morbidities of allografts are appealing, the critical function of mixed nerves should not be compromised solely to avoid time to harvest an autologous nerve and donor-site morbidity.[5] In conclusion, basic science studies have demonstrated that autografts remain superior when reconstructing a mixed nerve defect. The level of evidence for using processed allografts in major mixed motor/sensory nerve defects is insufficient to draw any conclusions about its usefulness in current clinical practice. There are no clinical studies directly comparing the outcomes of nerve allografts with nerve autografts, with similar

conditions, and few unbiased evaluations of outcomes. Future prospective studies are needed to directly compare outcomes following autograft and allograft reconstruction of mixed motor/sensory nerve defects, before considering reconstructions with allografts over autografts in nerve gaps larger than 3 cm.

Conflicts of Interest

No benefits in any form have been received or will be received related directly to this article.

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