EXPERIMENTAL STUDY

Effects of lercanidipine on traumatic spinal cord injury: an experimental study

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ABSTRACT

BACKGROUND: Spinal cord injury is a devastating trauma that leaves survivors at risk for several medical complications throughout their lives. Lercanidipine, a third-generation calcium channel blocker, possesses anti-apoptotic, anti-inflammatory, and antioxidative properties. This study aimed to evaluate the neuroprotective effects of lercanidipine in an experimental spinal cord trauma model.

METHODS: Twenty-one Wistar rats were randomly assigned to three groups. Group 1 (G1) underwent laminectomy. Group 2 (G2) were subjected to trauma following laminectomy. Group 3 (G3) were exposed to trauma following laminectomy and treated with lercanidipine. Lercanidipine was administered intraperitoneally for seven days. Histopathological and immunohistochemical evaluations were conducted.

RESULTS: Regarding Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining, there was no significant difference among the groups. However, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) levels were significantly different across the groups. G2 had significantly higher NF-κB levels compared to G1 and G3.

CONCLUSION: Lercanidipine, a third-generation calcium channel blocker, is effective against inflammatory responses induced in spinal cord injury. Further studies are required to determine its capability in preventing apoptosis or improving functional recovery. To the best of our knowledge, this study is the first in the literature to examine the neuroprotective effects of lercanidipine on spinal cord injury.

Keywords: Lercanidipine; neuroprotective effect; spinal cord injury; spinal trauma.

INTRODUCTION

Spinal cord injury (SCI) is a devastating trauma that leaves survivors at risk for several medical complications throughout their lives. Though SCI has historically occurred most frequently in young adults, the past few decades have shown an increasing incidence of SCI in older populations as well, which increases its burden on individuals and society.[1]

Several mechanisms causing tissue injury in SCI have been targeted in the search for an effective therapeutic agent, yet there is no agent universally accepted as useful in daily practice. Lercanidipine, a third-generation calcium channel blocker (CCB), possesses anti-apoptotic, anti-inflammatory, and antioxidative properties. Compared to similar CCBs, it has a longer duration of action and greater lipophilicity.[2,3] Its stable pharmacokinetics, minimal side effects, high tolerability, and safety profile make it a suitable candidate for use in a wide variety of populations.[3]

Cite this article as: Türk Ç, Bahadır S, Camlar M, Gürel Ç, Buhur A, Kuşçu GC. Effects of lercanidipine on traumatic spinal cord injury: an experimental study. Ulus Travma Acil Cerrahi Derg 2024;30:73-79.

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Ulus Travma Acil Cerrahi Derg 2024;30(2):73-79 DOI: 10.14744/tjtes.2024.03660
Submitted: 27.09.2023 Revised: 29.12.2023 Accepted: 10.01.2024 Published: 02.02.2024

The aim of this study was to evaluate the neuroprotective effects of lercanidipine in an experimental spinal cord trauma model.

MATERIALS AND METHODS

A total of 21 adult Wistar albino rats, each weighing 350 g, were used in this study. Approval for this study was obtained from the Animal Research Ethics Committee of Ege University (approval number 2022-113) and it was conducted in accordance with the Guide for the Care and Use of Laboratory Animals in the Animal Laboratory of Ege University. All animals were housed in separate cages under a standard 12-hour light/dark cycle at 21˚C-22˚C, with ad libitum access to food and water.

Animals were randomly assigned to the following groups, each containing seven rats: Group 1 (G1) underwent laminectomy. Group 2 (G2) was exposed to trauma following laminectomy. Group 3 (G3) was exposed to trauma following laminectomy and treated with lercanidipine (0.5 mg/kg, i.p.). G3 received lercanidipine 30 minutes after the trauma and once daily for seven days. There are no studies in the literature where lercanidipine was examined in a spinal trauma model. Therefore, we based the lercanidipine doses (0.5 mg/kg, i.p.) for our study on an article we found in the literature that describes its use in a stroke model.[4]

Injury Procedure

Following the subcutaneous administration of a prophylactic dose of 15 g/kg cefazolin sodium one hour before surgery, anesthesia was induced using an intraperitoneal injection of a ketamine hydrochloride (Ketalar, Pfizer) and xylazine (Rompun 2%, Bayer) combination (5 mg/kg and 10 mg/kg, respectively). After making a dorsal midline incision approximately between the T5-T9 levels, paravertebral muscles were dissected to expose thoracic vertebrae. Then, total laminectomies at T6, T7, and T8 were performed, leaving the dura intact. In groups 2 and 3, SCI was induced using a weight-drop technique involving a 10 g rod dropped through a 5-cm guide tube positioned perpendicular to the center of the spinal cord.[5] The trauma produced a dorsal surface SCI with an impact force of 50 g/cm^2. Rats in Group 1 were not exposed to trauma. Subsequently, the muscles and skin were sutured, and the animals were allowed to recover in temperature- and humidity-controlled chambers and were housed for a week.

Neurobehavioral Examination

Hind limb motor function was assessed using Tarlov's classification [6]: 0 (no voluntary hind limb function), 1 (poor hind limb motor function), 2 (joint motion present but unable to stand), 3 (able to stand and walk), and 4 (complete recovery). The absence of muscle tone and contractions was defined as paraplegia. This assessment was performed at 1, 24, and 48 hours, and again at one week following SCI. All rats were sacrificed on day seven after SCI.[7,8]

Histopathological Examination

At the end of one week, all animals were anesthetized with an intraperitoneal injection of ketamine (40 mg/kg) and xylazine (4 mg/kg), and perfused with 200 ml of 4% formaldehyde in 0.1M phosphate-buffered saline (PBS). Formalin-fixed spinal cord samples were embedded in paraffin blocks, sectioned at 5 µm, and stained with hematoxylin and eosin for histologic studies.

Immunohistochemical Examination

For immunohistochemical evaluation, paraffin-embedded blocks were cut into 5 µm sections. These sections were dewaxed and rehydrated following routine immunohistochemical protocols. They were then washed with distilled water and 0.1M PBS for 10 minutes, followed by treatment with 2% trypsin (Sigma-Aldrich, USA) in 50 mM Tris buffer (pH 7.5) at 37˚C for 15 minutes. To inhibit endogenous peroxidase activity, sections were outlined with a Dako pen (Dako, Glostrup, Denmark) and incubated in a solution of 3% H_2O_2 for 15 minutes.

Next, the sections were incubated with anti-nuclear factor kappa beta (NF-κB) primary antibodies (1/100) for 24 hours at 4˚C in a humid chamber. Sections were then incubated with a biotinylated secondary antibody (Zymed Histostain-Plus Peroxidase kit, 85-9043, Zymed Laboratories, San Francisco, California, USA), and subsequently, with streptavidin conjugated to horseradish peroxidase (Zymed Histostain-Plus Peroxidase kit, 85-9043, Zymed Laboratories, San Francisco, California, USA), prepared according to the manufacturer's instructions. To reveal immunolabeling, sections were incubated with 3,3'-diaminobenzidine (DeadEnd Colorimetric TUNEL system, Promega, Madison, Wisconsin, USA), prepared as per the manufacturer's instructions. All dilutions and washes between stages were with PBS.

Prepared sections were counterstained with Mayer's hematoxylin (Zymed Laboratories), and rinsed with tap water. As the final step, sections were dehydrated through a graded ethanol series, cleared in xylene, and mounted with Entellan (Merck, Darmstadt, Germany). Sections were photographed using an Olympus C-5050 digital camera mounted on an Olympus BX51 microscope. The number of positive cells was assessed by three blinded histologists who evaluated at least 100 cells per 10 viewfields of tissue sections at 20x magnification.

Semi-quantitative analysis was used to assess the immunoreactivity of the studied proteins. Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) immunohistochemical staining was evaluated using a modified histoscore (H-score). To calculate the H-score, semi-quantitative assessments of staining intensity (graded as 0 [non-staining], 1 [weak], 2 [moderate], and 3 [strong]) and the percentage of positive cells were performed. Possible scores ranged from 0 to 300. The expression level of each component was categorized as low or high according to the median value of the H-score.

Table 1. Statistical analysis of hind limb motor function at designated time points among groups

Time After Procedure	G1	G2	G3	p*	Post-hoc p**		
	m (IQR)	m (IQR)	m (IQR)		G1-G2	G1-G3	G2-G3
1 hour	4.0 (0.0)	0.0 (1.0)	0.0 (1.0)	0.001	0.001	0.001	1.000
24 hours	4.0 (0.0)	0.0 (1.0)	0.0 (1.0)	0.001	0.001	0.001	1.000
48 hours	4.0 (0.0)	0.0 (1.0)	0.0 (1.0)	0.001	0.001	0.001	1.000
1 week	4.0 (0.0)	0.0 (1.0)	1.0 (0.0)	0.001	0.001	0.001	0.298

IQR: Interquartile range; m: Median. *Kruskal-Wallis Test. **Mann-Whitney U test using Bonferroni Correction.

Terminal Deoxynucleotidyl Transferase dUTP Nick-End Labeling (TUNEL) Assay

Apoptosis was confirmed by the TUNEL assay. Following deparaffinization in xylene, the sections were rehydrated through a graded ethanol series. Then sections were then covered with a 20 mg/mL of proteinase K solution and rinsed with tap water. Endogenous peroxidase activity was inhibited with 3% hydrogen peroxide, followed by another rinse with tap water. The sections were then treated with terminal deoxynucleotidyl transferase enzyme in a humidified atmosphere at 37°C for 60 minutes. Subsequently, they were submerged in a prewarmed, working-strength stop/wash buffer at room temperature for 10 minutes and incubated with anti-streptavidin peroxidase for 45 minutes. Staining and counterstaining were performed with 3,3'-diaminobenzidine and Mayer's hematoxylin, respectively. Apoptotic cells stained with TUNEL were counted in the cross-section of each specimen by two independent, blinded observers under a light microscope at 40x magnification. The apoptotic index was defined as the apoptotic cell count per section (total apoptotic cell count/100). Cells in areas with necrosis, poor morphology, or at the margins of sections were not analyzed.

Statistical Analysis

Descriptive statistics are reported as medians, with interquartile range values. The distribution pattern of variables was investigated with the Shapiro-Wilk test. Comparison of data between groups was performed using the Kruskal-Wallis test. To evaluate pairwise differences, the Mann-Whitney U test was performed, with Bonferroni correction to adjust for multiple comparisons. A p-value < 0.05 was considered significant, with a 95% confidence interval. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software version 21.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Neurobehavioral Examination

Hind limb motor function was assessed using Tarlov's classification. All animals in G1 consistently scored 4 at all time points (1 hour, 24 hours, 48 hours, and 1 week after SCI). In G2, four animals consistently scored 0, while three had a score of 1 across all evaluations. In G3, four animals scored 0, and three scored 1, a pattern that persisted at 1 hour, 24 hours, and 48 hours, while at one week, five animals scored 1, and two scored 0. Overall, hind limb motor function exhibited a significant difference between the groups (p=0.001). G1 consistently had a significantly higher Tarlov motor score compared to both G2 and G3 at all time points (p=0.001 for all). However, there was no significant difference between G2 and G3 (p=1.00 at 1, 24, and 48 hours; p=0.298 at 1 week). The findings are summarized in Table 1.

Histopathological Examination

Pia mater, gray matter, and white matter structures were his-

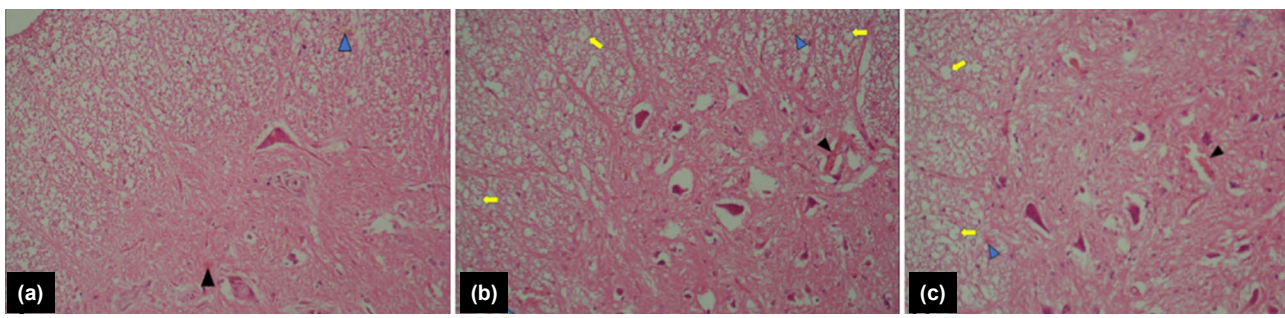

Figure 1. Representative histologic sections of the spinal cord after hematoxylin and eosin staining in the three experimental groups. **(a)** Diffuse hemorrhagic foci noted in both gray (blue arrowhead) and white (black arrowhead) matter in the control group; **(b)** In the trauma group, hemorrhages in the gray and white matter were accompanied by axonal edema (yellow arrow); **(c)** Axonal edema was less in the Trauma + Lercanidipine group than in the trauma group. (Hematoxylin and eosin, x20).

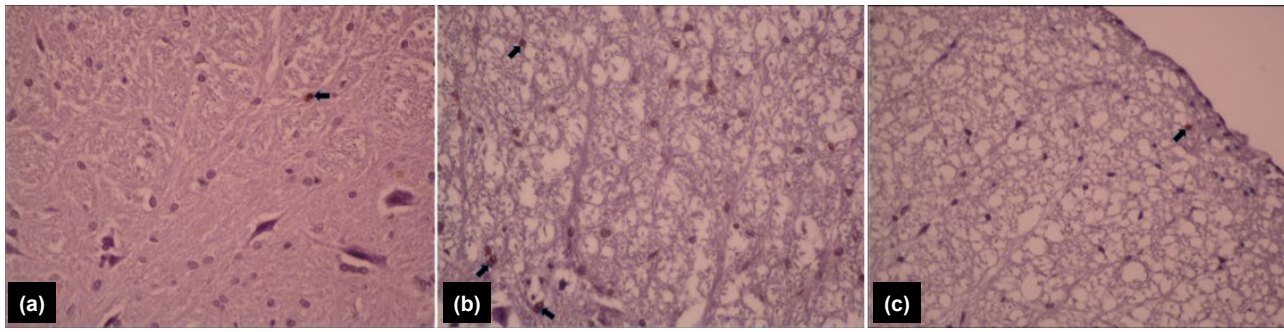

Figure 2. Representative histologic sections of the TUNEL staining in the three experimental groups. **(a)** Control group, **(b)** Trauma group, **(c)** Trauma + Lercanidipine group. The number of apoptotic cells (indicated by black arrows) was higher in the trauma group than in the other groups, but this was not statistically significant. (Diaminobenzidine, x40).

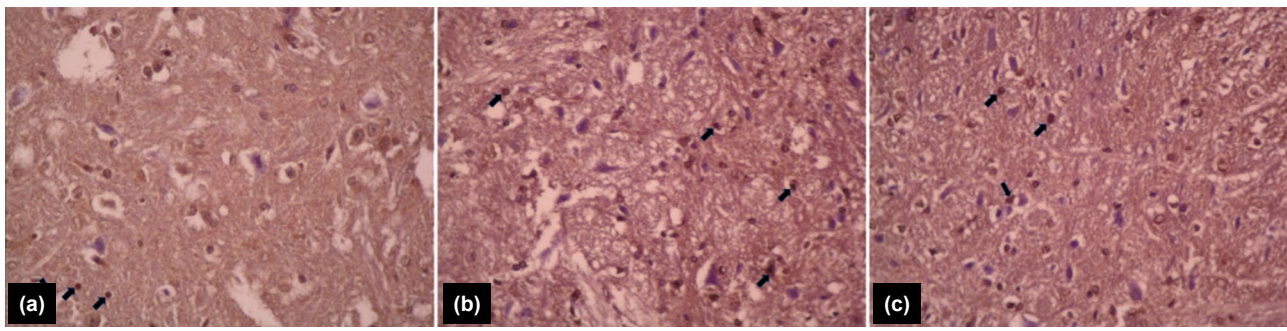

Figure 3. Representative histologic sections of the NF-κB staining in the three experimental groups. **(a)** Control group, **(b)** Trauma group, **(c)** Trauma + Lercanidipine group. The number of cells expressing NF-κB (indicated by black arrows) and the expression intensity were significantly higher in G2 compared to the other groups. (NF-κB immunohistochemistry, x20).

tologically evaluated and found to be intact in each group.

Diffuse hemorrhagic foci were observed in the white matter in G1. In contrast, the gray matter in G2 contained hemorrhagic foci. In G3, hemorrhagic foci were present in both gray and white matter. Axonal edema was observed in G2 and G3, with a greater abundance in G2 (Fig. 1).

Immunohistochemical Examination

Regarding TUNEL staining (Fig. 2), there was no significant difference among the groups (p=0.139).

On the other hand, NF-κB (Fig. 3) showed significant differences among the groups (p=0.009), with post-hoc tests revealing that G2 had significantly higher NF-κB levels compared to G1 and G3 (p=0.022 and p=0.027, respectively).

The findings are summarized in Table 2.

DISCUSSION

In this study, lercanidipine showed different effects on different aspects of SCI. Regarding functional recovery, lercanidipine was not effective during a 1-week observation period. However, it demonstrated significant anti-inflammatory properties, as evidenced by lower NF-κB levels compared to the trauma group throughout this 1-week study period. Interestingly, apoptosis levels were similar across all groups.

Injury in spinal cord trauma occurs in two phases. The unpreventable primary injury occurs at the time of trauma, directly

Table 2. Statistical analysis for TUNEL and NF-κB among groups, including post-hoc test results where applicable

	G1	G2	G3	P*	Post-hoc P**		
	m (IQR)	m (IQR)	m (IQR)		G1-G2	G1-G3	G2-G3
TUNEL	2.0 (3.0)	5.0 (5.0)	2.0 (2.0)	0.139	-†	-†	-†
NF-κB	25.0 (6.0)	37.0 (7.0)	26.0 (9.0)	0.009	0.022	1	0.027

IQR: Interquartile range; m: Median; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; TUNEL: Terminal Deoxynucleotidyl Transferase dUTP Nick-End Labeling. *Kruskal-Wallis Test. **Mann-Whitney U test using Bonferroni Correction. † Post-hoc test not applicable due to non-significance in multigroup analysis.

destroying neural tissues and other elements. This primary insult triggers a complex cascade of events that result in further tissue damage, spreading over days to months, depending on the extent of the trauma. Known as the secondary injury phase, this phase is particularly critical in determining the ultimate outcome of spinal cord trauma.[9] Events during the secondary injury include 1) overstimulation of glutamate receptors leading to increased intracellular calcium levels, which can cause necrosis as early as 4 hours following the trauma; 2) an inflammatory response triggered by hemorrhage, edema, ischemia, and necrosis; and 3) apoptosis, leading to axonal injury and neuronal cell loss, which depends on the balance between tissue damage and tissue repair.[9,10]

The extent of secondary injury is a crucial factor in determining outcomes for SCI patients. Consequently, it has become the primary target of treatment efforts. Several chemicals, ranging from immunosuppressive to anti-inflammatory agents, have been studied as therapeutic agents.[11,12] Methylprednisolone, a strong anti-inflammatory agent that was once thought to be effective and recommended in guidelines, was later found to be ineffective in subsequent studies. Considering the severe complications associated with high-dose steroids, their use has been widely abandoned.[1]

Increased intracellular calcium (Ca2+) levels play a major role in axonal injury in white matter.[13] Similar to excitation-contraction coupling observed in skeletal muscles, depolarizations activate L-type Ca2+ channels. This activation results in an excessive release of Ca^{2+} under pathological conditions, which, in turn, may progress to cellular death.[12] The extent of axonal damage has been shown to be limited by chelating intracellular Ca^{2+}.[13] It is thought that the endoplasmic reticulum (ER) is the source of intracellular Ca^{2+} during injury.[12]

Lercanidipine is an L-type CCB with anti-inflammatory and antioxidant properties.[2,4,14] It has been shown to have neuroprotective effects in conditions such as epilepsy,[3] ischemia,[4,15] and hypertensive retinopathy.[16] Its anti-inflammatory properties have been demonstrated to be comparable to diclofenac sodium.[2] Since the sole blocking of Ca^{2+} channels has not been found to be neuroprotective, lercanidipine's effect is mostly attributed to its anti-apoptotic, anti-inflammatory, and antioxidant effects.[4,15] To the best of our knowledge, its neuroprotective effects in spinal cord injury, either traumatic or not, have not been studied before.

Caspase-dependent apoptosis of oligodendrocytes in white matter reaches its maximum intensity at one week following injury.[17] In contrast, neurons are more susceptible to increased calcium, with maximum apoptosis occurring at 8 hours. After 24 hours, no neuronal apoptosis occurs in rats.[18,19] In rabbits, it has been demonstrated that apoptotic neuronal cells are removed by autophagy by the seventh day.[20] In this study, TUNEL staining did not differ among the groups. More interestingly, TUNEL-positive apoptosis was similar in both the sham and trauma groups. There are some possible explanations for this discrepancy.

Firstly, while our intention was to quantify apoptosis, it is crucial to note that new cell death mechanisms, beyond necrosis and apoptosis, have been identified.[21] Additionally, heterogeneous cell-death mechanisms are implicated in neuronal loss in spinal cord injury.[19] For example, in the central nervous system, cellular injury by oxygen radicals activates Poly (ADP-ribose) polymerase (PARP) enzymes. Although the PARP enzyme family is responsible for cell repair, their overactivation may cause cellular death.[19] In PARP-mediated apoptosis, deoxyribonucleic acid (DNA) fragmentation does not occur.[9] Since caspase involvement and DNA fragmentation do not occur in all cell death mechanisms, TUNEL staining may not detect these types of cell deaths.[19,22] It is theoretically possible that caspase-independent cellular death predominated in our samples, which would not be detected by TUNEL staining. However, considering other reports showing significant TUNEL-positive apoptosis in SCI, we believe this to be possible, but unlikely.[23]

Secondly, while apoptosis in white matter reaches its maximum level on the seventh day, peak apoptosis in gray matter occurs at the sixth hour, with no apoptosis observed after 24 hours. Although we sacrificed the animals on the seventh day to observe maximum injury, as seen in rabbits, a similar process may occur in rats, where dead neurons are autophagized by the seventh day following trauma. During microscopic evaluation, unintentional bias in sampling more gray matter than white matter might have influenced the quantification of apoptosis, which could have been present in the unsampled sections.

Finally, while it can be speculated that the applied trauma was not severe enough to cause apoptosis, the significant functional deterioration and presence of inflammation in the trauma groups prove that the trauma was capable of producing SCI.

Another factor that significantly contributes to neuronal injury and death is inflammation.[4] It is initiated and regulated by specific signaling molecules, particularly proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), in response to spinal cord trauma.[9] Proinflammatory cytokines, such as TNF-α and IL-1, cause NF-κB activation.[24] NF-κB is a transcription factor that regulates several cellular events, including, but not limited to, inflammation and apoptosis. Decreased levels of NF-κB are observed in conditions of reduced inflammation and apoptosis.[25,26] Most studies consider decreased NF-κB level as a sign of attenuated inflammation.[25] However, since it may play an anti-apoptotic or pro-apoptotic role depending on the conditions, an increase in NF-κB may also be observed in scenarios of decreased apoptosis.[5,27] Consequently, in a few studies that observe its inverse relationship with TUNEL staining, authors consider it an indicator of increased apoptotic activity.[5] In this study, NF-κB levels were significantly higher in the

trauma group compared to others. The number of anti-NF-κB stained cells did not differ between the sham and treatment groups. As we believe that apoptosis, at least through a caspase-dependent mechanism, did not occur as expected in our study, we think that NF-κB levels reflect inflammation, as most studies in the literature suggest. Our findings support other studies where lercanidipine exerts anti-inflammatory effects.

Although both groups exposed to trauma had significantly worse functional scores at all time points compared to the sham group, there was no significant difference between them. However, it should be noted that a slight increase in functional scores was observed in the treatment group by the first week, although it was not statistically significant. This raises the question of whether a significant change could be observed if they were followed for a longer period or if a different dosage was used.

Nevertheless, this study is not without limitations. A major limitation includes the mixed findings in different aspects of SCI, which may be attributed to sampling error, a short observation period, or insufficient dosage. With that said, this study failed to provide a definitive answer to the question of whether lercanidipine has an effect on apoptosis in SCI or not.

CONCLUSION

In summary, our study indicates that lercanidipine, a third-generation calcium channel blocker, exhibits promising anti-inflammatory effects in the context of SCI. However, the mixed results observed across various aspects of SCI in our study, which may be attributable to factors such as sampling error, a relatively short observation period, or an insufficient dosage, highlight the necessity for further research. While our findings suggest potential efficacy in mitigating inflammatory responses, definitive evidence of lercanidipine's effectiveness in preventing apoptosis or enhancing functional recovery requires more extensive research. Our study provides a foundation for future inquiries, advocating for a deeper exploration of lercanidipine's neuroprotective capabilities and its potential application in clinical treatments for SCI.

Ethics Committee Approval: This study was approved by the Ege University, Ethics Committee (Date: 28.12.2022, Decision No: 2022-113).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: Ç.T.; Design: Ç.T., M.Ç.; Supervision: M.Ç.; Materials: Ç.G.; Data collection and/or processing: Ç.T., C.G., A.B., G.C.U.; Analysis and/or interpretation: Ç.T., C.G., A.B., G.C.U.; Literature search: Ç.T., M.Ç.; Writing: Ç.T., M.Ç.; Critical review: S.B.

Conflict of Interest: None declared.

Financial Disclosure: The author declared that this study has received no financial support.

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DENEYSEL ÇALIŞMA - *ÖZ*

Lerkanidipinin travmatik spinal kord hasarına etkisi: Deneysel çalışma

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AMAÇ: Omurilik yaralanması, hayatta kalanları yaşamları boyunca çeşitli tıbbi komplikasyon riski altında bırakan yıkıcı bir travmadır. Lerkanidipin, anti-apoptotik, anti-enflamatuvar ve anti-oksidatif özelliklere sahip üçüncü nesil bir kalsiyum kanal blokeridir. Bu çalışmanın amacı, deneysel omurilik travması modelinde lerkanidipinin nöroprotektif etkilerini değerlendirmektir.

GEREÇ VE YÖNTEM: 21 adet Wistar sıçan rastgele 3 gruba ayrıldı. Grup 1'e (G1) laminektomi uygulandı. Grup 2 (G2) ise laminektomi sonrası travmaya maruz kaldı. Laminektomi sonrası travmaya maruz kalan Grup 3 (G3) ise lerkanidipin ile tedavi edildi. Lerkanidipin intraperitoneal olarak 7 gün süreyle uygulandı. Histopatolojik ve immünohistokimyasal değerlendirmeler yapıldı.

BULGULAR: TUNEL boyama açısından gruplarda anlamlı farklılık görülmedi. Öte yandan NF-κβ gruplar arasında anlamlı derecede farklıydı. G2, G1 ve G3'e kıyasla önemli ölçüde daha yüksek NF-κβ seviyelerine sahipti.

SONUÇ: Üçüncü kuşak bir kalsiyum kanal blokeri olan lerkanidipin, omurilik yaralanmasında oluşan enflamatuvar yanıtlara karşı etkilidir. Apoptozu önleyip önlemediği veya fonksiyonel iyileşmeyi iyileştirip iyileştirmediği daha ileri çalışmalara ihtiyaç duyar. Bildiğimiz kadarıyla lerkanidipinin omurilik yaralanması üzerindeki nöroprotektif etkilerini inceleyen bu çalışma literatürde ilk olma özelliğini taşımaktadır.

Anahtar sözcükler: Lerkanidipin; nöroprotektif etki; omurilik yaralanması; spinal travma.

Ulus Travma Acil Cerrahi Derg 2024;30(2):73-79 DOI: 10.14744/tjtes.2024.03660