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ARTICLE

Use of acellular dermal matrix in peripheral nerve reconstruction: an experimental study on rat sciatic nerve defect

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ABSTRACT

Background: In patients with nerve tissue defects, the use of autologous nerve grafts is the standard method of treatment. Alternatives to autologous, nerve grafts have attracted the attention of reconstructive surgeons. In this study, the results of nerve repairs using acellular dermal matrix (ADM) in an experimental rat sciatic nerve defect model are presented.

Methods: Thirty-six Sprague-Dawley rats were randomized into 5 groups: Group 1: control group, Group 2: negative control group ($n = 6$), Group 3: autologous nerve graft group ($n = 10$), Group 4: donor site entubulated with ADM group ($n = 10$); and Group 5: nerve graft entubulated with ADM group ($n = 10$). The animals in each group were evaluated for electrophysiologic functions, gastrocnemius muscle weight and histomorphology on the 3rd and 6th month.

Results: The compound muscle action potential was observed to be distinctly lower in Groups 3, 4 and 5 in comparison to the control group. In Group 4, the gastrocnemius ratio (GCR) values on the 6th month were statistically significantly lower than the GCR values in Group 3 and Group 5, The histological scores and myelinated axonal counts in Group 5 were statistically significantly higher than the values in Group 3 and Group 4.

Conclusion: The results of this study showed that wrapping ADM around nerve grafts resulted in better outcomes with respect to nerve healing.

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KEYWORDS
Acellular dermal matrix; peripheral nerve; reconstruction

Introduction

Peripheral nerve injuries are among the most common injuries [1]. Even when they are repaired under optimal conditions, sensory and motor functions may not completely recover.

For an ideal repair, intact peripheral nerve endings should be connected without tension and the repair should be conducted as soon as possible after the injury [2,3]. However, this may not be possible in cases with a loss in nerve substance. In these cases, autologous nerve grafts, which are currently accepted as the gold standard in clinical practice, may be used [4]. In order to avoid the problems related to donor site morbidity, other autologous tissues such as vein grafts or muscle tissues have also been used in repairs [4–6]. Repairs involving the use of cadaver nerve allografts and terminal-lateral nerve anastomoses are also reported in the literature [7].

As a result of developments in tissue engineering, various synthetic materials have been experimented to bridge nerve defects [8]. However, none of these have fulfilled the expectations.

Brunelli et al. [9] defined the certain characteristics that an ideal nerve bridge should possess: (1) harmony with the surrounding tissue; (2) easy and convenient preparation to fit the size of the defect; (3) provision of a suitable environment for axon regeneration; (4) prevention of the tissue migration from surrounding tissues to the regeneration area.

The acellular dermal matrix (ADM) is a material with widespread clinical applications in various areas of plastic surgery such as breast reconstruction and repair of abdominal Wall defects [10–12].

The aim of this study was to investigate the effects of ADM in nerve repairs, used either as a nerve conduit or being wrapped around nerve grafts, in an experimental sciatic nerve defect model in rats.

Methods

A total of 36 young male Sprague-Dawley rats weighing between 200 and 300 g were used. Before initiation of the study, all procedures were approved by the Committee on the Ethics of Animal Experiments of Bagcilar Training and Research Hospital. The rats were separated into 5 groups. In Group 1 (Control Group), the unoperated legs on the contralateral side were used as controls. In Group 2 (Negative Control Group) ($n = 10$), a 1-cm-wide defect was created in the right sciatic nerve and no repair was performed. In Group 3 (Nerve Autograft Group) ($n = 10$), a 1-cm-wide segment of the right sciatic nerve was excised, reversed, placed into the defect as a graft and the nerve was repaired. In Group 4 ($n = 10$), a 1-cm-long segment of the right sciatic nerve was removed and ADM was formed into a tube with microsutures and used as a conduit between the proximal and distal segments. In

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Group 5 ($n = 10$), a 1-cm-wide segment of the right sciatic nerve was excised. The excised nerve segment was reversed and coapted to the defect. Then ADM was wrapped as a cuff around the nerve by using sutures, beginning 5 mm proximal to the first coaptation area and ending 5 mm distal to the second.

The rats were anesthetized with intramuscular xylazine (10 mg/kg) and intraperitoneal ketamine (50 mg/kg). After the surgical area was shaved and disinfected, the rats were placed in prone position and a longitudinal gluteal skin incision parallel to the femur was made. After hemostasis, the muscles were dissected and the sciatic nerve was exposed from the sciatic notch proximally, and to the bifurcation point distally. Under the microscope, a 1-cm part of the nerve was marked with calipers and then excised. The nerves were repaired epineurally with three 9/0 polyamide sutures. An approximately $2 \times 1.2 \times 0.1$ cm piece of ADM (FlexHDR, MTF, NJ/USA) (Human biologic dermal graft) was prepared. It was transformed into a conduit with 8/0 polyamide single sutures placed at a distance of 5 mm from the proximal and distal segments, which were fixed also to the nerve by passing through the perineurium (Figure 1). In each group, the muscles and skin were repaired as separate layers after nerve procedures. After surgery, the rats were followed up in appropriate conditions regarding their daily care routine.

The rats were evaluated with electrophysiologic methods, gastrocnemius muscle weight measurements and histological evaluation. In all groups, one half of the rats were evaluated on the 3rd month, and the other half on the 6th month.

Electrophysiologic records

The electrophysiological recording was performed on the 3rd and 6th months. All animals were anesthetized and the sciatic nerves were exposed. A hook-tipped monopolar needle made of stainless steel was placed directly on the sciatic nerve bundle as the cathode, 5 mm proximal to the transected nerve, while another stainless steel monopolar needle placed 3 mm proximally to the cathode served as the anode.

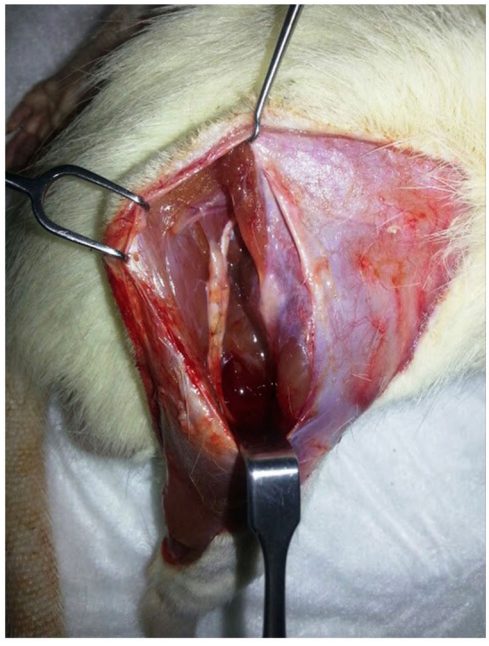

Figure 1. Preoperatively view of a repair with nerve graft wrapped with ADM (Group 5).

The earthing electrode was placed on the side of the stimulus on the femur and the stimulus was applied. The amplitude, latency and the neural transmission velocities or the stimulated muscle action potentials were digitally recorded through the needle electrode placed at the distal end of the gastrocnemius muscle. The recordings were made with the help of the BIOPAC MP 150 Acquisition System. The procedure was applied on both legs.

Gastrocnemius muscle weight ratios

After electrophysiologic recording, a longitudinal incision parallel to the fibers of the gastrocnemius muscle and the Achilles tendon was made. The gastrocnemius muscle was laid open through the dissections at both ends of the muscle in the femoral region, and along the Achilles tendon near the heel at the distal aspect. The muscle was excised through the incisions made at the origin and insertion points. Since the soleus muscle would not be included in the weight measurement, it was also resected. The excised gastrocnemius muscle was weighed using a precision balance and the result was compared to the muscle mass in the intact leg, which served as the control group. The gastrocnemius weight ratios were calculated according to the following formula:

$$GCR = (IMM/CMM) \times 100$$

(GCR: gastrocnemius muscle ratio; IMM: investigational group muscle mass; CMM: control group muscle mass.)

Histological evaluation

The sciatic nerve segments were embedded in 10% formaldehyde and the histological evaluation was performed through hematoxylin-eosin staining. Additional immunohistochemical assessments were made using CD 31 which demonstrates capillary reduction due to degeneration and increase in the capillaries through regeneration and S100 which indicates the presence of nerve strands. Tissue sections were examined under light microscopy ($\times$400) and the number of the myelinated axons counted within random high-power fields using a Nikon Optiphot 2 light microscope incorporating a square graticule in the eyepiece (eyepiece $\times$10, objective $\times$40, a total side length of 0.25 mm^2).

The obtained preparations were also semiquantitatively scored based on normal sciatic nerve morphology [13]. For semiquantitative analyses, the cross-section of nerves are graded giving scores of 1–10. The score 10 refers to a normal sciatic nerve. The criteria for this assessment were: nerve cell frequency decrease, loss of homogeneity in the thickness of perineurium, increase in distance between endonerurium and perineurium, decrease in the thickness of myelin, decrease in the diameter of axons and increase in endoneural edema

Statical analysis

The results of electrophysilogic assessments were defined as mean ± standard deviation. The readings from the groups were compared using Student's T-test and the variance analysis. The statistical analyses were performed using the PRISM (Statistical Software Package-Prism Version 4.03@ 1992-2005; Graph Pad Software Inc.) software package. The statistical analyses of the results obtained from the GCR and the histological evaluation were performed using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) software package.

Data were evaluated using descriptive statistical methods (mean, standard deviation, median, interquartile range) as well as the Kruskal Wallis test for inter-group comparisons, Dunn's multiple comparison test for subgroup analyses, and the Mann–Whitney U test for the comparison of paired groups. The threshold level for statistical significance was accepted as $p < 0.05$.

Results

Electrophysiological evaluation

The compound muscle action potential and distal latency measurements were obtained from the electrophysiologic records. No significant difference was observed between Groups 4 and 5 and the control group in terms of the distal latencies ($p > 00.5$). However, the distal latency values in Group 3 were found to be significantly higher ($p < 0.05$) (Figures 2 and 3).

The compound muscle action potential was observed to be distinctly lower in Groups 3, 4 and 5 in comparison to the control group ($p < 0.05$), although the difference was insignificant. In Groups 4 and 5, the measurements performed in the 6th month revealed no distinct amplitude increase in comparison to the 3rd month. Also, no significant compound muscle action potential was observed in the negative control group (Figures 4 and 5).

Muscle weight ratios

On the 3rd month, the GCR values were observed as 15.3% in Group 2, 51.9% in Group 3, 26.3% in Group 4, and 61.3% in Group 5. On the 6th month, the GCR values were 6.96% in Group 2, 57.5% in Group 3, 38.3% in Group 4 and 76% in Group 5 (Table 1).

In Groups 3, 4 and 5, the GCR values on the 6th month were statistically significantly higher than the values on the 3rd month ($p = 0.043$, 0.042, 0.043).

In Groups 2, 3, 4 and 5, a statistically significant difference was observed between the GCR values on the 3rd month ($p = 0.0001$). The GCR values on the 3rd month in Group 2 were statistically significantly lower than the GCR values in Groups 3, 4 and 5 ($p = 0.005, 0.010.001$). The 3rd month GCR values in Group 4 were also statistically significantly lower than the 3rd month GCR values in Group 3 and Group 5 ($p = 0.009$ vs. $p = 0.002$). The 3rd month GCR values in Group 3 were statistically significantly lower than the 3rd month GCR values in Group 5 ($p = 0.001$) (Table 2).

A statistically significant difference was observed between the 6th month GCR values in Groups 2, 3, 4 and 5 ($p = 0.0001$). In Group 2, the 6th month GCR values were statistically significantly lower than the 6th month GCR values in Groups 3, 4 and 5 ($p = 0.005$, 0.001). In Group 4, the GCR values in the 6th month were statistically significantly lower than the 6th month GCR

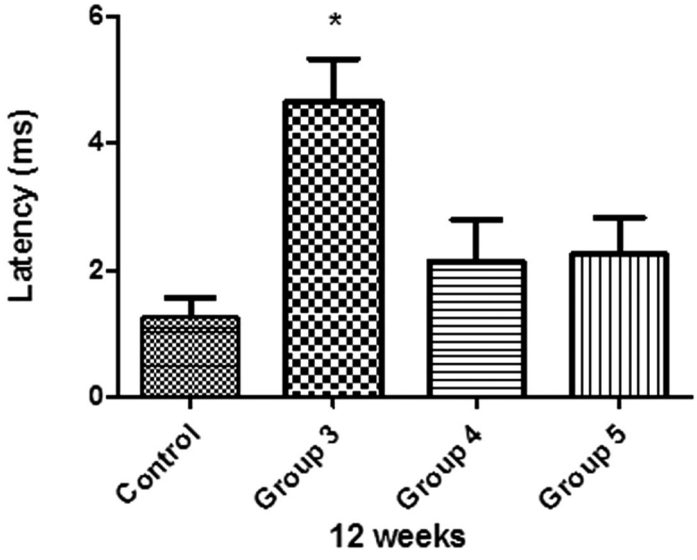

Figure 2. Latency of the groups at 12th week.

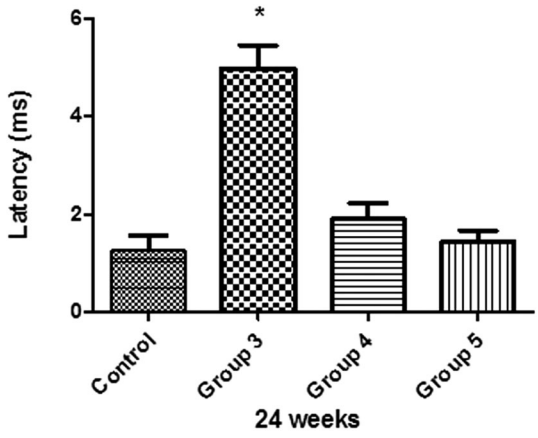

Figure 3. Latency of the groups at 24th week. The distal latency values in the autograft group. (Group 3) were found to be significantly higher.

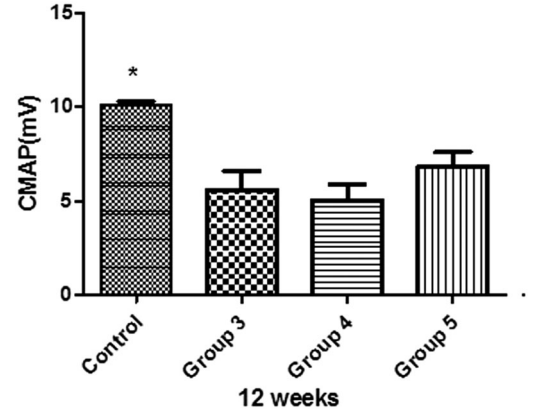

Figure 4. Compound muscle action potential of the groups at 12th week.

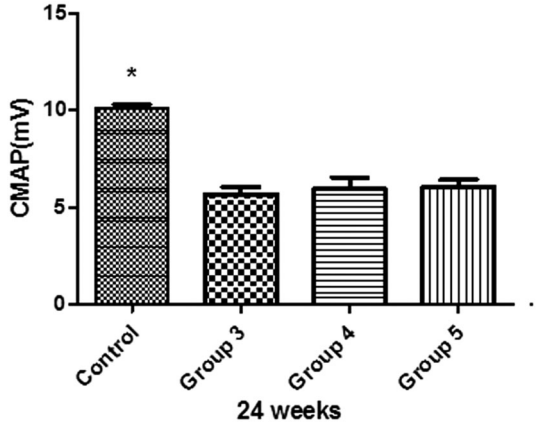

Figure 5. Compound muscle action potential of the groups at 24th week. The compound muscle action potential was observed to be distinctly lower in Groups 3, 4 and 5 in comparison to the control group.

Table 1. Gastrocnemius muscle weight ratios (GCR values).

	Rat nr.	3rd month (%)	Rat nr.	6th month (%)
Group 2	1	13.3	4	6
	2	14.3	5	4.7
	3	18.4	6	10.2
Group 3	1	50.4	6	57.9
	2	52.9	7	55.1
	3	52.2	8	57.6
	4	51.1	9	59
	5	48.9	10	58
Group 4	1	33.5	6	46.1
	2	28.6	7	35
	3	21.7	8	40
	4	21.8	9	37.5
	5	26	10	36.9
Group 5	1	56.4	6	61.7
	2	59.4	7	70.8
	3	65	8	85
	4	64	9	76.5
	5	62.1	10	75.7

Table 2. Statistical assessment of the GCR.

		3rd month	6th month	*p*
Group 2	Mean ± SD	15.33 ± 2.7	6.97 ± 2.88	0.109
	Median (IQR)	14.3 (13.3–18.4)	6 (4.7–10.2)	
Group 3	Mean ± SD	51.1 ± 1.56	57.52 ± 1.45	0.043
	Median (IQR)	51.1 (49.65–52.55)	57.9 (56.35–58.5)	
Group 4	Mean ± SD	26.32 ± 4.97	39.1 ± 4.3	0.042
	Median (IQR)	26 (21.75–31.05)	37.5 (35.95–43.05)	
Group 5	Mean ± SD	61.38 ± 3.51	73.94 ± 8.54	0.043
	Median (IQR)	62.1 (57.9–64.5)	75.7 (66.25–80.75)	
	p	0.001	0.001	

Table 3. Inter-group comparison of the GCR.

	3rd month	6th month
Group 2/Group 3	0.005	0.001
Group 2/Group 4	0.01	0.005
Group 2/Group 5	0.001	0.001
Group 3/Group 4	0.009	0.002
Group 3/Group 5	0.002	0.009
Group 4/Group 5	0.001	0.004

values in Group 3 and Group 5 ($p = 0.002$, $p = 0.004$). In Group 3, the GCR values on the 6th month were significantly lower than the 6th month GCR values in Group 5 ($p = 0.001$). In Group 2, no significant change was observed between the GCR scores on the 3rd and 6th months ($p = 0.109$) (Table 3).

Histological evaluation

In the histopathological examinations performed in the 3rd and 6th months of the study, the changes in the groups were revealed in detail (Figures 6 and 7).

In Groups 3, 4, and 5, the myelinated axon counts on the 6th month were observed to be significantly higher than the counts in the 3rd month ($p < 0.001$). Additionally, when the measurements on the 6th month were compared with those in Group 3, Group 5 had a significant increase in the number of myelinated axons (Figure 8). The histological evaluation of the extracted nerve samples performed using hematoxylin-eosin, S100 and CD31 were semiquantitatively compared.

In Groups 3, 4 and 5, the histological evaluation scores on the 6th month were observed to be statistically significantly higher than the values on the 3rd month ($p = 0.023$, 0.034, 0.038). A statistically significant difference was observed between the histological evaluation scores of Groups 3, 4 and 5 on the 3rd month

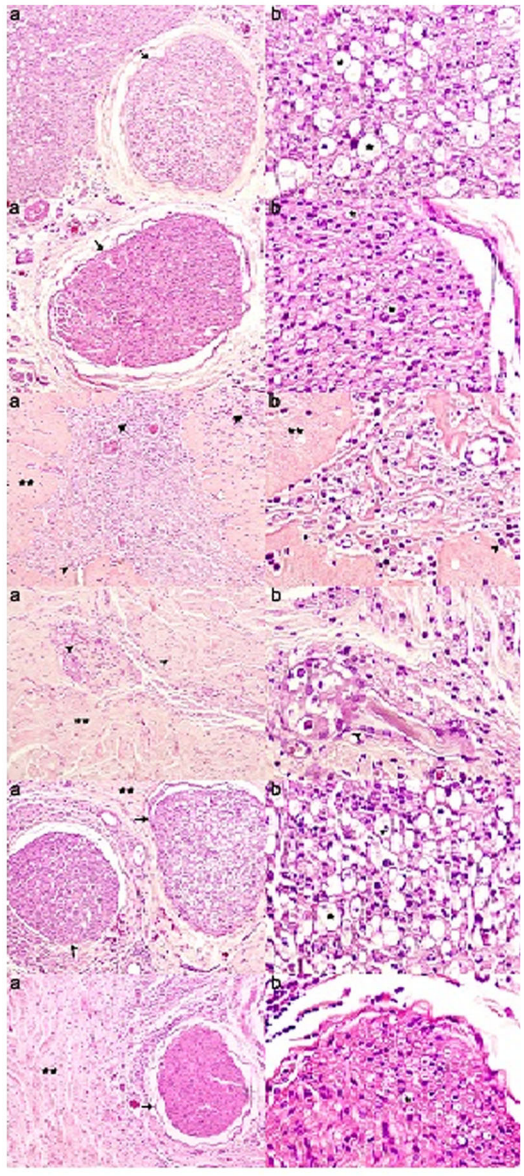

Figure 6. Representative light microphotographs showing the morphology of sciatic nerve tissue in different groups by hematoxylin-eosin. (a) 100× magnification and (b) 400× magnification (*arrow:* perinerium, *arrow head:* inflammatory cells, *double stars:* Alloderm, *star:* vacuolization).

($p = 0.004$). In Group 5, the histological scores on the 3rd month were statistically significantly higher than the values in Group 3 and Group 4 on the 3rd month ($p = 0.004$). On the other hand, no statistically significant difference was observed between the histological scores of Groups 3 and 4 on the 3rd month ($p = 0.531$) (Table 4).

Also, the difference between the histological scores in Groups 3, 4 and 5 on the 6th month were significant ($p = 0.001$). In Group 5, the histological scores on the 6th month were significantly higher than the values in Group 3 and Group 4 on the 6th month ($p = 0.005$, 0.003); while the histological scores in Group 4 on the 6th month were statistically significantly lower than the histological scores in Group 3 on the 6th month ($p = 0.006$) (Table 5).

Discussion

The repair of peripheral nerve defects is a frequently studied field because it is associated with the reduction of occupational losses

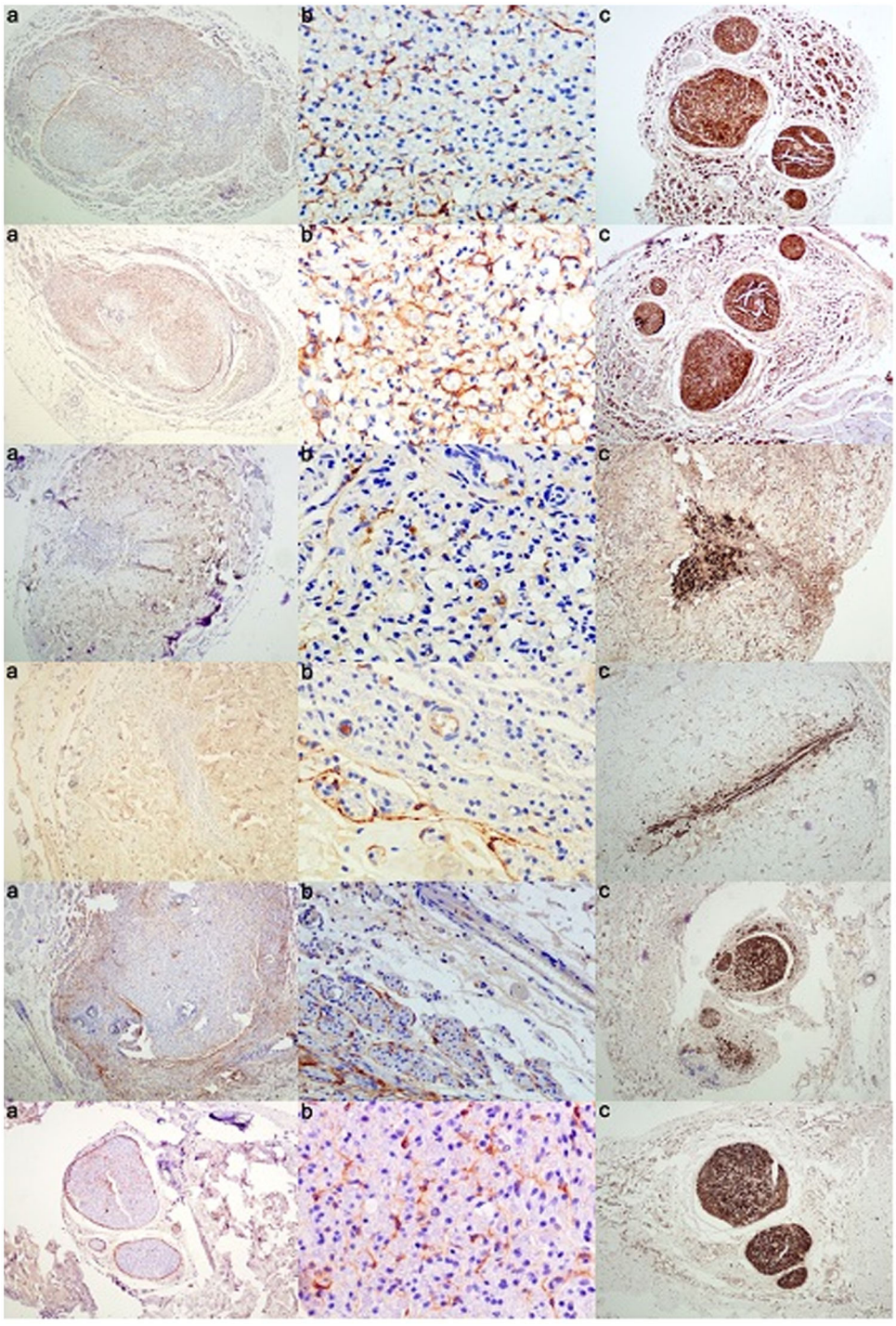

Figure 7. Representative light microphotographs showing the morphology of sciatic nerve tissue in different groups by immunohistochemical staining (a, b) CD31 immunoreactivity in 100× magnification and 400× magnification (c) S100 immunoreactivity in 100× magnification.

especially in the younger population and the prevention of life-long motor/sensory defects [1].

Although autologous nerve grafts are often accepted as the gold standard in bridging nerve defects due to their practical aspects and proven success, the associated donor area morbidity is a significant disadvantage [2–4]. In cases where autologous nerve grafts are not preferred, terminal-lateral nerve anastomoses are another choice. However with this method, the nerve is deprived of its anatomic source [8]. Another alternative for autologous nerve grafts is a nerve allograft of cadaver origin [7]. The greatest disadvantage of cadaver nerve allografts, which may be used in various sizes and widths, is that they are biomaterials foreign to the body.

Although nerve prefabrication has been shown to be a promising alternative in experimental studies; it is a complicated two-step technique [14]. In our study although ADM constituted a basis for new nerve regeneration when used as a nerve conduit, a successful functional recovery equal to nerve grafting could not be achieved based on GCR rates. Therefore we believe that such a use will not be a total alternative to nerve grafts.

Vein grafts from autologous tissues other than the nerves are already used alone or with muscle tissue placed inside. The

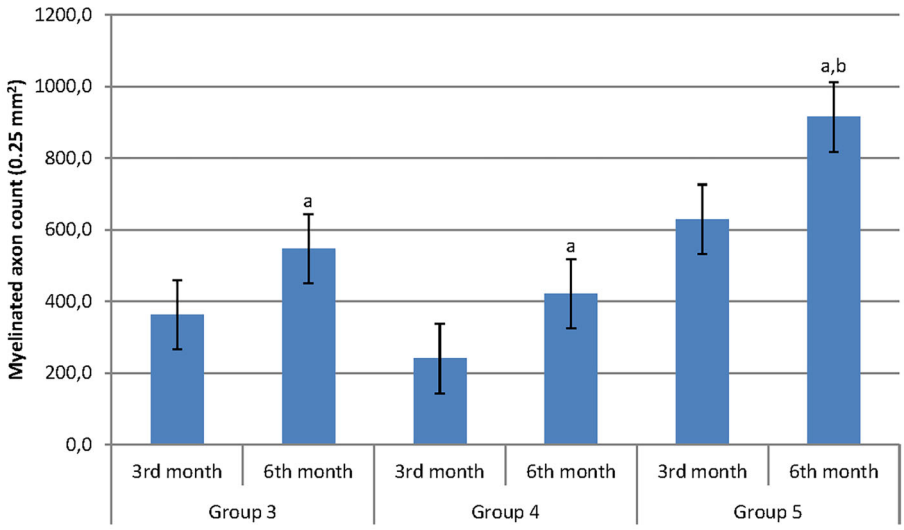

Figure 8. Myelinated axon numbers of groups (a: $p < 0.001$ when compared to their 3rd month groups; b: $p < 0.0001$ when compared to Group 3—6th month).

Table 4. Statical analysis: semiquantitative scorings of histological properties.

		3rd month	6th month	p
Group 3	Mean ± SD	3.33 ± 0.52	5.67 ± 0.52	0.023
	Median (IQR)	3 (3–4)	6 (5–6)	
Group 4	Mean ± SD	2.83 ± 0.75	4.33 ± 0.52	0.034
	Median (IQR)	3 (2–3.25)	4 (4–5)	
Group 5	Mean ± SD	6.17 ± 0.75	8.33 ± 1.75	0.038
	Median (IQR)	6 (5.75–7)	9 (7.25–9.25)	
	p	0.004	0.001	

Table 5. The statistical inter-group comparison of the semi-quantitative histological scoring.

	3rd month	6th month
Group 3/Group 4	0.531	0.006
Group 3/Group 5	0.004	0.005
Group 4/Group 5	0.004	0.003

modified version with muscle tissue placed inside has been proposed as an alternative [2,5,6]. However, since it is a complex and risky procedure with technical difficulties involved in the preparation, it is not reliable enough for routine use [15].

The use of certain bridging materials for the purpose of axon regeneration between nerve endings has been a promising alternative in complex nerve injuries. These tubular structures may be classified according to their characteristics as absorbable/non-absorbable, synthetic or natural., Silicone is the most commonly used material in experimental and clinical studies because it is flexible and does not react intensively with the surrounding tissues. However, it has also been observed to be prone to requirement for a secondary surgery due to its association with fibrosis, nerve compression and the need to be removed as a foreign material in the long term [16–18].

Since natural biomaterials such as collagen, hyaluronic acid and gelatine used for nerve bridging during repairs are usually of animal origin, they carry the risk of viral disease transmission or immunological reactions despite of the use of advanced purification methods [19–22]. Synthetic biomaterials are free of these risks. Absorbable materials such as polyglycolic acid, polylactic glycolic acid or polycaprolactones have been used for axon regeneration in experimental studies. It has been stated that the acidic degradation of these materials does not have an impact on axon regeneration. These absorbable materials have limited clinical uses due to their high costs. They are known to dissolve totally within 16 weeks [23–25]. According to the results we obtained at the 24th week of our study, we believe that the lifespan of these materials until total degradation is not long enough to maintain adequate stability for a healthy axon regeneration.

In previous studies on nerve bridges that have used similar experimental models, the evaluations were usually made on the 3rd month. In our study, we chose to evaluate the regeneration in the rats both on the 3rd and 6th months. Our results showed that when the results on the 6th month were compared with those on the 3rd month, there was a statistically significant difference between Groups 3, 4 and 5 in all the assessment parameters except for electrophysiologic assessments. In addition, according to electrophysiologic findings, the latency was longer in the group with nerve graft, compared to Groups 4 and 5. It is possible that the use of ADM could have affected conductance.

ADM is a material used in breast reconstructions, revision mammoplasty and for repairs in various anatomic areas such as the abdominal wall, thorax and the mouth. The versatility and success of this biological material can be associated with the good structural support that it provides for tissue regeneration in repair areas, and the rapid revascularization it allows [10–12,26–28]. In group 4 where the ADM was used as a nerve conduit, when GCR rates and histologic evaluations are considered, we believe that ADM will not be able to replace nerve grafts.

Although ADM is a widely used material, we did not across any studies where it was used in nerve repairs. In this study in addition to the use of ADM as a bridge in nerve defect repairs, its use through entubulation around nerve grafts was also evaluated. Similar electrophysiologic findings were observed with autologous nerve grafts in terms of regular axon regeneration in the area with the nerve defect. We believe that it fulfils the criteria for the ideal nerve bridge described by Brunelli et al. (1: Harmony with the surrounding tissue; 2: easy and convenient preparation to fit the size of the defect; 3: provision of a suitable environment for axon regeneration; 4: prevention of the tissue migration from surrounding tissues to the regeneration area) very satisfactorily. We

can also underline the long-term structural support provided by the ADM, which should also be added to these criteria. ADM can be easily shaped, prepared easily in all sizes according to the defect size. Its structure prevents collapse, therefore facilitating nerve regeneration.

Conclusions

In this study, we demonstrated concretely that ADM cannot be an alternative to nerve grafts. However, in the group where we entubulated the nerve graft within the ADM, we obtained results close to normal nerve morphology at the end of the 6th month, and the functional recovery was significantly better than compared to nerve grafts. We believe that the ADM may increase the success of nerve grafts in brachial plexus surgery where multiple nerve grafts are frequently used.

Acknowledgement

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Disclosure statement

None of the authors has a financial interest in any of the products, devices or drugs mentioned in this manuscript.

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