Distal Inside-Out Epineural Sliding Technique to Repair Segmental Nerve Defects

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Toni Luukkala^{1,2}, Jorma Ryhänen^{1,3}, Juha Näpänkangas¹,
and Teemu V Karjalainen^{1,2}

Abstract

Background: The repair of a segmental peripheral nerve injury is a clinical challenge. Several studies have been performed to determine superior methods for overcoming nerve gaps. The purpose of this study was to investigate if the inside-out slided epineurium of the distal segment of an injured nerve can serve as a conduit to bridge a short nerve defect (10 mm). **Methods:** Nineteen sciatic nerves in Sprague–Dawley rats were transected, and a 10-mm gap was left between the ends. A section of distal epineurium was pulled inside out to bridge the gap. Walking track analysis was performed, and the sciatic function index (SFI) was calculated. Wet muscle mass and withdrawal reflex were measured. The density of axon fibers at different levels of repaired nerves was determined, and histological analysis was performed at 16 weeks. **Results:** The mean SFI improved from –81.0 at 4 weeks to 36.3 at 16 weeks. The axon densities showed regeneration through the epineural tube, and 5 of the rats demonstrated a withdrawal reflex. The weight of the tibialis anterior muscle of the injured limb at 16 weeks was 59% that of the uninjured side. **Conclusions:** The distal epineural sheath tube provided a size-matched conduit between the nerve stumps, with no histological donor-site morbidity. Histologically, regeneration occurred through the epineural tube without neuroma formation, and functional recovery was comparable to that of previous studies of nerve repair techniques. Technique may be an addition to the armamentarium of tools used to treat segmental nerve defects.

Keywords: defect, epineural, graft, nerve injury, nerve repair

Introduction

The repair of a segmental peripheral nerve injury is a clinical challenge. Over the past decades, several studies have been performed to determine superior methods for overcoming nerve gaps. An ideal method would allow the axons to regenerate in an optimal environment, which would not only stimulate the axon growth but also guide the sprouting axons toward the proper sensory and motor organs within a reasonable time period.

Traditionally, autologous nerve grafts have been used to repair the defect.²⁶ Donor site morbidity is an obvious disadvantage of this technique.³⁴ In addition, the total amount of nerve graft material is limited in the body, and there may be a shortage of graft material in complex reconstructions. Moreover, the results are far from satisfactory.²⁶

The concept of a tubular nerve conduit has been well described in the literature, and different forms of it have been widely studied by several authors. The basic idea of tubulization is to direct the regenerating nerve fibers toward the distal nerve stump in a chamber, which can prevent scar

ingrowth between the nerve stumps. Tubulization also enables the accumulation of neurotrophic and neurotropic substances, which may stimulate the regeneration process.²¹ In most commonly used techniques, the nerve ends and intervening gap are enclosed within a cylinder-shaped tube. Several types of both biological and artificial conduits have been reported in experimental models. Autologous tissues, such as arteries, veins,^{7,35} and muscle,^{1,28} have been used. Artificial tubulization methods include silicone,^{11,19,20} collagen,^{2,16} polyglactin,²⁷ poly-L-lactic acid (PLLA),¹⁰ and polyglycolic acid (PGA),²² as well as combinations of these materials.¹⁷ Harvesting can also add to the operation time.

¹Oulu University Hospital, Oulu, Finland

²Central Finland Central Hospital, Jyväskylä, Finland

³Terveystalo Oulu, Finland

Corresponding Author:

Toni Luukkala, Keski-Suomen Keskussairaala, Keskussairaalantie 19,
40620 Jyväskylä, Finland.

Email: toni.luukkala@ksshp.fi

Using artificial products can increase the cost of the surgery and may cause a host reaction.¹¹

Use of the epineurium of the damaged nerve itself to protect the normal end-to-end anastomosis was first described by Snyder and colleagues³³ and later by Martini and Fromm, who used a rat sciatic nerve model.²⁴ The authors used an epineural cuff and observed no neuroma formation after repair. They did not report the functional results of this technique. Ayhan and colleagues described using a turnover epineural sheath tube from a proximal neural sheath to overcome a segmental gap.⁴ However, the use of proximal stump epineurium may cause disturbances to the blood supply of viable axons in the proximal stump. From this perspective, the distal stump would seem to be a more reasonable donor site. Chatdokmaiprai and colleagues described the use of the turnover epineural sheath from a distal stump to repair a 7-mm gap in a rat sciatic nerve model.⁶ However, they performed only histomorphometric analysis, which has been shown to correlate poorly with functional regeneration in rat sciatic nerve models.³²

The purpose of this study was to test the ability of the distal epineural sheath tube (DEST) to bridge a short segmental nerve defect in a rat sciatic nerve model. We report on the functional and morphometric effects of the DEST.

Materials and Methods

Nineteen adult male 2-month-old Sprague–Dawley rats weighing 200 to 250 g were used in the study. The right hind limb sciatic nerve served as a model for segmental nerve defect. Nine of the 19 rats underwent a 16-week follow-up. All procedures were carried out under a national license and according to the national guidelines for the care and use of laboratory animals.

Surgical procedures were performed with the animals under anesthesia: 0.08 mg fentanyl citrate + 2.5 mg flunisolone/mL water (Hypnorm; VetaPharma Limited, Leeds, UK) and 1.25 mg midazolam/mL water (Dormicum; Roche Inc). The combination was injected subcutaneously at 0.15 to 0.2 mL/100 g. In addition, 0.1 mL/100 g boluses were delivered as needed during surgery. The rats were placed in a prone position, and the right sciatic nerve was exposed through an oblique skin incision in the gluteal region and through a gluteal muscle-splitting approach under microscope magnification (OPMI 1; Carl Zeiss Meditec AG, Oberkochen, Germany) from sciatic notch to trifurcation. A 10-mm segment of nerve was excised 5 mm distal to the notch. The epineurium of the distal stump was circumferentially sectioned 12 mm distal to the transection site, proximal to trifurcation. The free edge was raised gently with 2 microforceps and rolled inside out over the gap slightly over the edge of the proximal stump (Figure 1). The epineurium was sutured over the proximal stump with four 10-0 nylon sutures (S&T AG, Neuhausen, Switzerland) placed

90° from each other. The muscle layer was closed separately, and skin was closed intracutaneously with 4-0 Monocryl (Ethicon Inc, Somerville, New Jersey). Postoperatively, rats were treated with 0.01 to 0.05 mg/kg buprenorphine (0.3 mg/mL, Temgesic; Reckitt & Colman Products Ltd, Hull, UK) and 0.1 mL/100 g carprofen (50 mg/mL, Rimadyl Vet; Pfizer Inc Animal Health) for 5 days. Rats were terminated at 16 weeks in a carbon dioxide chamber. Repaired and contralateral nerves, as well as tibialis anterior muscle, were removed for weight analysis by a microscale (GWB Mettler AM50; Mettler Toledo Inc, Greifensee, Switzerland).

Walking track analysis was performed using a 8.5 × 45 cm corridor that opened at 1 end into a darkened chamber. The rats' hind feet were dipped in black finger paint. Animals were allowed to walk the corridor on white paper. Before the actual test, rats were trained to walk in the corridor several times. The procedure was repeated until the animals walked steadily to the compartment and at least 5 clear prints were recorded. Animals with severe contracture and autotomy were not used in the analysis. Walking track analysis was performed 4 and 16 weeks after surgery. We used the sciatic function index (SFI) as a primary outcome measure described by deMedinaceli.⁸ SFI was measured by comparing the geometric representation of an affected hind paw from an injured limb with contralateral paw. 3 measurements were made: (1) print length between heel and tip of third digit, (2) toe spread between first and fifth digit, and (3) intermediate toe spread between second and fourth digit. SFI was calculated by the Bain–Mackinnon–Hunter modification of the deMenicali formula for SFI.⁵

Sensory recovery was evaluated at 4 and 16 weeks. The withdrawal reflex test was performed by applying a pinch with forceps to the heel of the injured and unaffected hind limbs. Withdrawal of the hind limb caused by stimuli was regarded as a positive test result.

The study nerve was harvested, including at least 5 mm of the segment proximal to the neurorrhaphy and at least 5 mm of the segment distal to the epineural tube donor site. A 2-cm segment of normal nerve from the unaffected site was removed and served as the control.

For overall histological analysis, 2 of the nerves were fixed in 10% buffered formalin solution and embedded in paraffin. Sections (5 µm thick) were cut and stained with hematoxylin and eosin.

For closer morphometric analysis of nerve fibers, excised nerves were fixed in a 1% glutaraldehyde, 4% formaldehyde mixture in 0.1 M phosphate buffer. They were post-fixed in 1% osmium tetroxide, dehydrated in acetone, and embedded in Epon LX 112 (Ladd Research Industries, Williston, Vermont). Transversal semi-thin (1 µm) sections were cut with a Leica Ultracut UCT ultramicrotome and stained with toluidine blue. The transversal levels were as follows: ¹ proximal to the transection site, ² epineural sheath

Figure 1. Distal epineural sheath tube technique.

Note. White arrow depicts circumferentially sectioned epineurium from the distal part of the nerve. Black arrow depicts inside-out slid sheath tube ready for segmental repair. White scale bars indicate 5 mm.

tube,³ epineural donor site, and⁴ distal to the epineural donor site. The untouched, normal nerves were cut in half and only the midsection was analyzed. The slides were then photographed with a Leica DFC420 camera, and area measurements were performed on a standard PC with an image analysis program. The histological morphology of the nerves was analyzed by a neuropathologist (J.N.). The large myelinated fibers, smaller fibers with thinner myelin sheath, and small fibers without myelination were counted and their density measured.

Summary measurements are presented as mean with standard deviation (SD). Comparisons between the affected and unaffected sides, as well as comparisons between the results of SFI at 4 and 16 weeks, were done using the paired-samples *t* test. The results of *t* tests are presented as mean difference with 95% confidence interval (95% CI). Correlation calculations were performed

using Pearson correlation coefficient. Two-tailed *P* values are presented.

Results

Walking Track Analysis and SFI

During follow-up, 2 rats died, 7 rats carried out autotomy before functional measurement at 4 weeks, and 1 rat developed hind limb contracture before functional assessment at 16 weeks. These rats were excluded from the final analysis.

The mean SFI improved from -81.0 (SD 7.2) at 4 weeks to -36.3 (SD 8.1) at 16 weeks (mean difference -44.7 , 95% CI -55.1 to -34.4 ; $P < .001$) (Figure 2).

The 5 rats with a positive withdrawal reflex had a worse SFI compared with those that did not have the reflex ($P = .003$),

Figure 2. Sciatic function index improved from -81.0 (SD 7.2) at 4 weeks to -36.3 (SD 8.1) at 16 weeks.

Note. Dashed lines depict rats in which the reflex reappeared at 16 weeks.

although the muscle weight was similar (Figure 2). The mean weight of the tibialis anterior muscle of the injured limb at 16 weeks was 59% that of the uninjured limb (0.55 mg [SD 0.05] vs. 0.94 mg [SD 0.13], mean difference 0.39 , 95% CI 0.32 to 0.47 ; $P < .001$). Tibialis anterior muscle mass did not correlate with SFI ($r = -.36$). The axon densities at different levels of the injured nerve did not correlate with SFI (Table 1). The axon densities, as well as the results of paired-samples t tests and correlation tests, are presented in Table 1.

Histology

Sixteen weeks after the transection, proximal to the transection site the epineurium appeared normal (Figure 3a). There was a loss of large myelinated nerve fiber density proximally from the transection site. However, there was an increase in the density and total axon count compared with the uninjured nerve (Table 1). This was due to the greater number of smaller myelinated and unmyelinated fibers, which were considered to be regenerating nerve fibers.

At the DEST level, the epineural sheath held the nerve sprouts inside the nerve. The loss of large myelinated fibers was more pronounced than proximal to DEST (Figure 3b), and there were even more small regenerating sprouts leading to a higher fiber density (Table 1). The fibers tended to form small bundles. However, there was no thickening of any of the nerves, which would be expected for neuroma. Distal to DEST, at the epineural donor site, intraneural blood vessels were large, 2 to 3 times the diameter of normal vessels, which

was regarded as neovascularization. There were more myelinated midsize nerves compared with DEST level and at the same time less small non-myelinated fibers. In all of the operated nerves, there were solitary nerve bundles each containing up to 10 nerve fibers outside of the nerve, but no macroscopically visible neuroma could be observed (Figure 3c and 3d). A structure that histologically resembled epineurium formed on the donor site (Figure 3c).

Distal to the epineural donor site, the overall scenario was comparable to the epineural donor site itself (Figure 3d): nerve fibers had regenerated inside the nerve area and nerve fiber bundles could be seen outside, next to the epineurium.

No inflammation was seen at any level.

Discussion

The rat sciatic nerve model has been well documented by several authors in different nerve repair studies. The regeneration potential has been shown to be equivalent in rats and nonhuman primates.^{13,14,23}

Histological analysis of the repair site showed that the axons regenerated nearly solely inside the sheath tube and only solitary fibers escaped outside; hence, macroscopical neuroma formation was not noted. At the donor site, some nerve sprouts could be seen outside the nerve itself, but even here there was no real neuroma formation. The histological analysis showed regeneration of small nerve fibers, and the inside-out slided epineural tube did not show degeneration or scarring. Histologically, a structure resembling epineurium was formed on the donor site, which corresponds with the findings of previous studies in which the epineurium was removed^{18,31,37} (Figure 3). The formation of small nerve bundles, microfascicular regeneration, is a known phenomenon after nerve transection or ischemic injury, as is the regrowing of these microfascicles outside the nerve trunk.⁹

Interestingly, the rats that exhibited sensory recovery (positive withdrawal reflex) had worse SFI compared with those with an absence of the reflex, although the muscle weight was similar ($P = .003$), suggesting equivalent motor innervation. This implies that sensory recovery may affect the gait of the animal and therefore the results of the walking track analysis. This has not been reported previously and warrants further evaluation.

The use of the epineurium as a conduit to bridge a nerve gap was first proposed by Ayhan.⁴ The same group later compared a proximal turnover sheath tube with autologous graft and found that the SFI improved similarly by 12 weeks, from approximately -90 to -60 . They also had a no-repair group, in which the SFI did not improve between 1 and 12 weeks.³⁷ Similar results have been obtained by studies that included segmental defect and no-repair groups.^{13,15,25,29}

Table 1. Mean Axon Densities/mm² at Different Levels of Repair.

Sites		DEST (SD)	Uninjured nerve (SD)	P	Mean difference (95% CI)	r
Proximal to transection site	Large	9614 (3452)	11°721 (4105)	.20	2107 (-771 to 4986)	.64
	Midsized	14°598 (7765)	10°526 (6783)	.50	-4072 (-15°265 to 7121)	-.22
	Unmyelinated	1030 (1340)	876 (649)	.33	-699 (-1997 to 598)	.54
	Total	26°671 (9629)	22°578 (7060)	.45	-4093 (-14°001 to 5815)	.51
Epineurial sheath tube	Large	5686 (3882)	11°721 (4105)	.09	6034 (244 to 10°290)	-.64
	Midsized	22°571 (10°940)	10°526 (6783)	.15	-12°045 (-26°149 to 2059)	.24
	Unmyelinated	6584 (3226)	876 (649)	.006	-6253 (-9240 to -3265)	.01
	Total	34°841 (10°726)	22°578 (7060)	.10	-12°263 (-24°639 to 113)	.02
Epineurium donor site	Large	6768 (3263)	11°721 (4105)	.12	4953 (-385 to 10°675)	-.63
	Midsized	35°955 (15°993)	10°526 (6783)	.03	-25°419 (-42°633 to -8226)	.55
	Unmyelinated	3128 (2356)	876 (649)	.04	-2749 (-4872 to -626)	.64
	Total	45°950 (14°261)	22°578 (7060)	.002	-23°372 (-37°261 to -9483)	.58
Distal to epineurium donor site	Large	6270 (4054)	11°721 (4105)	.09	5451 (227 to 10°674)	-.24
	Midsized	30°342 (13°088)	10°526 (6783)	.04	-19°817 (-34°678 to -4955)	-.05
	Unmyelinated	2018 (2482)	876 (649)	.18	-1687 (-3845 to 471)	.87
	Total	39°785 (13°034)	22°578 (7060)	.04	-12°451 (-28°405 to 3503)	-.06

Note. Paired-samples *t* test (*P*) was performed with uninjured nerve, and correlation coefficient (*r*) between axon densities at different levels of repair and SFI at 16 weeks was calculated. DEST, distal epineurial sheath tube; SFI, sciatic function index; SD, standard deviation; CI, confidence interval.

Figure 3. Histology at different levels of the repair site.

Note. (a) Proximal to the transection site, there was loss of large myelinated nerve fibers. Small nerve sprouts can be seen. (b) At the level of the epineurial sheath tube, there was loss of myelinated fibers and regenerating small and multiform fibers. Regenerating fibers formed bundles. (c) At the level of the epineurium donor site, changes were more pronounced than at the level of the epineurial sheath tube. Solitary nerve bundles have grown outside of the nerve area. (d) Distally, the changes resemble those seen at the epineurium donor site. Solitary fibers are just outside the nerve area, but most have found their way back inside. Black scale bars indicate 50 μ m.

Table 2. Comparison of Different Repair Techniques in Previous Studies With Distal Epineural Sheath Tube Repair.

Study	Technique	Defect (mm)	Regeneration time (weeks)	Rat strain	SFI	Withdrawal reflex (%)	TA mass (index)	Total axon count/mm ² (distal)
Hare et al ¹³	Transsection, epineural repair	0	16	Lewis	-65	n/a	n/a	n/a
Hall et al ¹²	Lengthened nerve	4	13	S-D	-57	n/a	n/a	n/a
	Autograft	4	13	S-D	-59	n/a	n/a	n/a
	Sham (no injury)	0	13	S-D	-13	n/a	n/a	n/a
Waitayawinyu et al ³⁶	Graft	10	15	S-D	n/a	n/a	0.81	33°867
	PGA conduit	10	15	S-D	n/a	n/a	0.53	18°912
	Type I collagen conduit	10	15	S-D	n/a	n/a	0.79	38°144
Siemionow et al ³¹	Epineural tube + BMSC	20	12	Lewis	n/a	100	n/a	23°000
	Epineural tube (isograft)	20	12	Lewis	n/a	100	n/a	25°000
	Autograft	20	12	Lewis	n/a	100	n/a	30°000
Lubiatowski et al ¹⁸	Autograft + epineural sleeve from nerve stump	10	12	Lewis	-60	100	n/a	22°000
	Autograft + epineural sleeve from graft	10	12	Lewis	-60	100	n/a	25°000
	Graft	10	12	Lewis	-80	100	n/a	29°000
Current study	Distal epineural sheath tube	10	16	S-D	-40	56	0.58	39°785

Note. S-D, Sprague-Dawley rat strain; SFI, sciatic function index; TA, tibialis anterior; PGA, polyglycolic acid; BMSC, bone marrow stromal cells.

Our tube was created from the distal stump, similar to the method described by Chatdokmaiprai et al, who only reported the Schwann cell counts.⁶ We found that after DEST repair, the SFI reached a mean of -36.3 at 16 weeks, which corresponds well with the results of previous studies performed with different conduits.^{12,13,18,31,36} Similarly, there was no neuroma formation, which has been reported in other tubular conduits.^{18,30,31,37}

MacKinnon et al measured the axon density of a healthy rat sciatic nerve to be 11°882/mm² and noted that the density increases distal to the repair site after experimental injury and subsequent repair. The density peaks at 3 months and then slowly decreases to reach preinjury levels by 24 months. Not only the axon density but also the total axon count increases both proximally and distally. This implies that there is regeneration in the retrograde direction as well as sprouting of individual fibers.²³ Our axon density analysis showed a similar pattern (Table 1). The axon density was elevated in all of the repair levels, including the tube level. The distal axon density after the distally elevated epineural sheath tube appears to be similar to that of other tubular repair techniques, as well as nerve grafts (Table 2).

The design of this study did not allow us to compare DEST with other repair techniques. Therefore, a comparison of SFI was possible only at different time points, and the tibialis anterior muscle mass, axon counts, and withdrawal reflexes could be compared only with the uninjured side. Thus, we can only conclude that regeneration of the nerve occurs. Comparative studies are needed to evaluate the

efficacy of this method compared with other methods designed to bridge nerve gaps. We feel that including a sham or a no-repair group would not have provided additional value, because the results of these procedures are well documented in several previous studies.^{13,15,25,29} Moreover, although walking track analysis is a well-standardized and described method, its validity in assessing nerve regeneration has been called into question.²⁹ However, it is currently the only standardized method to assess motor recovery.

In summary, DEST provides a size-matched conduit between the nerve stumps, with no histological donor site morbidity. It is always readily available at the injury site, and therefore no additional incisions are needed. Furthermore, the tissue is of neural origin, which may be biologically beneficial for the healing process. Instead of the 2 coaptations required by other techniques, only 1 is needed, thus decreasing the amount of foreign material and operation time. Theoretically, the DEST technique may cause less scarring and better axonal growth than tubes without turnover, as the outer epineural layer is exposed to less manipulation. Histologically, regeneration occurred through the epineural tube without neuroma formation, and functional recovery was comparable to previously published results. A comparative study is needed to assess the clinical results of this method.

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Ethical Approval

All procedures were carried out under a license provided by the South Finland Regional State Administrative Agency (license number ESAVI/3499/04.10.03/2011). All institutional and national guidelines for the care and use of laboratory animals were followed.

Statement of Human and Animal Rights

This article does not contain any studies with human subjects. All animal procedures were carried out under a national license and according to the institutional and national guidelines for the care and use of laboratory animals.

Statement of Informed Consent

This is an animal study. No informed consent was obtained.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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