Return of Motor Function After Segmental Nerve Loss in a Rat Model: Comparison of Autogenous Nerve Graft, Collagen Conduit, and Processed Allograft (AxoGen)

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Background: An effective alternative to nerve autograft is needed to minimize morbidity and solve limited-availability issues. We hypothesized that the use of processed allografts and collagen conduits would allow recovery of motor function that is equivalent to that seen after the use of autografts.

Methods: Sixty-five Lewis rats were divided into three experimental groups. In each group, a unilateral 10-mm sciatic nerve defect was repaired with nerve autograft, allograft treated by AxoGen Laboratories, or a 2.0-mm-inner-diameter collagen conduit. The animals were studied at twelve and sixteen weeks postoperatively. Evaluation included bilateral measurement of the tibialis anterior muscle force and muscle weight, electrophysiology, assessment of ankle contracture, and peroneal nerve histomorphometry. Muscle force was measured with use of our previously described and validated method. Results were expressed as a percentage of the values on the contralateral side. Two-way analysis of variance (ANOVA) corrected by the Ryan-Einot-Gabriel-Welsch multiple range test was used for statistical investigation ($\alpha = 0.05$).

Results: At twelve weeks, the mean muscle force (and standard deviation), as compared with that on the contralateral (control) side, was 45.2% ± 15.0% in the autograft group, 43.4% ± 18.0% in the allograft group, and 7.0% ± 9.2% in the collagen group. After sixteen weeks, the recovered muscle force was 65.5% ± 14.1% in the autograft group, 36.3% ± 15.7% in the allograft group, and 12.1% ± 16.0% in the collagen group. Autograft was statistically superior to allograft and the collagen conduit at sixteen weeks with regard to all parameters except histomorphometric characteristics ($p < 0.05$). The collagen-group results were inferior. All autograft-group outcomes improved from twelve to sixteen weeks, with the increase in muscle force being significant.

Conclusions: The use of autograft resulted in better motor recovery than did the use of allograft or a collagen conduit for a short nerve gap in rats. A longer evaluation time of sixteen weeks after segmental nerve injuries in rats would be beneficial as more substantial muscle recovery was seen at that time.

Clinical Relevance: On the basis of this study, the enthusiasm for use of processed allograft nerve grafts in motor nerve reconstruction should be tempered until additional studies are performed.

Despite advances in surgical technique, functional recovery following reconstruction for segmental nerve injuries often remains poor. Segmental lesions can result from traumatic loss, surgical excision, retraction and scarring after neglected sharp injury, and/or extensive longitudinal damage requiring excision after delayed treatment of stretch injuries. When direct end-to-end suture is not possible, autograft interposition is the time-proven treatment of choice\cite{1}. Autografts

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are associated with a risk of donor site morbidity and are limited to a few expendable nerves. An alternative treatment method with equal or better outcomes would be a major advance. Possible methods evaluated in experimental models have included autologous vein and muscle, allogenic nerves, and silicone or bioabsorbable artificial conduits. Nerve allografts and collagen conduits have resulted in successful recovery—based on axon growth and walking track analysis—similar to the recovery provided by autografts in the laboratory rat, but only when they were used for gaps smaller than 1.5 cm. A side-to-side comparison of different gap reconstruction methods has seldom been performed in the rat sciatic nerve model. This is due in part to shortcomings of the walking track analysis. Problems common after nerve-grafting in rats, including ankle stiffness, foot ulcers, and autophagia, compromise data acquisition.

We developed a method of tibialis anterior muscle force measurement that has proved to be a quantitative and reproducible measure of motor recovery. The underlying mechanisms of motor recovery are complex and time-dependent, involving many factors affecting motor neuron survival, proximal axon regeneration, synaptogenesis, and recovery of the denervated target muscle. In the present study, we investigated motor recovery after segmental nerve repair in rats using three different conduits: processed nerve allograft (AxoGen, Alachua, Florida) a collagen conduit (Stryker Orthopaedics, Mahwah, New Jersey), and autograft to determine which is the most effective in restoring motor function. Ultimately, the goal of achieving an effective nerve-graft substitute will rely on functional assessments of recovery as well as a better understanding of these recovery mechanisms.

Materials and Methods

This study was approved by the Mayo Clinic Institutional Animal Care and Use Committee. Sixty-five male inbred Lewis rats, weighing 200 to 300 g, were divided into three groups. Group I (the autograft group, n = 21) had a unilateral 10-mm sciatic nerve gap repaired with an ipsilateral reversed autologous graft. Group II (the decellularized allograft group, n = 22) had the same gap reconstructed with a 10-mm decellularized nerve allograft. The allografts were harvested from Sprague-Dawley rats, representing a major histocompatibility barrier, and prepared by AxoGen Laboratories in the same fashion as commercially available human nerve allografts are prepared. Group III (the collagen-conduit group, n = 22) received a 2.0-mm-inner-diameter collagen conduit (NeuroMatrix) to span the nerve gap. The sequence and side of the surgical procedures were randomized. During the survival period, the rats were given food and water ad libitum and housed individually with a twelve-hour light-dark cycle. Functional recovery was evaluated after twelve weeks (n = 30) and sixteen weeks (n = 32) in a nonsurvival procedure performed by an experimenter blinded to the repair type. We measured the maximum passive plantar ankle flexion angle as well as the compound muscle action potential (CMAP) and maximum isometric tetanic force of the tibialis anterior muscle bilaterally. After the animals were killed, the weight of the tibialis anterior muscle was recorded, and peroneal nerve histomorphometry was performed.

Nerve Allograft Processing

Fifteen male Sprague-Dawley rats (200 to 300 g) were killed, and a 15-mm segment of the sciatic nerve was harvested bilaterally, placed in Ringer lactate solution, and shipped on dry ice to AxoGen Laboratories. After processing, the allograft nerves were stored and used according to the manufacturer’s recommendations.

Survival Procedure

Anesthesia

The rats were anesthetized with an intraperitoneal injection of a 10/1 mixture of ketamine (Ketaset, 100 mg/mL; Fort Dodge Animal Health, Fort Dodge, Iowa) and xylazine (100 mg/mL; VetTek, Blue Springs, Missouri), respectively, at a dose of 1 mL/kg of body weight. Additional doses of ketamine were given intraperitoneally as needed to maintain anesthesia. Body temperature was maintained at 37°C with a heating pad, and 5 mL of Ringer lactate solution was administered subcutaneously to prevent dehydration. Infection prophylaxis was provided by a postoperative single subcutaneous injection of trimethoprim/sulfadiazine (Tribrissen, 30 mg/kg; Schering-Plough, Kenilworth, New Jersey).

Surgical Procedure

Anesthesia

The sciatic nerve on the randomly selected experimental side was fully exposed proximally from the inferior margin of the piriformis muscle to approximately 5 mm distal to the bifurcation. A 10-mm segment was marked with 10-0 epineurial sutures 5 mm distal to the early tibial branch, which leaves the sciatic nerve proximally to innervate the posterior thigh muscles, and was excised by sharp transection with microsurgical scissors under an operating microscope (Zeiss OpMi 6; Carl Zeiss Surgical, Oberkochen, Germany). The sural nerve, which branches off the sciatic nerve a few millimeters proximal to the bifurcation, was always included in the resected nerve segment. In group I, the nerve segment was removed, reversed, and placed as an interposition autograft with four, five, or six 10-0 nylon epineurial interrupted sutures. In group II, a 10-mm decellularized nerve allograft was used to bridge the 10-mm sciatic nerve gap with use of a similar suture technique. In group III, the nerve gap was bridged with a 12-mm collagen nerve conduit with two 8-0 nylon transverse epineurial loop sutures at each junction. The nerve ends were positioned and sutured to lie 1 mm within the tube on each side, resulting in a final gap of 10 mm (Fig. 1). The conduit lumen was flushed with saline solution. In all groups, fibrin glue (Baxter, Deerfield, Illinois) was used to complete the repair, preventing acute dislodgement of the nerve grafts as well as hematoma from entering the conduits. Wounds were closed in layers, with muscle approximated with 4-0 absorbable sutures and skin approximated with 4-0 nylon sutures. Following skin closure, 0.1 mL/kg of buprenorphine hydrochloride (Buprenex; Reckitt Benckiser Pharmaceuticals, Richmond, Virginia) was administered subcutaneously for pain control. Postoperatively, the rats were kept warm with towels, and 300 mg/kg of acetaminophen (Q-pap; Qualitest Pharmaceuticals, Huntsville, Alabama) was added once to the feed water.
Schematic view of the experimental setup for isometric tetanic force testing. The rat is prone with the limb to be tested in abduction and slight elevation. The femur and ankle are attached to the testing block with two Kirschner wires (a). The force transducer is attached to the tibialis anterior muscle by a custom clamp on the distal tibialis anterior tendon (b). A bipolar electrode is connected to the peroneal branch of the sciatic nerve (c), and the rat is electrically grounded (d). (Copyrighted and used with permission from Shin RH, Vathana T, Giessler GA, Friedrich PF, Bishop AT, Shin AY. Isometric tetanic force measurement methods of the tibialis anterior in the rat. Microsurgery. 2008;28:452-7.)

Non-surgical Procedure

Ankle contracture: At twelve or sixteen weeks, the rats were anesthetized as before. The ankle contracture angle was determined on the experimental side by measuring the angle between the anterior aspect of the tibia and the dorsal aspect of the foot with the ankle in maximal passive plantar flexion.

CMAP: The main sciatic trunk proximal to the graft was exposed, and the CMAP was measured with use of a miniature bipolar electrode. The contralateral, control side was tested in an identical fashion. The skin was reapproximated with suture on completion of CMAP testing until force measurements were conducted. See the Appendix for a detailed description of CMAP measurements.

Maximum isometric tetanic force: Maximum isometric tibialis anterior muscle force measurements were performed as previously described (1) (Fig. 2). This method provides reproducible quantitative evaluation of motor recovery through use of careful methodology. See the Appendix for a detailed description of muscle force measurement.

Tissue collection: The tibialis anterior muscle was removed and weighed. The sciatic nerve and its distal branches were exposed bilaterally and were fixed in situ for five minutes with use of 2% Trump fixative. Immediately afterward, a 5-mm segment of the peroneal nerve was harvested and was stored in the same fixative. The animals were killed with an overdose of phenobarbital.

Histomorphometry: The nerve tissue samples were embedded in spur resin, cut into 1-μm sections with use of an ultramicrotome with a glass knife, and stained with a 3% solution of phenylenediamine. Histomorphometric analysis was performed with use of a proprietary imaging system (Peripheral Nerve Laboratory, Mayo Clinic, Rochester, Minnesota) as previously described (15).

Nerve area was measured at 5× magnification, and detailed evaluation of the axons was performed at 63× magnification. In essence, random fields were selected at 63× magnification, and all axons and their respective myelin were manually marked with a digital pen. Nerves were analyzed in relation to axon density, myelin fiber diameter, axon diameter, myelin thickness, and G ratio (the ratio between the axon diameter and fiber diameter). A total of 500 to 600 myelinated fibers were selected per slide to represent the entire nerve.

Statistical Analysis

The three different groups were compared with respect to animal weight gain, ankle contracture, CMAP, maximum isometric tetanic force, muscle weight, and results of nerve histomorphometry. Except for the ankle contracture and animal weight, all results were expressed as a percentage of the value on the contralateral side to diminish the effect of normal biologic variability between animals. A two-way analysis of variance (ANOVA) corrected by the Ryan-Einot-Gabriel-Welsch multiple range test was used to determine statistical differences. The Pearson coefficient test (r) was used for correlation analysis. A relationship was considered positive when r values were 20.6 with linear distribution. All results were reported as the mean and standard deviation, and the level of significance was set at 0.05.

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This study was funded by an unrestricted educational research grant provided by Stryker Orthopaedics. The nerve conduits were provided by Stryker Orthopaedics, and the nerve allografts were processed by AxoGen.

Results

Of the sixty-five rats, five either were excluded or provided limited data. These included four that died (group I, n = 1; group II, n = 2; and group III, n = 1). The animal from group I died under anesthesia during the muscle force testing at sixteen weeks; all data were recorded except the maximum tetanic force. No testing was possible in the other three animals. One additional group-I animal was excluded from CMAP analysis because of technical problems with data acquisition.

At the sacrifice procedure, the macroscopic appearance of the allograft and autograft nerves was similar, except in one group-II animal with visible separation at the distal nerve coaptation site. The collagen conduits were still present without collapse at twelve and sixteen weeks. No blood clots or substantial obstructions were observed in the lumen of the collagen tubes. A summary of all results is presented in the Appendix.

Animal Weight

At twelve weeks, the percentage of weight gain was 46.0% ± 13.0% in group I, 47.2% ± 12.0% in group II, and 43.1% ± 10.6% in group III. At sixteen weeks, the percentage was 50.1% ± 12.1% in group I, 50.1% ± 14.5% in group II, and 48.9% ± 12.8% in group III. The differences among the groups were not significant (p = 0.77).

Muscle Weight

The normalized results for tibialis anterior muscle weight at twelve weeks were 55.1% ± 7.1% in group I, 55.1% ± 4.8% in group II, and 22.6% ± 8.8% in group III. At sixteen weeks, they were 64.1% ± 7.2% in group I, 50.4% ± 13.0% in group II, and
28.9% ± 17.9% in group III. The groups were significantly different, with autograft performing better (p < 0.001). No difference was seen over time (Fig. 3).

Ankle Contracture
At twelve weeks, the ankle plantar flexion angle was 137.5° ± 14.0° in group I, 130.6° ± 20.8° in group II, and 101.4° ± 11.5° in group III. At sixteen weeks, it measured 142.2° ± 17.5° in group I, 120.5° ± 15.7° in group II, and 97.6° ± 11.5° in group III. Differences between groups were significant (p < 0.001). Values at twelve and sixteen weeks were not significantly different (p = 0.46) (Fig. 3).

CMAP
At twelve weeks, the results of CMAP amplitude in the experimental side as a percentage of the control side were 54.5% ± 63.0% in group I, 37.3% ± 15.4% in group II, and 5.2% ± 7.2% in group III. At sixteen weeks, the results were 70.5% ± 34.5% in group I, 39.4% ± 20.2% in group II, and 18.8% ± 30.5% in group III. Differences between all groups were significant (p < 0.001), whereas there was no significant difference between values at the two different time points within the groups (p = 0.22). The decellularized allograft group was superior to the collagen conduit group but performed worse than the autograft group (Fig. 3).

Maximum Isometric Tetanic Force
The recovery of tibialis anterior isometric tetanic force at twelve weeks was 45.2% ± 15.0% in group I, 43.4% ± 18.0% in group II, and 7.0% ± 9.2% in group III. At sixteen weeks, group I presented 65.5% ± 14.1% recovery; group II, 36.3% ± 15.7%; and group III, 12.1% ± 16.0%. An interaction between sacrifice time and the type of graft was observed. The autograft group did not differ significantly from the allograft group at twelve weeks. However, at sixteen weeks, the value in the autograft group was significantly superior to that in the allograft group (p < 0.001). The autografts and allografts were superior to the collagen conduits at both time points (Fig. 4). The ability to generate tibialis anterior muscle contraction (the recovery rate) was 100% (twenty of twenty) in group I, 95% (nineteen of twenty) in group II, and only 38% (eight of twenty-one) in group III (Fig. 4).

Histomorphometry
The normalized results in the autograft group did not differ significantly from those in the allograft group with regard to any of the histomorphometric parameters (axon density, myelin fiber diameter, axon diameter, myelin thickness, and G ratio). The collagen-conduit group had a significantly smaller nerve area than did groups I and II at all time points (p = 0.03),
and it had a smaller number of axons only at twelve weeks (p = 0.001). The axon numbers did not differ significantly among the groups at sixteen weeks (p = 0.03). The axon diameter, myelin fiber diameter, and myelin thickness improved in all three groups from twelve to sixteen weeks (p < 0.05) (Fig. 5).

**Correlations**

Correlations among all outcome tests are shown in the Appendix. Significant differences between groups, based on a Pearson correlation coefficient value of 20.6, were seen in muscle force, muscle weight, CMAP, and ankle angle.

In general, the results in the autograft group were better than those in the decellularized allograft and collagen-conduit groups. The results in the autograft group were significantly superior with respect to recovery of muscle weight, CMAP, and ankle contracture at both twelve and sixteen weeks and with respect to muscle force at sixteen weeks. The axon counts and peroneal nerve area of the collagen-conduit nerves were significantly inferior to those in the other groups, which did not differ from one another. The remaining histomorphometric parameters, including fiber diameter, axon diameter, and myelin thickness, improved over time in all groups but showed no intergroup differences (Fig. 5).

**Discussion**

The goal of finding an effective peripheral nerve substitute for autogenous nerve graft is laudable. It would reduce patient morbidity while providing an unlimited supply of material with which to repair complex nerve injuries. To be justifiable, such a method should prove to be at least as effective as the time-proven nerve autograft. Collagen conduits and allografts have demonstrated great potential for axon growth in some animal models, and may provide sensory recovery similar to that achieved with autografts in patients with digital nerve injuries. Neither recovery of sensibility nor demonstration of axon growth across a gap is sufficient, however, to advocate general use of any autograft substitute. The ultimate goal of the reconstruction of motor and mixed nerves is functional recovery of motor function. Analysis must also include direct measures of motor reinnervation in the experimental animal, such as CMAPs, muscle weight, and muscle force as well as quantitative nerve histomorphometry distal to the gap. Such data provide the precise information needed to demonstrate the true potential of any new nerve substitute for returning both sensory and motor function.

Among all of the outcomes assessed in the statistical analysis, only three appeared to have potential departures from residual normality or equal variance on the basis of diagnostic plots, as a result of a very small number of outliers. When these outliers were removed from the analyses of the outcomes and the results were compared with the original findings, the conclusions from the ANOVA models were the same. Therefore, we considered that ANOVA was generally robust to mild departures from its underlying assumptions.

The muscle force test is a reliable and important measure for evaluation of small differences in motor recovery among experimental groups. While the recovery of crush or single laceration/repair nerve injuries in a rat model can be easily analyzed with a walking track, segmental nerve defects result in joint contracture and healing problems that make walking track data difficult to acquire. Direct muscle force measurement provides consistent results when muscle preload and electrical stimulation parameters are carefully optimized.

Decellularized nerve allografts proved to be inferior to autografts after sixteen weeks but better than 2.0-mm collagen conduits for providing motor recovery at twelve and sixteen weeks. There have been many published studies of allografts, but to our knowledge only two of them compared their efficacy with nerve autografts. Whitlock et al. bridged 14 and 28-mm gaps with acellular nerve allografts and, at twelve weeks, measured axon count, gastrocnemius muscle weight, and walking track (Sciatic Functional Index [SFI]) patterns. They found autograft to be superior when it was used for 28-mm gaps, but not when it was used for 14-mm gaps. Their explanation for the lack of difference in the 14-mm-gap group was that it was obscured by the excellent regeneration capacity of rats. Dubuisson et al. used electrophysiology, histomorphometry, and walking track testing (SFI) to analyze recovery at twelve weeks after treatment of 15-mm nerve gaps; their results also suggested similarity between autografts and allografts. However, the absence of a difference does not necessarily imply that the animals had extraordinary regeneration.
capacity or that the grafts had similar performance. Methodology needs to be closely analyzed before assuming similarities, especially involving small-group studies. Using a different approach, we tested motor nerve recovery, focusing on the analysis of the tibialis anterior muscle with previous validated methods. The differences that we observed between autografts and allografts were mainly appreciated at sixteen weeks, in contrast to the twelve-week time period commonly used as an end point in the rat sciatic nerve model. Some investigators have even suggested that an earlier time point should be used because of the perceived exceptional neuroregenerative capacity of rats. In contrast, we demonstrated that twelve weeks is not enough time for autograft muscle recovery in rats and conclusions at this time point might not represent reality. Interestingly, muscle force in the allograft group decreased from twelve to sixteen weeks. While this suggests an interaction, there was no significant interaction and no macroscopic or microscopic changes were observed that could support such a finding.

Independent of the recovery time, use of collagen conduits with a 2.0-mm inner diameter resulted in poor motor recovery. Collagen has been considered an ideal material for nerve conduits because it is the principal component of the extracellular matrix, has the capacity to attach to proteins and cells, is immunologically inert, is completely biodegradable in a few months, and allows nutrient diffusion from surrounding tissues. Both experimental and clinical studies have shown 1.5-mm-inner-diameter collagen conduits to be equivalent to autografts when used for small nerves. In a previous study comparing motor recovery with the use of the most common commercially available nerve conduits, we demonstrated that 1.5-mm-inner-diameter collagen conduits do not result in muscle function recovery at twelve weeks equivalent to that following use of autograft. The results of the larger-diameter conduits used in the present study did not differ from our previous data. The structural, biochemical, and physical differences between an autogenous nerve graft and a collagen tube are complex, likely requiring considerable future research to understand the mechanisms underlying effective nerve regeneration in large mixed nerves and across long gaps. The ideal parameters for synthetic conduits, such as the inner diameter, conduit thickness, degradability, material fiber morphology, and manufacturing process, remain unclear and deserve further investigation.

Histomorphometric analysis of the peroneal nerve did not show differences among groups other than a reduced nerve area in the collagen-conduit group (Fig. 6). The number of axons has been directly related to motor recovery and should represent a good indication of motor reinnervation. The large variability in the results contributed to the lack of statistical differences in our study. The methodology used in this study might not have been sufficient to accurately represent axon regeneration, although we did see a significant increase in values related to axon myelination (myelin thickness, axon diameter, and myelin fiber diameter) over time, suggesting nerve maturation. For example, in the autograft group, fiber diameter increased from 55% of that on the normal side at twelve weeks to almost 85% at sixteen weeks. We believe that, for this reason, sixteen weeks represents a better end point than earlier time points for motor function analysis. Notably, the absolute number of myelinated fibers also increased compared with that on the contralateral side in all groups at sixteen weeks, although the significance of this increase was not statistically tested. The so-called enhanced axonal regeneration has been described before and might increase the number of fibers up to 50%. One possible explanation for this phenomenon is the neurotrophic effect of the distal target end-organs on the growing axons.

All animals developed some degree of ankle contracture on the experimental side. The chronic absence of active ankle
motion will lead to joint contracture in either flexion or extension, depending on the joint resting position. Rats spend most of their time resting in the prone position, which favors ankle contraction limiting plantar flexion. Lin et al. previously reported significant changes in the passive ankle angle of rats after segmental nerve reconstruction and demonstrated its correlation with recovery of muscle weight. Although the passive ankle angle is not often used to evaluate nerve recovery, the method was quite sensitive, showing significant differences among all of the groups and strong correlations with traditional outcomes (see Appendix). In addition, the animals gained approximately 40% to 50% of their initial weight at the end of the experiment. Factors related to confinement, decreased activity after surgery, and availability of food and water might have contributed to an excessive weight gain. No statistical differences in weight gain were seen among the groups, demonstrating that animals were comparable and had similar treatment during the recovery time. Confinement and increased body weight might also have contributed to joint contracture in the operatively treated ankles.

Processed nerve allografts greatly diminish immunoreactivity. Fresh nerve allografts normally induce a strong immune reaction, which compromises nerve regeneration. Methods involving chemical, physical, or combined processes have been developed to diminish this response. By measuring interferon-gamma (IFN-γ) levels in transplanted mice, Whitlock et al. demonstrated the efficacy of a proprietary process (AxoGen, which was also used in our group-II animals) in reducing immunoreactivity of allograft nerves. In conclusion, nerve autografts statistically outperformed both decellularized nerve allografts and collagen conduits twelve to sixteen weeks after their use to reconstruct a 10-mm rat sciatic nerve gap. We clearly demonstrated that autograft was the superior nerve reconstruction when maximum motor recovery was desired. Assuming that the regeneration capacity of rats is similar or greater than that in humans, only the nerve substitutes that were similar or superior to autograft have a higher probability of good clinical performance. At present, use of nerve autograft remains the method of choice for reconstruction of segmental gaps in motor nerves. The enthusiasm for use of processed allograft nerves for motor nerve reconstruction should be tempered until additional animal studies are conducted.

Appendix

A detailed description of CMAP and maximum isometric tetanic force measurements and tables showing the test results for all groups and the correlations between the test results are available with the online version of this article as a data supplement at jbjs.org.

References