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ORIGINAL ARTICLE

Comparison of collagen biomatrix and omentum effectiveness on peripheral nerve regeneration

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Abstract Despite the presence of various nerve *coaptation* materials and techniques, achievement of the functional nerve regeneration is still inadequate. This study was aimed to compare the effectiveness of conduit composed of collagen biomatrix and omentum graft on peripheral nerve regeneration. Thirty-five male Wistar rats were divided into four groups. In the control group, the right sciatic nerve was skeletonized from the sciatic notch till the point of bifurcation. In the primary epineural repair group, the nerve was transected 1 cm proximal to the bifurcation with a sharp pair of micro scissors and then repaired with four epineural sutures. In the collagen biomatrix group, the epineural repaired nerve was wrapped with collagen biomatrix. In the omentum group, the epineural repaired nerve was wrapped with the nonpediculated omentum. Assessment of the nerve regeneration was based on functional (Walking Track Analysis, Electrophysiological Measurements), histological, and morphometric criteria. Light microscopic examination showed that collagen-biomatrix-wrapped specimens have the best regeneration. The electrophysiological study confirmed the recovery of electrical activity in the regenerated axons.

Keywords Collagen biomatrix · Omentum · Peripheral nervous system · Regeneration

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Introduction

The peripheral nervous system is able to regenerate. Following complete nerve transection, several surgical techniques have been proposed to improve the functional outcome of peripheral nerve repair. Vessel grafts [4, 28], denatured muscle fibers [5, 11, 13, 17], fascial or synovial sheets [18, 20] are the natural tubulization options. Polyglycolic acid, polyglactin, polytetrafluoroethylene, polyethylene, and silicone are some examples of synthetic counterparts [22, 32, 34, 36, 37]. The biological fact that the tubular nerve guide made from impermeable material could not supply enough nutrients and oxygen from the outside to the regenerating nerve tissue.

Collagen as a major component of the extracellular matrix is broadly used in various surgical prostheses. Smooth microgeometry and transmurale permeability (100,000 D) allows diffusion processes through collagen matrices. Also, the adhesiveness of collagen for different cell types permits their long-time survival and proliferation

including angiogenesis [2]. Previously, Dubey et al. developed an in vitro assay to study neurite elongation into the magnetically aligned collagen gel rods from dorsal root ganglia (DRG) explants placed onto one end of the rods [10].

The omentum has been used in different areas of surgery for more than 30 years. Omental transposition has been demonstrated to be beneficial in the surgical treatment of neurological injuries [12], as a graft material in treating chronic leg ulcers, necrotizing fasciitis and soft tissue defects, and also used to wrap bowel anastomosis site.

Application of bioresorbable materials derived from animals, including collagen, has been attempted for nerve regeneration [23, 24, 31]. In clinical practice, collagen has been widely used in order to support regeneration for a long time. In contrast, the omentum has been only used in restricted area and there are also few lectures concerning peripheral nerve regeneration in English literature [1, 2]. In this study, we compared effectiveness of collagen and omentum graft on peripheral nerve regeneration in an animal model.

Materials and methods

Surgical procedure

Thirty-five male Wistar rats, weighing between 180 and 220 g were used. The rats were anesthetized with ketamine hydrochloride 100 mg/kg (Ketalar, Eczacıbası, Turkey) and xylazine 5 mg/kg (Rompun, Bayer, Germany). All surgical procedures were performed by the same surgeon using standard microsurgical techniques with the operative microscope (Zeiss-OPMI 9FC; Carl Zeiss, Goettingen, Germany). The right sciatic nerve was used for the surgical procedures. The evaluations were performed in a double-blind way.

Through an oblique gluteal incision, the muscles were split to expose the sciatic nerve from the sciatic notch to its bifurcation of the tibial and peroneal nerves. After this step, the animals were separated into four groups:

The control group (N=5), the right sciatic nerve was skeletonized from the sciatic notch to the point of bifurcation and no additional surgery was performed.

The primary epineural repair group (N=10), the nerve was transected 1 cm proximal to the bifurcation with a sharp pair of micro scissors and then repaired with four epineural sutures (10-0 Ethilon sutures).

The collagen biomatrix group (N=10) in which the collagen biomatrix (TISSUDURA™, Baxter AG, Vienna/Austria) was wrapped and sutured around the epineural repaired nerve (10-0 Ethilon sutures).

The omentum group (N=10) in which the nonpedicu-lated omentum graft was wrapped and sutured around the epineural repaired nerve (10-0 Ethilon sutures; Fig. 1). The omental graft was obtained from the same rat through an abdominal incision at the time of nerve transection and used as a free graft (without blood supply).

All animals were housed individually. Standard laboratory food and water were provided to the rats' ad libitum. Rats were sacrificed at the end of the experimental time (12 weeks) for histological assessment.

Walking track analysis

Motor function was monitored by analysis of the free walking pattern. This method was originally described by De Medinacelli et al. [8, 9]. Walking track analyses were performed preoperatively and at 4th, 8th, and 12th postoperative weeks. The following parameters were measured: the print length, which is the distance from the heel to the toe; the toe spread, which is the distance from the first to the fifth toes; and the intermediary toe spread, which is the distance from the second to the fourth toes. The measurements were performed on both the experimental and unoperated side. The sciatic functional index (SFI) was calculated for each animal by using the formula proposed by Bain et al. [3, 16]. SFI is a measure of dysfunction and is expressed as a percentage. SFI equals to −100% indicates that a complete sciatic nerve lesion is present, whereas SFI ranges from −10% to +10% is considered to reflect normal function.

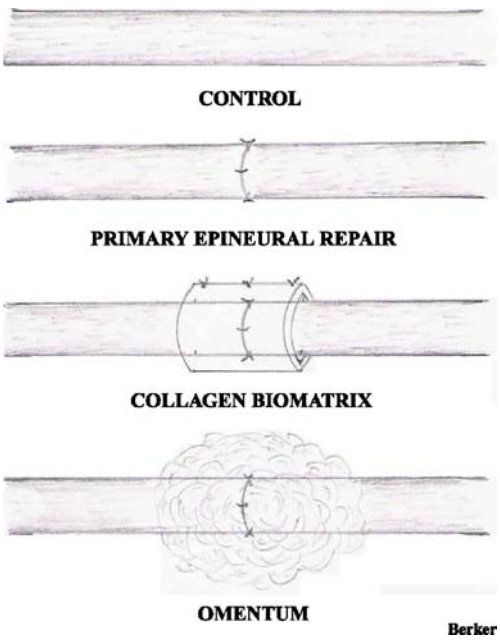

Fig. 1 Schema presenting the plan of the control group and the test groups

Electrophysiological measurements

Nerve conduction studies were performed 12 weeks after the surgical procedure. The electrophysiological procedure was used previously in another study performed by Demirci M et al. [27]. After anesthesia with ketamine hydrochloride 50 mg/kg (Ketalar), the sciatic nerves on both sides were exposed through a gluteal splitting incision. The nerve was stimulated with supramaximal stimuli at the most proximal and the distal points from the coaptation line on the experimental side with a commercial electroneuromyography device (Nihon-Kohden, Japan) and evoked compound muscle action potentials (CMAP) were recorded on the corresponding gastrocnemius muscle using a surface electrode (8-mm diameter disk electrode, NE-132B, two-pin plug, DIN type). The onset latency, negative peak's amplitude, and negative peak's duration of CMAPs were measured on both sides for stimulation.

Muscle mass

Recovery assessment was also indexed as the weight ratio of the gastrocnemius muscle. After sacrificing the animals, gastrocnemius muscle from operated as well as noninjured sides were dissected under an operating microscope and weighed damp, using an electronic balance (Precisa XB 220A, Switzerland). The weights of muscles from the nerve-injured side were divided by those of the normal side to obtain the weight ratio (i.e., operative side, nonoperative side), given in percentages. All counts were made by two independent observers unaware of the analyzed group.

Histological investigation

The rats were sacrificed and 2 cm of the sciatic nerve segment centered on the coaptation line was excised. Samples fixed in 2% glutaraldehyte solution of phosphate-buffered were obtained from the specimen 1 cm proximal and distal to the repair site. The specimens were dehydrated through serial alcohols and embedded in epoxy resin (Araldite CY212). Two-micrometer-thick sections, taken from plastic blocks and stained with methylene blue, were examined and photographed by (Leica Microsystems, Germany). Quantitative morphometric analysis was performed on semi-thin sections by computerized image analysis software "BABSOFT BS200Pro imaging system". Measurements were conducted at a ×100 magnification. Per each cross section, five random fields were chosen and myelinated fibers were counted. Additionally, the axon diameters, the nerve diameters, the myelin diameters and the G ratios (the ratio of the axon diameter to the fiber diameter) were determined.

Statistical analysis

Mann–Whitney U test was used to compare the results. p values less than 0.05 were considered statistically significant. Variables were expressed as mean±standard deviation.

Results

At the end of the 12 week, one rat in the collagen biomatrix and two rats in primary repair died, and 32 rats were evaluated. Functional and histological results were obtained in a blind fashion.

Walking track analysis

SFI values in the both groups were evaluated, and there was statistically significant difference between the test groups and control group ($p<0.05$). Therefore, only test groups were evaluated. When the mean SFI values in the collagen biomatrix, omentum graft, and the primary epineural repair groups were evaluated, no statistically significant differences were detected between the test groups in 4th week, in 8th week, and in the 12th week (Fig. 2).

Electrophysiological measurements

The amplitudes decreased at the experimental sides compared to the normal sides but no statistically significant difference ($p>0.05$) was found between the test groups (Table 1). Actually, the normalized CMAP areas of the experimental sides were compared to the normal sides in all of the surgical groups, and showed no statistically significant difference ($p>0.05$). When the mean nerve velocity values were compared, there was statistically significant difference between the test groups and the control group ($p<0.05$). Similarly, there was statistically significant difference between the test groups ($p<0.05$). That is, the mean nerve velocity of collagen biomatrix group was greater than the primary epineural repair group and the mean nerve velocity of the primary epineural repair group was greater than omentum graft group.

Muscle weight measurement

The ratios of the mean gastrocnemius muscles weight were evaluated (Table 2). There was statistically significant difference between the muscle weight ratios of the test groups and control group ($p<0.05$). The results indicated that in the primary epineural repair group muscle weight ratio is bigger than the group of omentum graft, and the

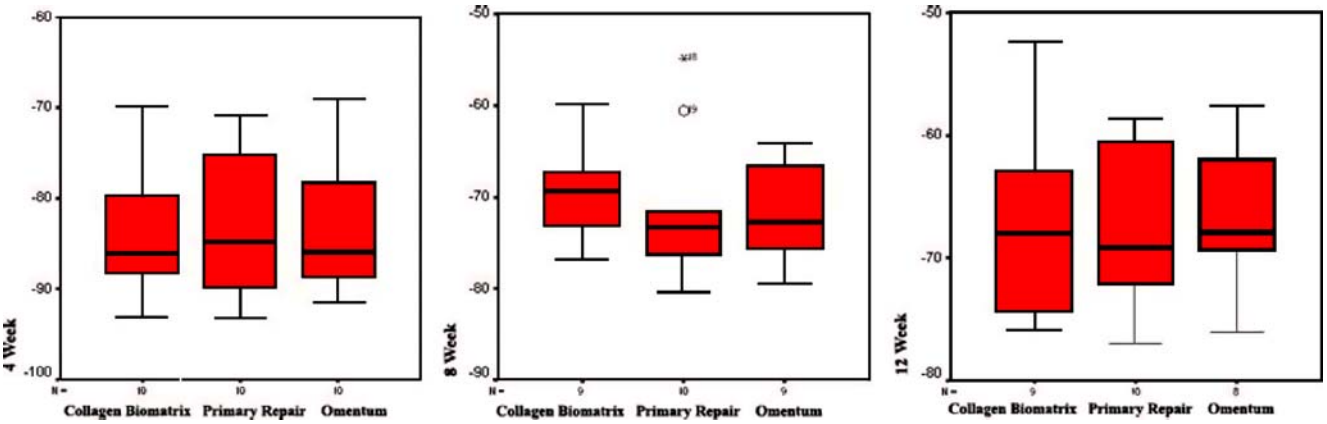

Fig. 2 Box-and-whisker plots of sciatic function index values. Statistically significant difference between the test groups in 4th week, in 8th week, and in 12th week ($p>0.05$) was not shown

group of collagen biomatrix muscle weight ratio was bigger than the group of primary epineural repair ($p<0.05$).

Histological investigation

Sections from the proximal and distal part of the sciatic nerve were examined. There was no statistically significant difference between the test groups and control group regarding the sections taken from the proximal part of the repaired sciatic nerve ($p>0.05$). By contrast, there was a statistically significant difference between the test groups and control group regarding the sections taken from the distal part of the repaired sciatic nerve ($p<0.05$). Therefore, only the distal sections were evaluated.

When the control group was thoroughly assessed on the light microscopy, the perineurium and the endoneurium was normal. The fibers in the fascicules were observed homogeneously distributed (Fig. 3a).

When the primary epineural repaired group was thoroughly assessed on the light microscopy, regenerated fascicules were observed. In one rat, the regeneration was not seen. Regenerated fascicules were thinner than in the control groups. In the sections, irregular and thin perineurium was seen. Expanded connective tissue lain around myelinated axons were irregular. Besides, the increased vascularity lain around the fibers were seen in regular formation. No lymphocytes or plasma cells were detected except for a few giant multinucleated cells containing remnants of surgical material in their cytoplasm. The regenerated small axons were surrounded by thin myelin sheaths. When being compared with the control group, the regenerated sciatic nerve was characterized by numerous small myelinated axons associated with an increase in the number of Schwann cell nuclei. Occasionally, large axons with thick and irregular myelin sheaths were observed in the distal segment. Some degenerated axons were also observed (Fig. 3b).

When the omentum group was thoroughly assessed on the light microscopy, the fascicular formations were observed in eight of ten rats. Therefore, these two rats were not used in the histological assessment. In these two rats, the fascicules were thinner and irregular, and surrounding perineurium was not observed. In the sections of other eight rats, fascicular formations were fine. Large lipid cells were examined around perineurium. The expanded connective tissue lain around myelinated axons were irregular. In addition, too many blood vessels were seen in the connective tissue. No lymphocytes or plasma cells were detected except for a lot of giant multinucleated cells containing remnants of surgical material and degenerating axons in their cytoplasm. A lot of Schwann cells were detected around regenerated small axons which had very thin myelin sheaths. Occasionally, large axons with a thick myelin sheath but irregular symmetry were observed in the distal segment (Fig. 3c).

Table 1 The normalized CMAP amplitude, the normalized CMAP area values, and the nerve conduction velocity of test groups and control group; *CMAP* compound muscle action potential

	Collagen Biomatrix	Primary epineural repair	Omentum	Control
Normalized CMAP amplitude	85.88%±19.99	84.42%±17.90	71.47%±33.72	104.24%±8.95
Normalized CMAP area values	102.68%±42.06	105.62%±49.39	79.18%±41.01	102.28%±10.89
Nerve conduction velocity (cm/sn)	42.84±10.48	39.95±9.25	32.94±13.03	63.26±4.47

Table 2 The mean gastrocnemius muscles weight ratios of test groups and control group

	Collagen biomatrix	Primary epineural repair	Omentum	Control
Weight ratio	0.65±0.14	0.59±0.13	0.50±0.06	0.92±0.17

When the collagen biomatrix group was thoroughly assessed with the light microscopy, the completed fascicular formations were observed. Nevertheless, the fascicules were thinner than the control legs fascicules. The connective tissue lain around myelinated axon was seen in an irregular formation, but its density was fewer than primary epineural repaired group. The amount of the collagen fibers was similar to the control group. The lymphocytes, the plasma cells, and the giant multinucleated cells containing remnants of surgical material in their cytoplasm were detected in four rats. The regenerated axons in different diameter were surrounded by myelin sheaths in different thickness. When we compared with the control nerve, the regenerated sciatic nerve was characterized by numerous small myelinated axons associated with an increase in the number of Schwann cell nuclei. Occasionally, large axons with a thick myelin sheath but irregular symmetry were observed in the distal segment (Fig. 3d).

The test groups and control group were compared for the average number of myelinated fibers, the thickness of myelins, the diameter of axons, the diameter of nerves and the G ratios (Table 3). When the average number of myelinated fibers, the thickness of myelins, the diameter of axons, the diameter of nerves, and the G ratios were matched, there was statistically significant difference between the test groups and control group ($p<0.05$). There was no statistically significant difference between the average number of myelinated fibers, the diameter of axons between the test groups ($p>0.05$). In addition, there was statistically significant difference between thickness of myelins, the diameter of nerves, and the G ratios between the test groups ($p<0.05$). Comparing the thickness of myelins, the diameter of nerves, and the G ratios of the test groups showed that collagen biomatrix group was greater than the primary epineural repair group and the primary epineural repair group was greater than omentum graft group.

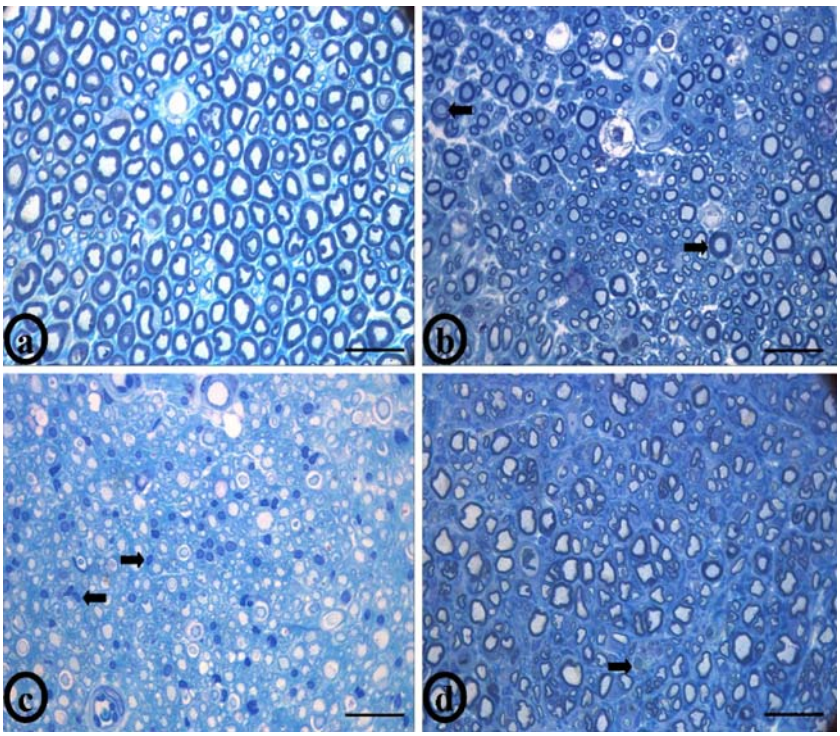

Fig. 3 **a** Control groups transverse semi-thin sections demonstrate homogeneously distributed fibers. Methylene blue, original magnification ×100. **b** Primary epineural repaired groups' transverse semi-thin sections demonstrate thin regenerated fascicules and some degenerated axons. *Arrow* Degenerated axon. Methylene blue, original magnification ×100. **c** Omentum groups transverse semi-thin sections demonstrate Schwann cells around thin myelinated small axons. *Arrow* Schwann cell. Methylene blue, original magnification ×100. **d** Collagen biomatrix groups transverse semi-thin sections demonstrate myelinated axons in different diameter and the giant multinucleated cells containing remnants of surgical material in their cytoplasm. *Arrow* Giant cell. Methylene blue. Original magnification ×100. *Scale bar*=20 μm

Table 3 Morphometrical parameters of the regenerated nerve at distal levels of the graft in the test groups, and control group; *D-Nerve* diameter of the nerve, *D-Myelin* diameter of the myelin, *D-Axon* diameter of the axon, *G-Ratio* the ratio of the axon diameter to the fiber diameter

	Collagen biomatrix	Primary epineural repair	Omentum	Control
D-Nerve	3.42±0.99 μm	3.19±1.35 μm	2.78±0.85 μm	7.14±2.75 μm
D-Myelin	1.20±0.21 μm	0.88±0.16 μm	0.65±0.19 μm	3.04±1.28 μm
D-Axon	2.22±0.78 μm	2.31±1.19 μm	2.13±0.66 μm	4.09±1.64 μm
G-Ratio	0.72±0.09	0.65±0.10	0.57±0.08	0.59±0.04
The average number of myelinated fibers	11812±1179	12378±955	12097±1381	8486±342

Discussion

Many different technical improvements have been aimed to achieve better coaptation in peripheral nerve repairs, such as CO2 laser welding, ring coupling, fibrin glue, and freeze-trimming, but none of them proved to be superior over conventional epineural suture technique [5, 15, 25, 30, 33].

Collagen, which is used in peripheral nerve repair as a bridging source has the uniqueness of less antigenicity and easy resorption in the body [2]. The formation of a properly aligned extracellular matrix (ECM) scaffold is essential to enhance Schwann cell proliferation in a tubular prosthesis, over which blood vessels and other cell types migrate and form primordial assembly for the formation of a new nerve structure [35]. Schwann cells have great importance in organizing the structure of the peripheral nerve because they produce a basement membrane containing ECM proteins that support robust axonal growth and form the endoneurial tubes through which regenerating axons grow. Therefore, a major rate-limiting step in the induction of nerve repair across long lesion gap is the proliferation, and migration of Schwann cells between the nerve stumps [19].

In our study, the collagen biomatrix group was showed the best healing. Collagen biomatrix group was showed greater ratios of the mean gastrocnemius muscles weight. Also, collagen biomatrix group had improved histological architecture at the repair site (less epineural and perineural proliferation, less intra neural scar tissue, and better alignment) compared with omentum group and primary epineural repair group. Comparison of the thickness of myelin between the test groups showed that collagen biomatrix group had greater scores. Thus, nerve velocity values of the collagen biomatrix group were greater. Sciatic nerves favorable healing may be related with collagen biomatrix's minimizing the foreign-body reaction and providing a properly aligned matrix scaffold which caused regular Schwann cell proliferation and less blocked axons. Ahmed et al. previously reported that collagen-based conduits provide excellent orientation and anchorage effects to the regenerating nerves [2]. Our findings are compatible with the study of Ahmet et al. The average number of myelinated fibers of the collagen biomatrix group, the omentum group, and the primary epineural repair group seems greater than the control group. Previously, Mackinnon SE et al. have reported an increase of the number of axons at the distal end of the nerve repair [21]. Results of our study indicate that multiple aberrant axons were sprouting from one proximal nerve fiber and that the regenerated nerve fibers had not matured completely in the regenerated segment by a 12-week period. Thus, average number of myelinated fibers may be counted too many.

The omentum has been extensively used in neurosurgery since the beginning of the 1970s. For many years, however, it has been thought that the increase in blood flow was the only factor involved on the effects of the transplant [6, 7, 14]. Nonetheless, the discovery of several substances in the omentum such as AFGF, bFGF, VEGF, CGRP, GABA, 5-HT, norepinephrine, beta-endorphin, IL-2, IL-6, IL-8, IL-1, met-enkephalin, and VIP, as well as the evidence for their control by growth factors point towards another possible explanation: the omentum is a dynamic organ, capable of being adapted to the environment of the transplant. There were only few reports about omentum and peripheral nerve regeneration in the literature; yet, all reports have been imposed that omentum activates the nerve regeneration [1]. Due to regeneration-activating character of the omentum we decided to use omentum graft. However, the result of the omentum group is the worst in our study. Worse alignment of the omentum group might also be the result of poorer quality nourishing of the omentum cells. Thus, it could promote extraneural scarring, which is mainly caused by collagen production by fibroblasts and Schwann cells around the nerve. In fact, the omentum's residual fat tissue may decrease vascularization from surrounding tissues. The importance of the vascularization from surrounding tissue for regeneration was reported by Odaka et al. Odaka et al. have also remembered that tubulization may interfere with vascular access to the regenerating portion of the nerve. Our results have been suggested by Odaka's findings [26]. In addition, Salonen V et al. reported that layer of the regenerated axons would be thick if the axonal regeneration do not reach the distal stump [29]. Our results are compatible with Salonen et al. Another reason of the bad results may be the

prevention of axonal regeneration by nonpediculated omentum graft.

Our results about the omentum were contradictory to the findings in the literature. In the present study, the omentum group could not show effective peripheral nerve regeneration as the collagen biomatrix group showed. This study has also suggested that collagen-derived products could affect peripheral nerve regeneration. Collagen biomatrix is a new collagen-derived agent which has been used in clinical practice as a dura mater graft. It could be used safely and effectively to promote peripheral nerve regeneration.

Conclusion

Biological and mechanical structure of the graft material is an important factor in order to achieve an effective nerve regeneration. Our study demonstrates that a conduit constructed with collagen biomatrix will support nerve regeneration. In addition, it was examined that omentum graft could not effect regeneration positively.

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Comments

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The authors have provided a clear and concise experimental study that assessed peripheral nerve regeneration in Wistar rats. The authors transected the sciatic nerve and compared the effectiveness of a conduit composed of a collagen biomatrix and omentum graft on peripheral nerve regeneration. They made a functional assessment of the regeneration with the Walking Track Analysis and electrophysiological measurements. The authors have supported their findings with a histological assessment and electron microscopy.

A comparison of the thickness of myelin between the test groups showed that the collagen biomatrix group had greater scores, and the nerve velocity values of this group were also greater. The authors noted that the collagen biomatrix minimizes the foreign-body reaction and provides a properly aligned matrix scaffold that allows regular Schwann cell proliferation and blocks fewer axons.

Interesting findings of the study are the results of the Omentum Group. The results in this group were even worse than those of patients undergoing primary epineural repair. These findings are not in accordance with the regeneration-activating character of the omentum. The authors associate this worse alignment with a poorer quality of nourishment of the omentum cells. Another interesting finding is the average number of myelinated fibers. In all groups, this number is higher than in the control group. The authors believe this result is from multiple aberrant axonal sprouting from the proximal nerve fiber and that the regenerated nerve fibers had not matured completely in the regenerated segment by a 12-week period.

The results of this study have implications for neurosurgeons who perform peripheral nerve surgery. The take-home message is that the biological and mechanical structure of the graft material is very important in achieving an effective nerve regeneration and the collagen biomatrix may really support nerve regeneration. We may have further information to contribute. Dubey et al. (1) noted that, in repairing transected nerves, a solution could be to find bioresorbable collagen nerve guides with magnetically aligned collagen gel implanted in the surgical gaps. This procedure might stimulate the correct orientation and fasten both the speed and functional success of the regeneration.

Reference

1. Dubey N, Letourneau PC, Tranquillo RT. Guided neurite elongation and Schwann cell invasion into magnetically aligned collagen in simulated peripheral nerve regeneration. Exp Neurol. 1999 Aug;158(2):338-50.