EXPERIMENTAL STUDY

Influence of galantamine on peripheral nerve degeneration after experimental compression injury of the rat sciatic nerve

Fatih Alagöz, M.D.,[1] Mert Sahinoglu, M.D.,[2] Deniz Billur, M.D.,[3] Sevim Aydın, M.D.,[3] Rifat Akdağ, M.D.,[4] Durmuş Oğuz Karakoyun, M.D.,[5] Ergun Daglioglu, M.D.[1]

[1]Department of Neurosurgery, University of Health Sciences, Bilkent City Hospital, Ankara-*Turkey*
[2]Department of Neurosurgery, Selcuk University Faculty of Medicine, Ankara-*Turkey*
[3]Department of Histology and Embryology, Ankara University Faculty of Medicine, Ankara-*Turkey*
[4]Department of Neurosurgery, University of Health Sciences, Şevket Yılmaz Hospital, Bursa-*Turkey*
[5]Department of Neurosurgery, Ordu University Faculty of Medicine, Ordu-*Turkey*

ABSTRACT

BACKGROUND: Galantamine is well-known for its neuroprotective effects and is currently used in the treatment of individuals with Alzheimer's disease. In this study, we induced experimental sciatic nerve injury (SCI) in rats to test the beneficial effects of galantamine.

METHODS: Thirty male Wistar albino rats were divided into three groups, as follows: sham, SCI + saline, and SCI + galantamine. After the administration of an intraperitoneal ketamine and xylazine mixture, which was used for anesthesia, SCI was induced by surgical clip compression at the midthigh region of the rats. After surgery, a single daily intraperitoneal dose of galantamine was administered for 7 days, and nerve tissue sections were obtained 1 week after injury. Histopathology studies were performed to assess neural thickness and apoptotic cell counts, and light microscopic morphological examination was used to determine a potential beneficial effect of galantamine on peripheral nerve degeneration.

RESULTS: We observed a markedly increased microvasculature, increased nerve fiber thickness, and a statistically significant increase in apoptotic cell counts distal to the level of injury in the saline group compared with the sham group. However, the increases in nerve fiber thickness and apoptotic cell counts were less in the galantamine group compared with the saline group.

CONCLUSION: In our experimental model, pharmacological intervention with galantamine demonstrated a protective effect on degeneration after peripheral nerve injury.

Keywords: Infratrochlear sinir bloğu; orbital kompartman sendromu; perioküler anestezi, probing; retrobulbar hemoraji.

INTRODUCTION

Peripheral nerve injuries can result in functional losses or chronic pain in affected individuals due to insufficiency of the regeneration process. Pharmacological intervention early after peripheral nerve injury has been shown to result in neuroprotective effects and may accelerate functional recovery.[1,2] Experimental sciatic nerve injury (SCI) results in increased levels of neurotransmitters such as glutamate and aspartate at the axonal terminals.[3] In an experimental study in rats, nicotine and acetylcholinesterase (AChE) inhibitors such as galantamine were found to protect cortical neurons against glutamate neurotoxicity partly by inhibiting apoptosis.[4]

Galantamine is a well-known AChE inhibitor used in the treatment of Alzheimer's disease. In neurodegenerative disease models, neuroprotection has been shown to occur through nicotinic receptors.[5] The primary mechanism of action of galantamine is through nicotinic receptors and inhibition of excitotoxicity. The neuroprotective effects of galantamine have been demonstrated in several experimen-

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Address for correspondence: Fatih Alagöz, M.D.
Sağlık Bilimleri Üniversitesi Bilkent Şehir Hastanesi, Beyin ve Sinir Cerrahisi Kliniği, Ankara, Turkey
Tel: +90 312 - 552 60 00 E-mail: fatihalagoz06@gmail.com

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tal models. Galantamine increases hippocampal insulin-like growth factor 2 expression via α7 nicotinic acetylcholine receptors in mice, which may contribute to its neuroprotective and neurogenic effects.[6] The neuroprotective effects of galantamine on vascular dementia were shown in a rat model by Tayebati et al.[7] In another study, the combined use of 5-HT6 receptor antagonists and galantamine was shown to reverse learning impairments in rats.[8] Galantamine was also shown to be neuroprotective in a gerbil model of transient cerebral ischemia.[9] Moreover, in organotypic hippocampal cultures, the combination of galantamine and melatonin exhibited anti-apoptotic effects and a reduction in Alzheimer's disease-related pathological hallmarks.[10]

Besides its neuroprotective role, galantamine also has important effects on the microvasculature. Almasieh et al.[11] reported its marked protective effect on retinal vessels in an experimental model of glaucoma. In the present study, we investigated the influence of galantamine in a rat model of experimental SCI.

MATERIALS AND METHODS

The experimental protocol was carefully reviewed and approved by the Animal Studies Ethics Committee (Ministry of Health Ankara Hospital, Ankara, Turkey) with a reference number of 2012\89.

Experimental Design and Surgical Procedures

Thirty male Wistar albino rats weighing between 180 and 210 grams were used for these experiments. They were housed in plastic cages at room temperature and had free access to food and water. Rats were divided into three experimental groups, as follows:

Sham Group: only a linear incision was made and closed without any intervention to the sciatic nerve.
Saline Group: SCI + SF
Galantamine Group: SCI + Galantamine

All rats were weighed, and the induction of anesthesia was performed with a mixture of intraperitoneal ketamine (50 mg/kg) and xylazine (10 mg/kg). For the saline and galantamine groups, the sciatic nerves were exposed at midthigh level with preservation of the mesoneurium. A meticulous dissection was then performed to expose the sciatic nerve. Neural injury was induced by compression of the sciatic nerve for 2 min using an aneurysm clip (Yasargil FE 693 temporary aneurysm clip, Aesculap) with a closing pressure of 50 g/cm^2.[12,13] The mid-crush site was labeled with a single suture before closure. After surgery, the rats were housed in separate cages under a 12-h light/dark cycle and allowed free access to standard requirements. After SCI, 2.5 ml/kg saline (serum physiologic 0.9%) or 2.5 mg/kg galantamine (Galantamine Hydrobromide G1660, 10 mg, Sigma Inc., USA) was administered daily as a single dose via the nasogastric route for 7 days.[7,14] After 7 days, tissue for histological sections was obtained simultaneously from each group under anesthesia. After the procedure, all rats were sacrificed by decapitation.

Histopathology

Tissue Harvest

After sciatic nerve dissection with microscissors, a half-centimeter length from the compressed segment was removed from the marked area. For light microscopic examination, nerve tissue samples were fixed in 10% neutral-buffered formalin for 72 h. After fixation, tissues were rinsed in running tap water for 1 h. All samples were dehydrated in a graded series of ethanol (75%, 96%, and 100%), while xylene was used to clear the tissue prior to embedding the tissue in paraffin blocks. Sections (5 µm in thickness) were cut using a Leica RM 2125RT microtome after which the slides were stained with hematoxylin and eosin and Mallory Azan. The sections were examined and imaged using an AxioScope A1 (Carl Zeiss, Oberkochen, Germany) light microscope by two separate histologists who were blinded to the groups.

For each experimental group, the proximal and distal ends of the injury sites were examined under ×40 magnification with the aid of Axiovision software to determine nerve diameter thicknesses.

TUNEL Staining

The TUNEL (in situ end labeling) method was used to detect apoptotic cells in the tissues. An in situ Cell Death Detection Kit (POD Roche, Mannheim- Germany) was used according to the manufacturer's instructions. First, 5-µm-thick sections were transferred to polylysine-coated slides and incubated overnight at 60°C. Then, they were deparaffinized in xylene after which they were rehydrated in a graded series of 75%, 96%, and 100% ethanol and washed with PBS. Slides were immersed in 0.1 M citrate buffer and microwaved for 5 min for antigen retrieval and then washed with PBS. Next, sections were incubated with the TUNEL reaction mixture (labeling solution + terminal deoxynucleotidyl transferase enzyme solution) at 37°C for 1 h and washed with PBS. For the negative control, some sections were incubated with label solution only (without terminal transferase) instead of the TUNEL reaction mixture. The tissues were then incubated with an anti-fluorescein antibody (Converter-POD) for 30 min at 37°C and rinsed twice with PBS. Finally, the sections were treated with 3,3-diaminobenzidine at room temperature and rinsed twice with PBS. A positive color reaction was detected by microscopy after 2–3 min of incubation. The sections were dehydrated by washing in a graded series of alcohol. Xylene was used as a clearing agent, and then, the sections were coverslipped with Entellan for light microscopic examination.

Evaluation of Apoptosis

Immunohistochemically, cells in tissues that were immunoreactive for TUNEL staining were counted in 3 different areas per section using an AxioScope-A1 light microscope at a magnification of ×40. The apoptosis index of each group was calculated as a percentage (%) according to the following formula:

$$\text{Apoptosis index } \% = \frac{\text{Number of TUNEL - Positive cells}}{\text{Total number of cells}} \times 100$$

Statistical Analysis

The Kruskal-Wallis test was used to compare the apoptotic index as well as the distal and proximal nerve thicknesses among the study groups. The Dunn test was used for post hoc comparisons. P<0.05 was considered statistically significant. Data were analyzed using SPSS software (Version 11.0 for Windows).

RESULTS

Histopathological Findings

Sham Group

Transverse and longitudinal sections from the sham group were found to be morphologically normal by light microscopy. Axons and surrounding myelin sheaths formed by Schwann cells and their nuclei were normal in appearance (Fig. 1a and b).

Saline and Galantamine Group, Findings Proximal to the Injury

No difference was observed between the morphology of rats in the saline and galantamine groups and the morphology of rats in the sham group. Axons and peripheral myelin sheaths as well as Schwann cells were normal. The nuclei of fibroblasts were noted in the endoneurium, and the perineurium surrounding the nerve fibers was also normal.

Saline and Galantamine Group, Findings Distal to the Injury

Marked degeneration and increased nerve fiber thickness were noted distal to the injury in the saline group (Fig. 1c and d). Similar findings were also noted in the galantamine group (Fig. 1e and f). Another prominent finding was increased microvasculature as well as dilation of capillaries and distinct areas of hemorrhage.

The thickness of the nerve proximal and distal to the injured segment was measured separately for each group. When these numbers were compared between each group, no statistically significant difference was observed in the proximal nerve thickness measurements among the study groups (p=0.573) (Table 1 and Fig. 2a).

The mean distal nerve thickness in the sham group was 6.4±1.0 µm, while the thickness values were 12.8±1.4 µm in the saline group and 9.0±1.1 µm in the galantamine group. This difference was statistically significant (p<0.001) (Table 1 and Fig. 2b). We found that the nerve thickness in the galantamine group was statistically significantly lower than that in the saline group but was higher than that in the sham group (p<0.001 and p<0.001). Moreover, a statistically significant difference was observed between the saline and sham groups (p<0.001) (data not shown).

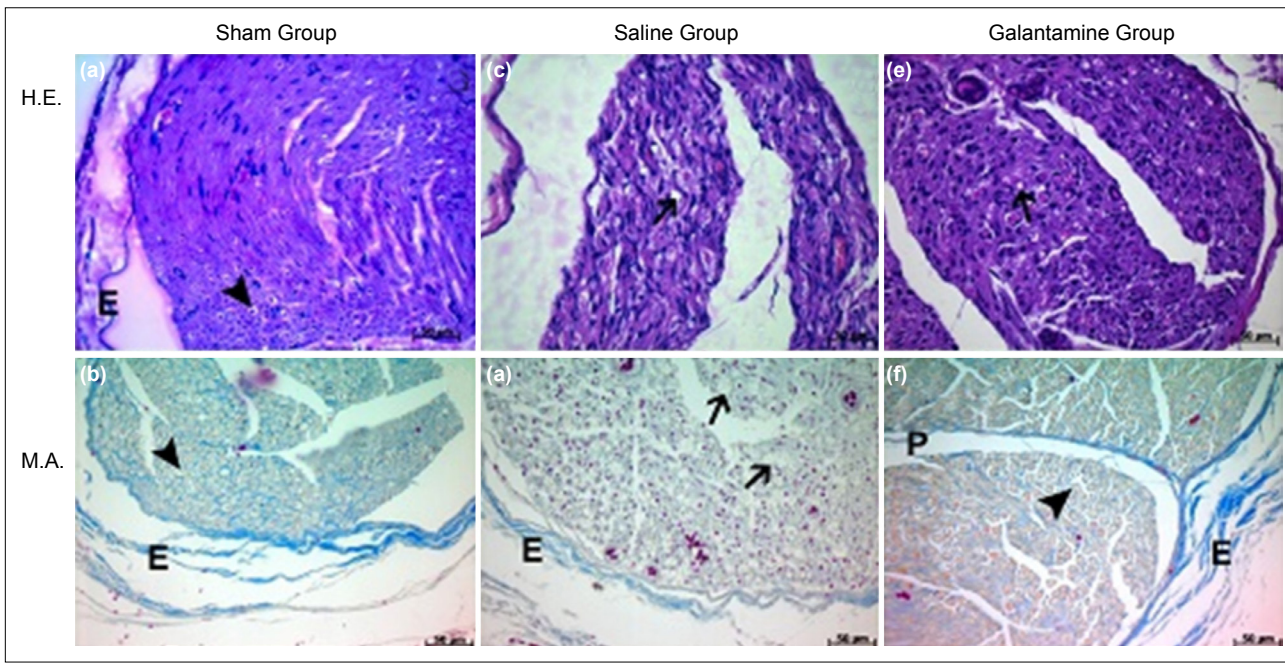
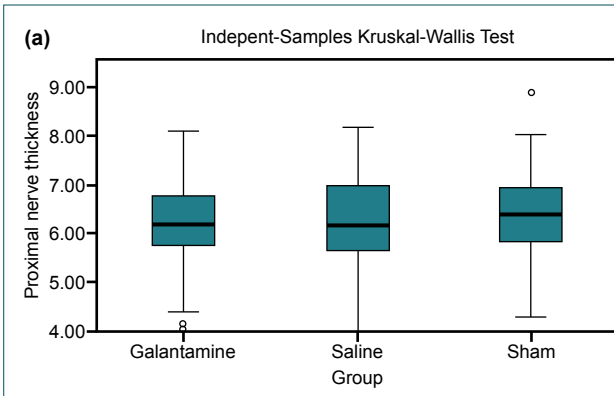
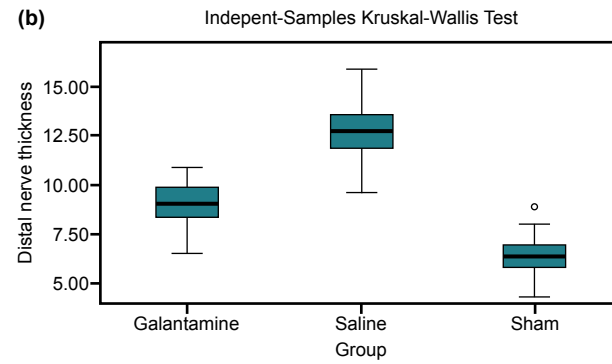


Figure 1. Light micrographs of peripheral nerve sections. Symbols: Arrowhead, myelinated axonal cross-section; arrow, degenerated axon; P: Perineurium, E: Epineurium.



Total N	150
Test Statistic	1.112
Degrees of Freedom	2
Asymptotic Sig. (2-sided test)	.573

1. The test statistic is adjusted for ties.
2. Multiple comparisons are not performed because the overall test does not show significant differences across samples.



Total N	150
Test Statistic	124.418
Degrees of Freedom	2
Asymptotic Sig. (2-sided test)	.000

1. The test statistic is adjusted for ties.

Figure 2. Distributions of **(a)** proximal nerve thickness (µm), **(b)** distal nerve thickness (µm).

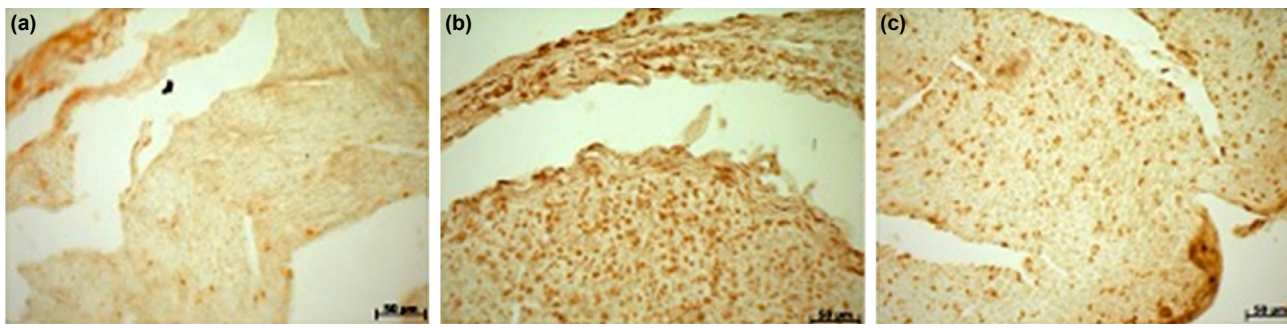


Figure 3. Immunohistochemistry. **(a)** dark brown nuclei demonstrating immunoreactivity were scarce in a sample from the sham group. **(b)** marked immunoreactivity of apoptotic cells was noted distal to the sciatic nerve injury in a sample from the saline group. **(c)** a smaller number of apoptotic cells was noted in a sample distal to the sciatic nerve injury in the galantamine group.

TUNEL staining was used to evaluate apoptosis. A positive reaction was found to be minimal in the nuclei of Schwann cells and fibroblasts of the sham group (Fig. 3a). Similar findings were also noted in the proximal segments of the saline and galantamine groups. However, apoptotic cells were increased in number in areas distal to the injury site in the saline and galantamine groups (Fig. 3b and c).

The mean apoptotic index was 5.5±2.0, 40.8±6.7, and 17.9±3.8 in the sham group, saline group, and galantamine group, respectively. The differences among these groups were statistically significant ($p<0.001$) (Table 2 and Fig. 4). For the post hoc comparisons, we found that the apoptotic index of the saline group was statistically significantly higher than that of the sham and galantamine groups ($p<0.001$ and

Table 1. Comparison of the apoptotic index and the thickness of the distal and proximal areas of the nerve in the study groups

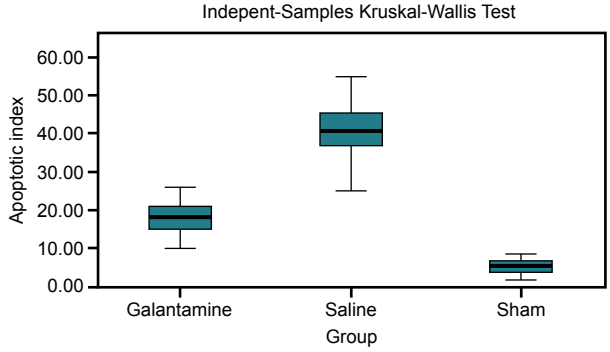
		Sham	Saline	Galantamine	p*
Proximal nerve thickness (µm) (n=0)	Mean±SD	6.4±1.0	6.2±1.0	6.1±1.0	0.573
	Median (IQR)	6.4 (5.8–7.0)	6.2 (5.6–7.0)	6.2 (5.8–6.8)	
Distal nerve thickness (µm) (n=50)	Mean±SD	6.4±1.0	12.8±1.4	9.0±1.1	<0.001
	Median (IQR)	6.4 (5.8–7.0)	12.7 (11.9–13.6)	9.0 (8.3–10.0)	

SD: Standard deviation; IQR: Inter Quantile Range.

Table 2. Comparison of the apoptotic index in the study groups

		Sham	Saline	Galantamine	p*
Apoptotic index (n=30)	Mean±SD	5.5±2.0	40.8±6.7	17.9±3.8	<0.001
	Median (IQR)	5.5 (4.0–7.0)	40.5 (36.8–45.3)	18.0 (15.0–21.0)	

SD: Standard deviation; IQR: Inter Quantile Range.



Total N	90
Test Statistic	79.127
Degrees of Freedom	2
Asymptotic Sig. (2-sided test)	.000

1. The test statistic is adjusted for ties.

Figure 4. Distributions of the apoptotic index.

p<0.001). The apoptotic index of the galantamine group was statistically significantly higher than that of the sham group (p<0.001) (data not shown).

DISCUSSION

Traumatic injuries of peripheral nerves may result in complete loss of function due to the limited ability of neural tissue to regenerate. Some injuries may cause chronic pain, weakened extremities, and a decrease in the quality of life of these patients. Even after long-term therapies, it is difficult to expect a full recovery after serious nerve injuries. Early intervention, whether surgical or pharmacological, has been demonstrated to exert a substantial effect on long-term outcomes.[15] In neurodegenerative diseases and cerebral ischemia, excitotoxicity is the basic mechanism in the process that leads to cell death. Galantamine is a reversible acetylcholinesterase inhibitor used in the treatment of Alzheimer's disease whose neuroprotective role is through inhibition of excitotoxity. Glutamate excitotoxicity is one of the primary mechanisms in neural injury, and galantamine might play an inhibitory role in glutamate-induced cytotoxicity and associated apoptosis. In the present study, we evaluated the effects of galantamine on the peripheral nerve degeneration process by generating experimental SCI in rats. When the distal segments of the injury site were analyzed for degeneration, increased nerve fiber thickness, marked degeneration, and apoptosis was observed in the rats that were given saline solution after the surgical procedure, which was an expected result of nerve compression. However, rats in the galantamine group showed a smaller increase in distal nerve thickness compared with rats in the saline group. In addition, a lower number of apoptotic cells was found in the galantamine group samples compared with the saline group samples. Therefore, galantamine administration after surgery seems to exert a neuroprotective effect on this experimental model of peripheral nerve injury.

Regeneration after injury is a multifactorial process that is influenced by various mechanisms. The biological response to compression includes endoneurial edema, demyelination, inflammation, distal axonal degeneration, fibrosis, new axon growth, remyelination, and thickening of the perineurium and endothelium.[16] In peripheral nerves, neural compression leads to impairment of the microvasculature, a decrease in cell nutrients, and the formation of free radicals, which occurs during reperfusion and leads to lipid peroxidation and membrane damage. Studies have shown that antioxidant and anti-inflammatory agents may be effective in promoting regeneration.[17] In a recent study, boric acid administration after SCI reduced axonal and myelin damage, probably through antioxidant mechanisms.[18] In our experimental model of peripheral nerve compression, galantamine showed a neuroprotective effect, which may have been related to anti-inflammatory mechanisms. Previous studies have shown that suppression of neuroinflammation by acetylcholinesterase inhibitors and galantamine was accompanied by alleviation of inflammation in metabolic syndrome.[19,20] In a recent study, galantamine was shown to reverse early postoperative cognitive deficit by alleviating inflammation and enhancing synaptic transmission in the mouse hippocampus.[21] In our study, galantamine may have suppressed neuroinflammation, and in the process, may have also prevented neural degeneration. Further studies are needed to explain the relationship between inflammatory processes and apoptosis during degeneration and regeneration after traumatic nerve compression.

Conclusion

In this experimental study of sciatic nerve compression, galantamine showed a neuroprotective effect in the peripheral nervous system as has also been observed in the central nervous system. Galantamine is therefore a potential pharma-

cological intervention that can be used to prevent peripheral nerve degeneration.

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Ethics Committee Approval: This study was approved by the Ankara Hospital Ethics Committee (Date: 23.02.2012,, Decision No: 2012\319).

Peer-review: Internally peer-reviewed.

Authorship Contributions: Concept: F.A., E.D.; Design: F.A., E.D.; Supervision: F.A., E.D.; Resource: M.S., R.A.; Data: M.S., R.A.; Analysis: M.S., R.A., D.O.K.; Literature search: M.S., R.A., D.O.K.; Writing: D.B., S.A.; Critical revision: F.A., M.S., D.B., S.A., R.A., D.O.K., E.D.

Conflict of Interest: None declared.

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DENEYSEL ÇALIŞMA - *ÖZ*

Sıçan siyatik sinirinin deneysel kompresyon hasarı sonrası galantaminin periferik sinir dejenerasyonu üzerindeki etkisi

Dr. Fatih Alagöz,[1] Dr. Mert Sahinoglu,[2] Dr. Deniz Billur,[3] Dr. Sevim Aydın,[3] Dr. Rifat Akdağ,[4] Dr. Durmuş Oğuz Karakoyun,[5] Dr. Ergun Daglioglu[1]

[1]Sağlık Bilimleri Üniversitesi Bilkent Şehir Hastanesi, Beyin ve Sinir Cerrahisi Kliniği, Ankara
[2]Selçuk Üniversitesi Tıp Fakültesi, Beyin ve Sinir Cerrahisi Anabilim Dalı, Ankara
[3]Ankara Üniversitesi Tıp Fakültesi, Histoloji ve Embriyoloji Anabilim Dalı, Ankara
[4]Sağlık Bilimleri Üniversitesi Şevket Yılmaz Hastanesi, Beyin ve Sinir Cerrahisi Kliniği, Bursa
[5]Ordu Üniversitesi Tıp Fakültesi, Beyin ve Sinir Cerrahisi Anabilim Dalı, Ordu

AMAÇ: Galantamin, nöroprotektif etkileri ile bilinir ve şu anda Alzheimer hastalığı olan bireylerin tedavisinde kullanılmaktadır. Bu çalışmada da galantaminin yararlı etkilerini test etmek için sıçanlarda deneysel siyatik sinir hasarı (SCI) oluşturduk.

GEREÇ VE YÖNTEM: Otuz erkek Wistar albino sıçanı üç gruba ayrıldı: Sham, SCI + salin ve SCI + galantamin. Anestezi için kullanılan bir intraperitoneal ketamin ve ksilazin karışımının uygulanmasından sonra, siyatik sinir hasarı sıçanların orta uyluk bölgesinde cerrahi klips sıkıştırma ile indüklendi. Ameliyattan sonra tek bir günlük intraperitoneal galantamin dozu yedi gün boyunca uygulandı. Yaralanmadan bir hafta sonra da sinir dokusu kesitleri alındı. Nöral kalınlık ve apoptotik hücre sayılarını değerlendirmek için histopatoloji çalışmaları yapıldı. Galantaminin periferik sinir dejenerasyonu üzerindeki potansiyel yararlı etkisini belirlemek için ışık mikroskobu morfolojik inceleme için kullanıldı.

BULGULAR: Kontrol grubuna kıyasla salin grubundaki yaralanma seviyesinin distalindeki mikrovaskülaritede, sinir lifi kalınlığında ve apoptotik hücre sayısında istatistiksel olarak anlamlı bir artış gözlemledik. Bununla birlikte, sinir lifi kalınlığı ve apoptotik hücre sayısındaki artışlar galantamin grubunda salin grubuna göre daha azdı.

TARTIŞMA: Deneysel modelimizde kullandığımız galantamin, periferik sinir hasarından sonra gelişen dejenerasyon üzerinde koruyucu bir etki göstermektedir.

Anahtar sözcükler: Apopitoz; galantamin; siyatik sinir; travma.

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