Turk Neurosurg 36(2):264-274, 2026
DOI: 10.5137/1019-5149.JTN.48165-24.2

Original Investigation
Spine and Peripheral Nerves

Received: 26.11.2024
Accepted: 21.08.2025
Published Online: 04.03.2026

Comparison of the Effects of Amantadine, Methylprednisolone and Nimodipine in Sciatic Nerve Crush Injury

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ABSTRACT

AIM: To assess the therapeutic effects of methylprednisolone, nimodipine, and amantadine on peripheral nerve injury using a rat sciatic nerve compression model, simulating potential treatments for humans.

MATERIAL and METHODS: A total of 36 adult male Wistar albino rats were divided into five groups. In Group 1, right sciatic nerve compression was performed, while the left side was used as a sham group (Group 2). Groups 3, 4, and 5 received methylprednisolone, nimodipine, or amantadine for one week following injury. In histopathologic analysis, nerve diameter, myelin diameter, axon diameter, G ratio, fibroblast count, mast cell count, and nerve number were measured.

RESULTS: Significant differences were observed across the groups. Amantadine showed the most positive effects on nerve regeneration, improving nerve diameter, myelin diameter, G ratio, fibroblast number, and nerve number compared to the controls. Nimodipine was effective in improving nerve diameter and G ratio but had no effect on other parameters. Methylprednisolone showed significance only in the G ratio. No drug was found to be superior to the others when compared in combination. Overall, amantadine had the most positive cellular effects after sciatic nerve injury; however, further research is required to explore the optimal dosage, frequency, administration route, and additional clinical parameters.

CONCLUSION: In this study, amantadine was found to have the most favorable effects on nerve regeneration, but other drugs showed limited effects on some parameters. However, the lack of superiority in combined applications and the lack of clarification of ideal treatment conditions suggest the need for more comprehensive research in the future.

KEYWORDS: Peripheral nerve, Crush injury, Amantadine, Methylprednisolone, Nimodipine

INTRODUCTION

As a result of peripheral nerve injuries, serious permanent effects occur in 13-23 people per 100,000 per year and affect life (2,8,31). Peripheral nerve injuries are generally caused by motor-motor vehicle accidents, penetrating injuries, cutting injuries, gunshot wounds, falls, burns, fractures, ischemia, stretching, and crushing (3).

Nerve injuries are problems that seriously affect the quality of life and whose treatment is complex. These injuries may occur as a result of physical trauma or compression of the nerves and may adversely affect nerve conduction (5). Sciatic nerve crush injury frequently manifests with symptoms, including marked pain, numbness, and muscle weakness, and it may limit the patient's daily activities (30).

Amantadine is an N-methyl-D-aspartate receptor antagonist and plays a potential role in reducing the effects of nerve damage on neuropathic pain (20). Methylprednisolone is a corticosteroid with anti-inflammatory properties that may promote nerve healing by reducing the inflammatory processes of nerve injury (33). Nimodipine acts as a calcium channel block-

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er and may provide neuronal protection by reducing calcium influx in nerve cells (5).

The aim of this study was to compare the effects of amantadine, methylprednisolone and nimodipine on sciatic nerve crush injuries. Comparing the effects of these three drugs on sciatic nerve crush injuries may help determine the most effective and safe option in the treatment of nerve injury. Using both clinical and experimental data, this study will evaluate the efficacy, safety, and possible side effects of each drug and thus contribute to developing better treatment strategies for patients with sciatic nerve crush injuries.

The results of this research could make an important contribution to the field of the treatment and rehabilitation of nerve injuries and could provide a basis for future studies in this field. Therefore, a comparative analysis of pharmacotherapeutic approaches used in the treatment of sciatic nerve crush injuries may help develop more effective treatment strategies in clinical practice.

MATERIAL and METHODS

Surgical Method

After the approval of the Animal Local Ethics Committee of Kahraman Maras Sutcu Imam University (Date: 30.09.2020; Decision no: 02), the study was conducted in an experimental animal laboratory in accordance with ethical rules (Institute of Laboratory Animal Resources. Guide for the Care and Use of Laboratory Animals, 8th edition, 2011, The National Academies Press, Washington D.C.). In the experiment, 36 adult male Wistar albino rats weighing 300 ± 50 g were used. To acclimatize the rats to the environment, they were fed standard pellet feed for 10 days under a room temperature of 22 ± 2°C, humidity conditions of 60 ± 5% and periodic white fluorescent light (12 h dark and, 12 h light) in the laboratory environment. Feed and drinking water were given ad libitum to the rats throughout the experiment. The rats were randomly divided into four groups of nine rats each. Groups 1 and 2 consisted of the same rats, and the left and right sciatic nerves of the rats were used for the sham and control groups, respectively.

Groups 1 and 2 (control and sham group, n=9): The right sciatic nerves of the rats were opened and crush damage was induced with a clamp; the right side was determined as the control group. On the left side, the skin over the sciatic nerve was opened and the nerve was accessed, but no damage was caused, and the left sciatic nerves were determined as the sham group; primary closure was performed on both sides.

Group 3 (methylprednisolone group, n=9): The right sciatic nerves of the rats were opened, and crush injury was induced with a clamp; primary closure was performed. After the injury, 2 mg/kg/day methylprednisolone was administered intraperitoneally for 1 week.

Group 4 (nimodipine group, n=9): The right sciatic nerve of the rats was opened, and crush injury was induced with a clamp; primary closure was performed. After the injury, 0.5 mg/kg/day nimodipine was administered intraperitoneally for 1 week.

Group 5 (amantadine group, n=9): The right sciatic nerve of the rats was opened, and crush injury was induced with a clamp; primary closure was performed. After the injury, 45 mg/kg amantadine was administered intraperitoneally at 6.4 mg/kg/day for 1 week.

The exclusion criteria were infection, decreased nutritional function, death during and after the operation, and approval of the veterinary surgeon.

A crush injury model to the sciatic nerve was used to create an axonotmesis injury model for sciatic nerve injury. A single dose of 20 mg/kg cefazolin sodium was given intraperitoneally 30 min before the operation for prophylaxis. A dose of 50 mg/kg of ketamine hydrochloride and 10 mg/kg dose of xylazine hydrochloride were administered intraperitoneally and general anesthesia was achieved. After the lower legs of the rats were positioned, the operation area was prepared for the surgical procedure by brushing them with a povidone iodine scrub and povidoneiodine solution (Figure 1A). An Approximately 1.5 cm incision was made on the thighs of the rats to be operated on, and the muscle was reached through the subcutaneous skin (Figure 1B). The sciatic nerve was reached by dissecting the muscles (Figure 1C). The sciatic nerve was exposed by dissecting around the sciatic nerve and was then clamped; the surgeon then waited for one minute (Figure 1D). At the end of one minute, the clamp was removed, and the bleeding was checked. Macroscopically, it was observed that the crush damaged part of the sciatic nerves was distinguishable from the normal parts (Figure 1E). Although compression-induced flattening was observed in the damaged area, nerve integrity was preserved. The skin was sutured with 4/0 silk suture (Figure 1F). All surgical procedures were performed by a single surgeon.

Following recovery after surgery, the rats were placed in separate cages. In rats with sciatic nerve injury, flaccid paralysis was observed in the damaged side leg. The drugs planned to be administered were given intraperitoneally on the first day of the experiment immediately after the experiment. The administration of the drugs was continued for one week at the same time every day. At the end of one week, the administration of the drugs was discontinued and the rats were followed up to meet their physiological needs under normal conditions. At the end of one month, all rats were sacrificed by giving a high-dose anesthetic agent. The operation sites of the sacrificed rats were re-opened. No signs of infection were found in any of the rats. The damaged sciatic nerves in the drug-treated groups and the sciatic nerves in the control-sham group were dissected. The damaged site could be distinguished with the naked eye (Figure 2). The sciatic nerve was dissected 5 mm proximal and distal to the injury site and immediately placed in formaldehyde solution. The specimens were transferred to the pathology laboratory.

Histopathological Method

After the tissues were fixed in 10% formaldehyde solution for 48 hours, three sections of 3 mm thickness were taken perpendicular to the long axis of the nerve fiber and embedded vertically in paraffin after routine follow-up procedures. Two

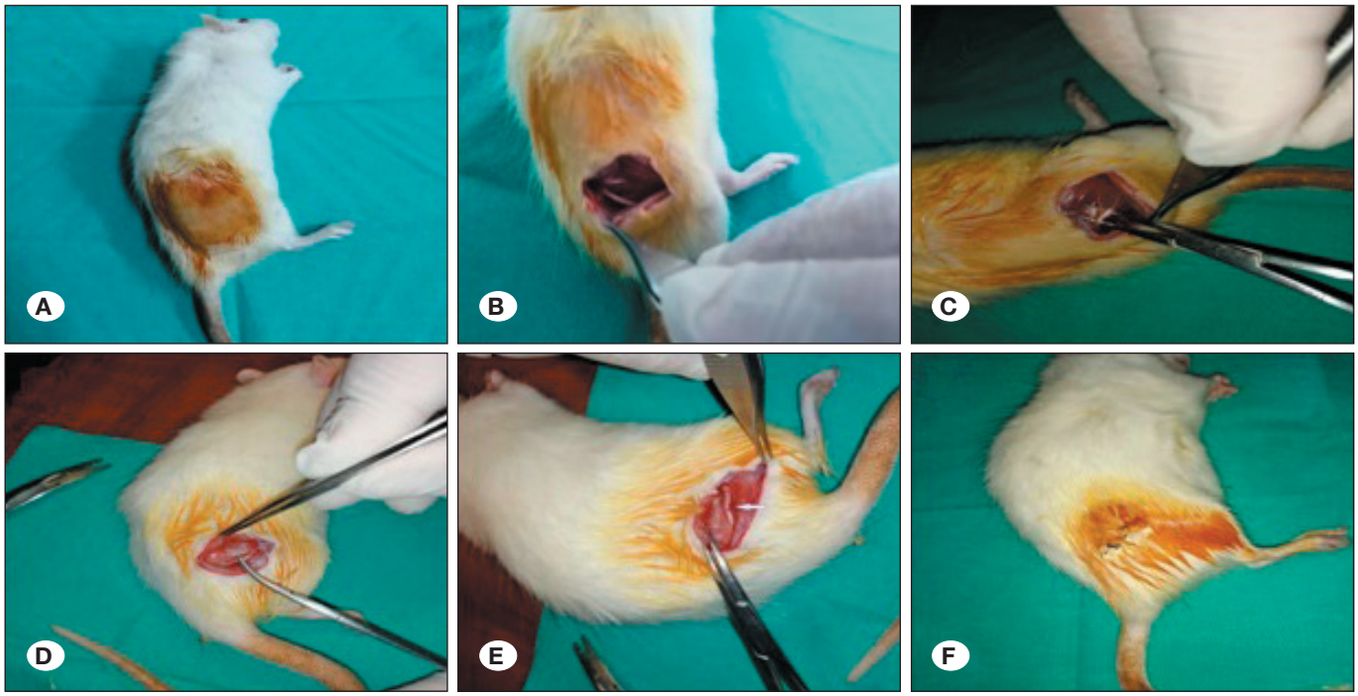

Figure 1: A) Preparation of the rat for the operation, **B)** Incision of the rat and access to the sciatic nerve after muscle dissection, **C)**Dissection of the sciatic nerve from surrounding tissues, **D)** Crush injury to the sciatic nerve, **E)** Image of the sciatic nerve after crush injury and the damaged area (indicated by arrow), **F)** Skin closure.

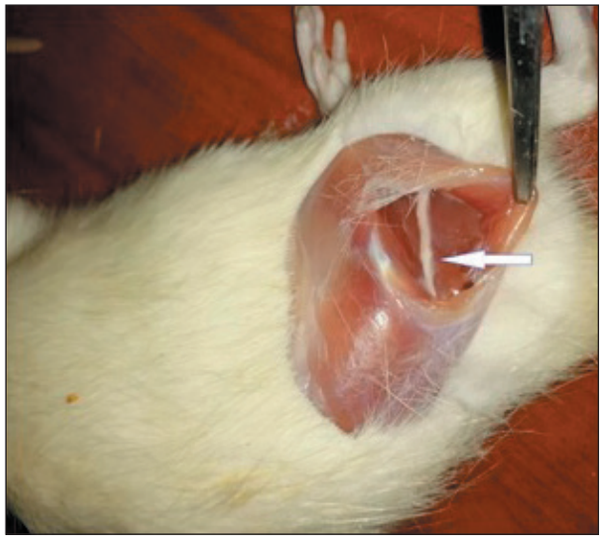

Figure 2: Visualization of the damaged area of the sciatic nerve after sacrification (arrow).

sections of 5 mm and 2 mm (semi-thin) were made from each sample; 5 µm thick sections were stained with hematoxylin eosin, and 2 µm thick sections were stained with Luxol Acid Fast, a myelin stain. Quantitative morphometric analyses were performed on Luxol Acid Fast-stained slides using computerized image analysis software (Olympus BX51 microscope and DP2-BSW image analysis system). Measurements were made at 1,000 magnification. The nerve diameter, axon diameter, and myelin thickness of the 25 nerve fibers were measured in each nerve section. In addition, the ratio of axon diameter to nerve diameter (myelinated axon), the G ratio, was calculated for each nerve fiber. The mean axon diameter, nerve diameter, myelin thickness and G ratio were then calculated for each sample. The numbers of myelinated axons, mast cells and fibroblasts were counted in randomly selected 2,500 µm2 areas in each group.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) program version 21 was used for the statistical analysis of the data. Categorical data were given as numbers and percentages, and numerical data were given as mean, standard deviation, median, and minimum-maximum. A one-way analysis of variance test was used to compare the groups. For statistical significance, $p<0.05$ was accepted.

RESULTS

Histopathological Findings

When hematoxylin- and eosin-stained preparations were examined, intact myelinated axons surrounded by epineurium were observed in the sham group. In the control (trauma) group, marked stromal edema, vacuolization, axonal swelling, and myelin damage were observed in many neurons with mild inflammation. In the treatment groups, less edema and neuronal damage were observed compared to the control group, and the presence of many regenerated axons was remarkable. In the control group, mast cells (long arrows) and increased

fibroblasts (short arrows) were observed in the edematous stroma (Luxol Acid Fast x 400) (Figure 3A). When the control group was examined at a larger magnification (Figure 3B), very prominent nerve degeneration, axonal swelling and myelin damage were observed (arrows indicate vacuolized, swollen degenerated neurons with damaged myelin).

In the sham group, intact nerve tissue surrounded by intact perineurium (arrow) was observed (Luxol Acid Fast x 400) (Figure 4A). In the sham group, axons with intact myelin sheaths were observed (Figure 4B).

In the methylprednisolone group, edema (asterisk) was reduced compared to the control group, but was slightly more prominent compared to the amantadine group (Figure 5A). Fewer vacuolized, swollen degenerated neurons (red arrows) and more regenerated myelinated axons (long black arrows) were observed compared to the control group (Figure 5B).

In the nimodipine group, edema (star) was reduced compared to the control group but was slightly more prominent than in the amantadine group (Figure 6A). Fewer vacuolized, swollen degenerated neurons (red arrows) and more regenerated myelinated axons (long black arrows) were seen compared to the control group. Short black arrows indicate mast cells (Luxol Acid Fast x 1,000) (Figure 6B).

In the amantadine group, compared to the control group, edema decreased, and more regenerated axons were observed (Luxol Acid Fast x 400) (Figure 7A). Edema (star) decreased in the amantadine group compared to the control group. Fewer vacuolized, swollen degenerated neurons (red arrows), fewer myelin figure corrugations (short black arrows), and more regenerated myelinated axons (long black arrows) were seen (Luxol Acid Fast x1000) (Figure 7B).

Statistical Findings

According to the analysis performed for nerve diameter comparison according to the groups, the mean of the sham group was 5022.77 ± 414.38 nm, the control group was 2441.47 ± 296.45 nm, the amantadine group was 3787.44 ± 684.02 nm, the nimodipine group was 3585.09 ± 792.78 nm, and methylprednisolone group was 3025.10 ± 459.25 nm. A statistical-

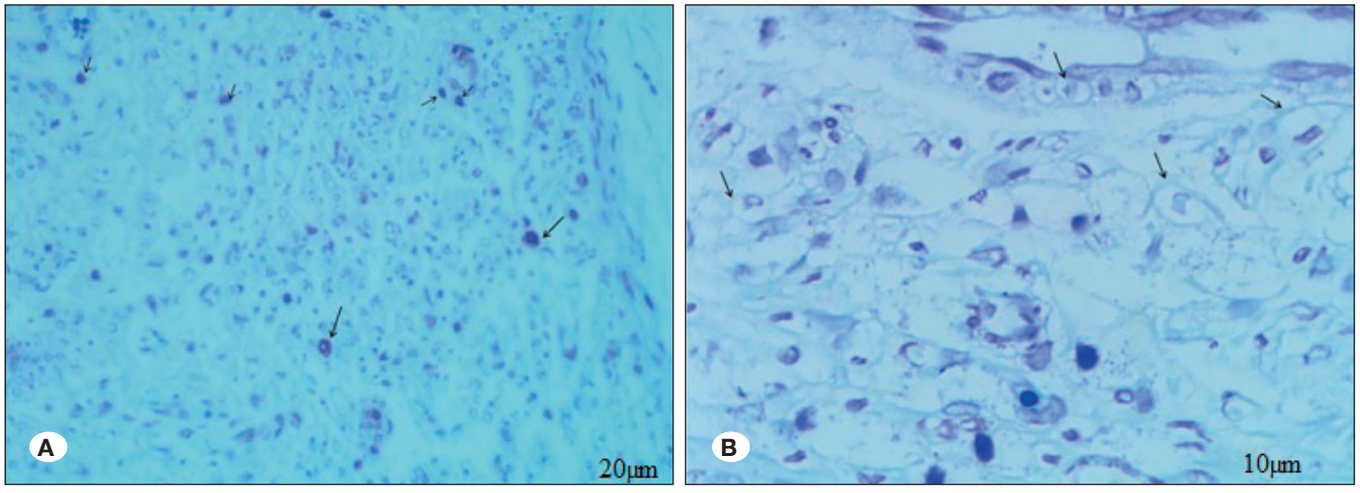

Figure 3: Histopathological image of the control group **A)** Luxol Asit Fast x400, **B)** Luxol Asit Fast x1000.

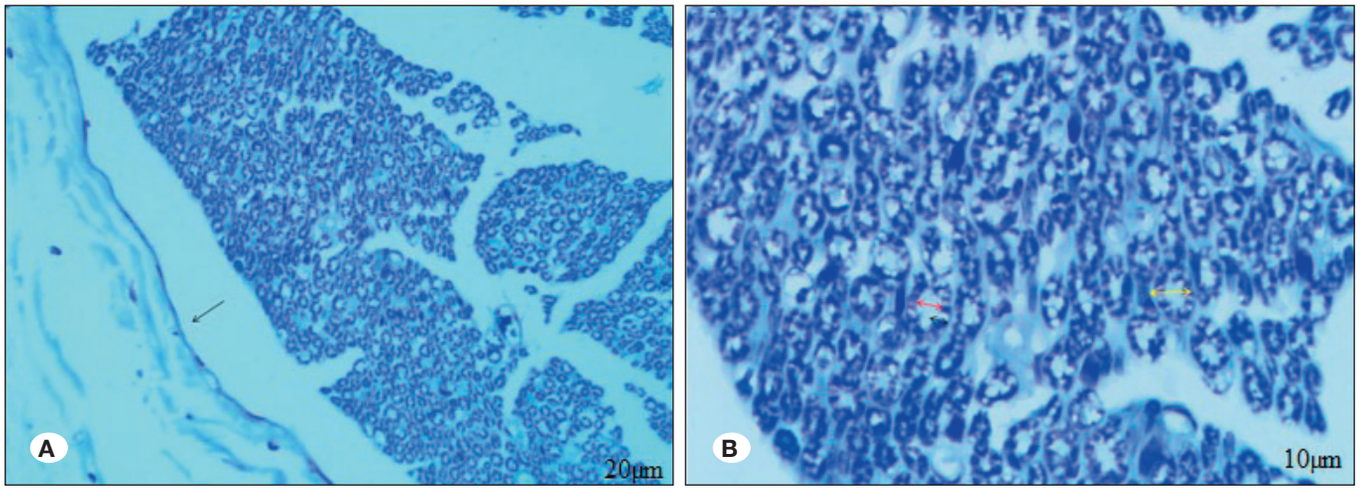

Figure 4: Histopathological image of the sham group **A)** Luxol Asit Fast x400, **B)** Luxol Asit Fast x1000.

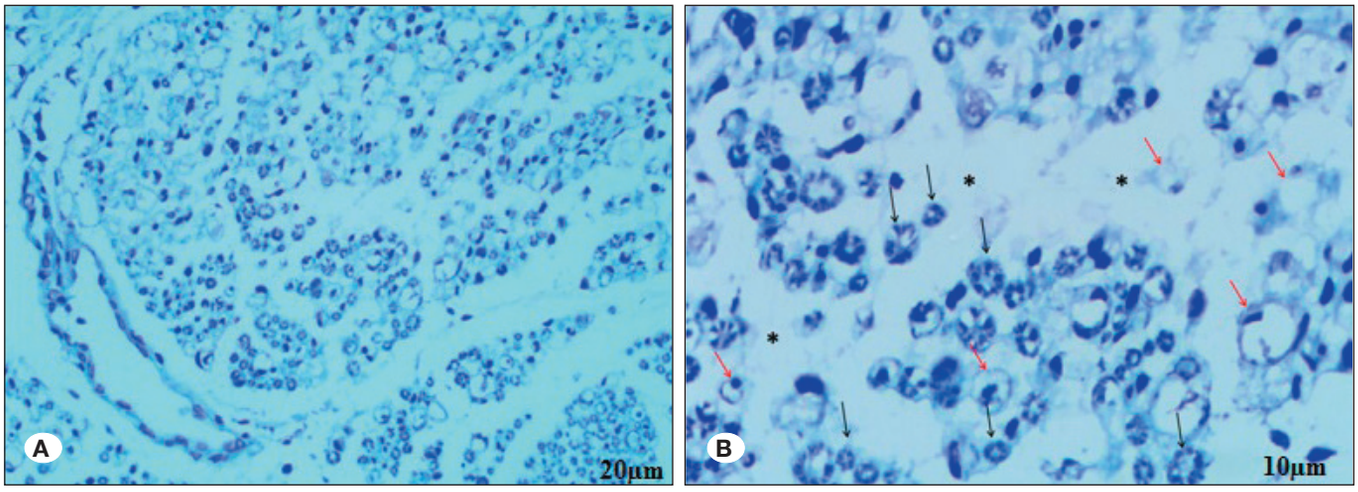

Figure 5: Histopathological image of the methylprednisolone group **A)** Luxol Asit Fast x 400, **B)** Luxol Asit Fast x 1000.

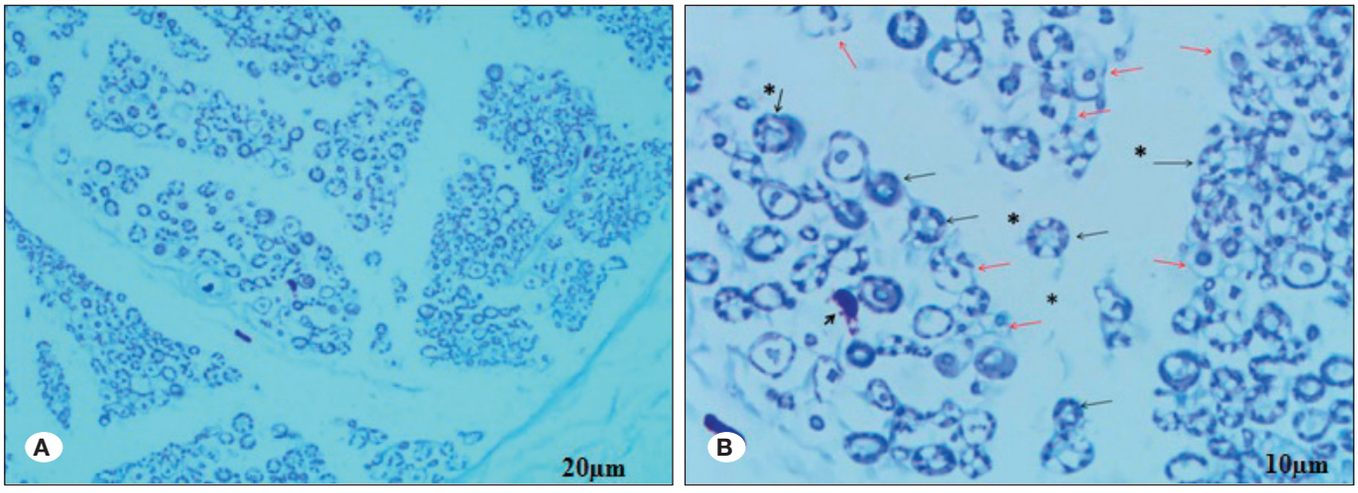

Figure 6: Histopathological image of the nimodipine group **A)** Luxol Asit Fast x 400, **B)** Luxol Asit Fast x 1000.

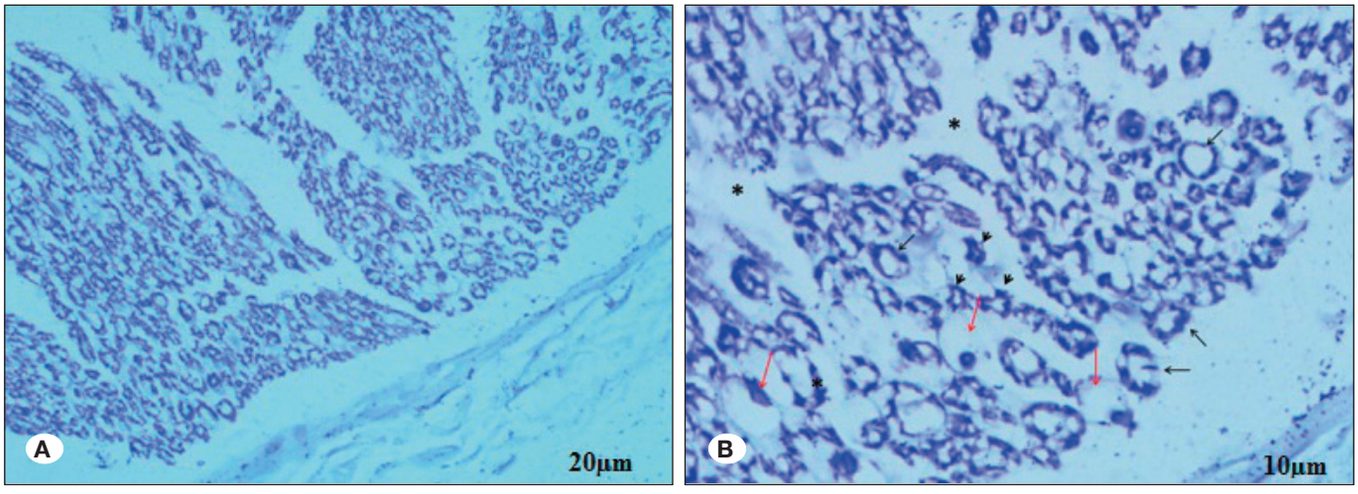

Figure 7: Histopathological image of the amantadine group. **A)** Luxol Asit Fast x 400, **B)** Luxol Asit Fast x 1000.

ly significant difference was found between the groups. According to the analysis performed for pairwise comparisons of the groups, it was determined that there was a statistically significant difference between the sham group and the other groups, the control group and the amantadine and nimodipine groups, and the amantadine group and the methylprednisolone group (p<.001; Table I).

Myelin diameter was significantly higher in the sham group than in the other groups. Myelin diameter was significantly lower in the control group compared to the amantadine group, and was significantly higher in the amantadine group compared to the methylprednisolone group (p<0.001; Table II).

As a result of our study, axon diameter was found to be significantly higher in the sham group compared to the other groups (p<0.001; Table III).

It was found that the G ratio was significantly higher in the control group compared to the other groups (p<0.001; Table IV).

Fibroblast count was found to be significantly higher in the control group compared to the sham and amantadine groups and in the amantadine group compared to the sham group (p<0.05; Table V).

The mast cell count was significantly lower in the sham group compared to the control and nimodipine groups (p<0.05; Table VI).

According to the analysis performed for nerve cell count/2,500 μm^2 comparison according to the groups, the mean of the sham group was 26.67 ± 1.36, the control group was 14.33 ± 2.42, the amantadine group was 20.33 ± 3.27, the nimodipine group was 17.78 ± 3.11, and the methylprednisolone group was 15.40 ± 3.80, and a statistically significant difference was found between the groups. According to the analysis performed for pairwise comparisons of the groups, statistically significant differences were found between the sham group and the other groups, between the control group and the amantadine group, and between the amantadine group and the methylprednisolone group (p<0.001; Table VII).

Table I: Nerve Diameter Comparison according to Groups

Group	n	x̄±SD	F	p-value*
Sham	9	5022.77±414.38[a,b,c,d]		
Control	9	2441.47±296.45[a,e,f]		
Amantadine	9	3787.44±684.02[b,e,g]	17.3	**0.000**
Nimodipine	9	3585.09±792.78[c,f]		
Methylprednisolone	9	3025.10±459.25[d,g]		

*****One Way ANOVA,* ***Note:*** *There is a significant difference between the same exponential letters.*

Table II: Myelin Diameter Comparison according to Groups

Group	n	x̄±SD	F	p-value*
Sham	9	1263.30±112.54[a,b,c,d]		
Control	9	645.49±247.41[a,e]		
Amantadine	9	976.64±100.14[b,e,f]	13.2	**0.000**
Nimodipine	9	826.41±195.24[c]		
Methylprednisolone	9	734.70±168.35[d,f]		

*****One Way ANOVA,* ***Note:*** *There is a significant difference between the same exponential letters.*

Table III: Axon Diameter Comparison according to Groups

Group	n	x̄±SD	F	p-value*
Sham	9	3019.71±221.37[a,b,c,d]		
Control	9	1907.72±292.65[a]		
Amantadine	9	2090.42±249.90[b]	24.7	**0.000**
Nimodipine	9	1990.84±303.22[c]		
Methylprednisolone	9	1767.88±210.83[d]		

*****One Way ANOVA.* ***Note:*** *There is a significant difference between the same exponential letters.*

Table IV: Comparison of g Ratio by Groups

Group	n	x̄±SD	F	p-value*
Sham	9	0.60250±0.04[a]		
Control	9	0.78050±0.05[a,b,c,d]		
Amantadine	9	0.56144±0.07[b]	6.870	**0.000**
Nimodipine	9	0.56978±0.11[c]		
Methylprednisolone	9	0.59490±0.10 [d]		

***** One Way ANOVA. **Note:** There is a significant difference between the same exponential letters.

Table V: Comparison of Fibroblast Counts according to Groups

Group	n	x̄±SD	F	p-value*
Sham	9	0.83±0.75[a,b]		
Control	9	5.17±2.71[a,c]		
Amantadine	9	2.44±1.23[b,c]	6.332	**0.001**
Nimodipine	9	3.44±1.42		
Methylprednisolone	9	3.00±1.33		

** One Way ANOVA. **Note:** There is a significant difference between the same exponential letters.*

Table VI: Mast Cell Count Comparison according to Groups

Group	n	x̄±SD	F	p-value*
Sham	9	0.17±0.40[a,b]		
Control	9	1.33±0.51[a]		
Amantadine	9	0.56±0.52	5.165	**0.002**
Nimodipine	9	1.00±0.00[b]		
Methylprednisolone	9	0.70±0.67		

** One Way ANOVA, **Note:** There is a significant difference between the same exponential letters.*

Table VII: Nerve Cell Count Comparison according to Groups

Group	n	x̄±SD	F	p-value*
Sham	9	26.67±1.36[a,b,c,d]		
Control	9	14.33±2.42[a,e]		
Amantadine	9	20.33±3.27[b,e,f]	16.708	**0.000**
Nimodipine	9	17.78±3.11[c]		
Methylprednisolone	9	15.40±3.80[d,f]		

** One Way ANOVA, **Note:** There is a significant difference between the same exponential letters.*

DISCUSSION

Peripheral nerve damage is a common condition in both humans and animals and affects the physiology and functions of the body in the long term (10). Factors such as ischemia, inflammatory diseases, radiation, compression, traction, electric shock, and burns-most commonly trauma-cause peripheral nerve injury (16,29).

Peripheral nerve injuries may result in partial or total injuries. Permanent motor and sensory deficits and neuropathic pain secondary to peripheral nerve injury will decrease the quality of life of the patient and also dramatize the situation socially (11,26,34).

Regeneration is essential for nerves to regain function, as it allows damaged nerve fibers to repair and restore neural communication. However, functional recovery following nerve injury is not always achieved. Nerve regeneration involves complex processes like axon growth, synapse formation, and myelination, which can be hindered by factors such as injury severity, distance to target tissue, age, and health status. Scar tissue and inhibitory glial cells at the injury site may also impair regeneration, leading to suboptimal healing. It is estimated that traumatic peripheral nerve injuries cause over 500,000 new cases annually, highlighting the need for effective treatments and rehabilitation strategies (25). Current approaches include surgical techniques, nerve grafts, growth factor therapies, and biomaterials, but individual treatment outcomes vary, indicating a need for further optimization. Despite peripheral nerves' higher regeneration capacity compared to central nervous system nerves, the process is often slow and incomplete, with patients potentially experiencing lasting motor and sensory deficits. This underscores the importance of research into new regenerative therapies, such as stem cell therapy, gene therapy, and neuroprostheses. In conclusion, while nerve regeneration is crucial for recovery after traumatic injuries, optimal functional outcomes are not always achieved, emphasizing the need for continued research into effective treatment options.

The recovery time of the injured nerve depends on various external factors, including the location of the injury and nerve repair. However, it should not be ignored that the axonal regeneration rate is 1-2 mm/day, and there is no treatment to accelerate this process (23). The medications applied after peripheral nerve injury aim to support the regeneration process of the damaged nerve tissue in a healthy way and to make functional recovery close to complete. Therefore, many drugs have been tried at the point of treatment for peripheral nerve injuries and are still being tried.

In our study, when the sciatic nerve injury and medication groups were compared with the sham and control groups, it was observed that methylprednisolone, nimodipine, and amantadine were effective in the healing of sciatic nerve injury in the parameters examined histopathologically separately. In nerve diameter, amantadine and nimodipine were statistically equally effective for recovery, whereas there was no statistical difference between them in the methylprednisolone group compared to the control group. In myelin diameter, amantadine was statistically significant, whereas no statistically significant difference was observed in the nimodipine and methylprednisolone groups compared to the control group. There was no statistically significant difference in axon diameter in the parameters of the three drugs compared to the control group. In the G ratio, amantadine, nimodipine and methylprednisolone were found to be equally effective for nerve healing and no statistically significant difference was found between the groups. The G ratio is defined as the ratio of the axon (inner diameter) to the axon and myelin (outer diameter) in the nerve fiber. The G ratio is expected to associate the complex interaction of demyelination, remyelination, and axonal degeneration with neurophysiological abnormalities and thus with clinical symptoms (4). When fibroblast counts were analysed, a statistically significant difference was found in the amantadine group compared to the methylprednisolone and nimodipine groups. No statistically significant difference was found in the number of mast cells among the three drug groups. It has been reported that fibroblast cells make important contributions to the regeneration and recovery of nerve tissue after damage to nerve tissue and that growth factor released from fibroblasts contributes to this process (13,32,35). In the number of nerves, amantadine was found to be effective in nerve healing, but no statistically significant difference was found among the nimodipine, methylprednisolone, and control groups.

In a study conducted by Hydman et al., it was shown that nimodipine used in damaged recurrent laryngeal nerves was effective in the recovery of peripheral nerve damage, and this study showed that nimodipine can be used in peripheral nerve damage (10).

In a study published by Mattsson et al., patients with recurrent laryngeal nerve injuries were repaired with microsurgery, and nimodipine was then given to the patients for three months. In the long-term follow-up of the patients, it was reported that all showed functional improvement, and no nimodipine-related side effects were observed (17). In our study, it was observed in histopathological parameters that nimodipine was effective in nerve injury healing, but long-term results and functional recovery were not examined.

In a study conducted by Lindsay et al., a crush damage model was applied to facial nerves, and then the effect of nimodipine was investigated; it was reported that rats receiving nimodipine showed earlier recovery compared to those not receiving nimodipine (15). In this study, subcutaneous pellets providing nimodipine release were placed in rats four days before the operation, and the aim was continuous release. In our study, nimodipine was given daily at an equal dose for seven days and then discontinued, and histopathological results were obtained in terms of efficacy.

In a study published by Scheller and Scheller, it was observed that oral nimodipine administered to patients who had undergone maxillofacial surgery and subsequently had traumatic facial nerve paralysis improved facial nerve function (28). In our study, nimodipine was administered intraperitoneally. The nimodipine used in Scheller's study was in oral form and administered to real patients. This suggests

that nimodipine may be effective in peripheral nerve damage independent of the route of administration.

In a study published by Zheng et al., it was reported that nimodipine applied after facial nerve crush injury in rats increased remyelination and improved damage (36). However, in this study, nimodipine of 6 mg/kg/day was given to rats via oral lavash, and when we compared it with our study, there was a difference in dose and route of administration; it was observed that it did not affect myelin diameter.

In a randomized multicenter study conducted by Scheller et al., nimodipine and hydroxyethyl starch were given prophylactically and until the 7th postoperative day in patients operated on for vestibular schwannoma and facial nerve functions. No statistically significant difference was found between the nimodipine group and the starch group (27). The fact that the effect of nimodipine, which was found to be effective histopathologically in our study, could not be shown statistically in Scheller's study was considered multicenter and that each patient included in the study may not be the same at the point of surgery.

In a study by Hota et al. comparing the efficacy of nimodipine, gabapentin, imipramine, and ketamine in neuropathic pain due to transection injury in rats, it was observed that nimodipine was also effective in neuropathic pain (9). Although the efficacy related to neuropathic pain was examined in this study, it supports our results because neuropathic pain can be observed after peripheral nerve damage, and the efficacy of nimodipine in neuropathic pain shows that it provides nerve regeneration. This may indicate recovery in neural tissue in basically the same way.

In a study conducted by Ohlsson et al. on the therapeutic efficacy of methylprednisolone on optic nerve damage in rats, no therapeutic effect of methylprednisolone on neural tissue was observed (21). In our study, although methylprednisolone was not found to be statistically effective in many histopathological parameters, it was found to be equally effective with other drugs used in the G ratio.

In an experimental study conducted by Li et al., rats were subjected to sciatic nerve transection injury, and then a membrane containing microspheres releasing methylprednisolone was applied locally to the damaged area (14). In this study, it was observed that local application of methylprednisolone reduced fibrosis around the damaged neural tissue and positively affected myelin thickness. In our study, it was observed that methylprednisolone did not affect myelin diameter but positively affected the G ratio. It was thought that the difference might be related to the dose, duration and route of administration. In addition, in our study, methylprednisolone had no statistically significant effect on fibroblast counts.

In a rat study of sciatic nerve crush injury published by Ozturk et al., the groups given methylprednisolone were compared with the groups given methylprednisolone and ozone, and histopathologically, a significant decrease in degeneration was observed in the group given methylprednisolone and ozone (22). No change was observed in the group given methylprednisolone. The results of this group were similar to those of our methylprednisolone experimental group in terms of histopathological results.

In a study conducted by Mehrshad et al. on rats, sciatic nerve damage was created in rats, and then methylprednisolone-loaded hydrogel was applied locally. As a result of this study, it was stated that a local methylprednisolone-loaded hydrogel was effective in sciatic nerve damage (19). However, in our study, methylprednisolone was not found to be effective in other parameters except for affecting the G ratio. At this point, it was thought that factors such as the dose and duration of drug administration would make a difference.

In the experimental sciatic nerve injury model performed by Jiang et al. on rats, methylprednisolone was given at three different doses, and it was shown to be more effective on nerve regeneration at low and medium doses, but high doses were not recommended (11). In our study, the contribution of methylprednisolone to regeneration was not observed in general, and the G ratio was statistically better than in the control group.

In an experimental animal study conducted by Karlidag et al., the facial nerve was cut and re-anastomosed and then the subjects were divided into groups, and N-acetylcysteine and methylprednisolone were given (12). Regeneration in the facial nerve was then examined, and it was reported that the weakest results were found in the methylprednisolone group. The results of Karlidag et al.'s study were similar to the results of our study.

Many clinical studies have been conducted on amantadine. In a double-blind, randomized, and placebo-controlled study conducted by Pud et al. on cancer patients, amantadine was found to be effective in cancer patients, especially in neuropathic pain, compared to a placebo (24). In our study, amantadine was found to be effective in many histopathological parameters after peripheral nerve damage, and it was thought that a drug with histopathological efficacy might also be effective in neuropathic pain as a clinical reflection of a drug with histopathological efficacy. This was evaluated in correlation with the study conducted by Pud et al. (24).

In a randomized, double-blind, controlled study conducted by Medrik-Goldberg et al., the effects of lidocaine and amantadine administered intravenously on sciatic pain were compared (18). In this study, Medrik-Goldberg et al. showed that lidocaine had an analgesic effect and better results on the straight leg-raising test, as reflected in the clinic (18). However, since the histopathological effect of amantadine was examined in our study, unfortunately, its clinical reflection could not be examined. However, more studies may be required to provide evidence of the clinical effects of amantadine, whose histopathological efficacy was observed.

In a randomized, double-blind, controlled study conducted by Amin and Sturrock, the efficacy of amantadine in pain due to peripheral neuropathy in diabetic patients was investigated, and a decrease in neuropathic complaints was observed in patients receiving amantadine (1). In our study, amantadine was found to be histopathologically effective in peripheral nerve damage, and the study by Amin and Sturrock supports our results clinically (1).

In a study conducted by Eisenberg et al., it was reported that amantadine was not significantly more effective than a placebo in neuropathic pain, defined as postmastectomy pain syndrome in mastectomized patients (7). Unfortunately, neuropathic pain could not be analyzed in the subjects in our study, so no clinical comparison could be made.

In an experimental study conducted by Dogan and Karaca on rats, rats with spinal cord injury were given amantadine, and it was reported that amantadine could improve spinal cord injury by inducing angiogenesis and affecting apoptosis and inflammation compared with the control group (6). In this study conducted by Dogan and Karaca it was observed that amantadine provided regeneration and neuroprotection histopathologically; similar results were observed in our study.

CONCLUSION

Although all three drugs have various effects on peripheral nerve damage, further studies are needed in terms of dosage, frequency of administration, and route of administration. In addition, different parameters should be considered to evaluate the clinical-physiological effects of the drugs. In our study, amantadine, the efficacy of which had not been studied before, was histopathologically effective in peripheral nerve injury recovery. It was thought that this efficacy could be investigated in clinical studies.

Firstly, the effects of therapeutic agents such as amantadine, methylprednisolone and nimodipine in the treatment of sciatic nerve crush may also be of potential benefit in human clinical practice. However, dosage optimization is a critical factor for the applicability of these drugs in humans. In particular, the efficacy and side effects of each therapeutic agent should be individually tailored to patient characteristics.

Future clinical trials should evaluate the efficacy of different dosages, treatment durations and treatment combinations of these therapeutic agents. Furthermore, the use of biomarkers to identify individuals who respond to treatment could be an important step towards personalizing treatment. In terms of human applicability, further research is needed on how these treatment options can be optimized in specific disease groups and types of nerve injury, taking into account their safety profiles and risks of side effects.

In this context, it is clear that future studies that will provide more information on how to integrate the findings of our study into clinical practice and how to optimize treatment dosages will contribute to the development of treatment protocols.

Our study does not include evaluations on functional recovery after sciatic nerve crush. This is a limitation to fully understand the long-term effects and clinical benefits of treatment modalities. In future studies, a more comprehensive examination of functional recovery will provide more precise information on the efficacy of treatment protocols.

The study focused on short-term histopathologic parameters and did not examine long-term outcomes. Nerve healing and regeneration are long-term processes, so evaluating the longer-term effects of treatment modalities will increase the clinical validity of the findings.

Declarations

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: IS, RE

Data collection: IS, RE, IES, IA

Analysis and interpretation of results: IS, RE

Draft manuscript preparation: IS, RE, IES, IA

Critical revision of the article: IS, RE, IES, IA

Other (study supervision, fundings, materials, etc...): IS, RE, IES, IA

All authors (IS, RE, IES, IA) reviewed the results and approved the final version of the manuscript.

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