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Effects of Felbamate on Tissue Caspase-3 Levels, Histopathology, and Neurological Function in Rats with Early Spinal Cord Ischemia-Reperfusion Injury

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ABSTRACT

AIM: To evaluate the potential neuroprotective effect of felbamate in a rat model of spinal cord ischemia-reperfusion injury.

MATERIAL and METHODS: Twenty-one male Wistar albino rats were randomly assigned to three groups (n=7 each): control, ischemia, and felbamate-treated. Transient spinal cord ischemia was induced by abdominal aortic occlusion for 20 minutes, followed by reperfusion. Felbamate was administered via a nasogastric tube immediately after reperfusion at a dose of 20 mg/kg. Twenty-four hours after surgery, tissue caspase-3 levels were measured using an enzyme-linked immunosorbent assay, spinal cord sections were evaluated histopathologically using a semiquantitative composite injury score, and neurological function was assessed using the modified Tarlov scoring system.

RESULTS: Tissue caspase-3 levels differed significantly across the three groups (ANOVA, F=205.19, p<0.001). Compared with the ischemia group, the felbamate-treated group displayed lower caspase-3 levels and reduced histopathological injury. Overall histopathological injury scores also differed significantly across the groups (Kruskal-Wallis test, p<0.001). Scores were higher in the ischemia group than in the control group and lower in the felbamate-treated group than in the ischemia group, although they remained higher than those in the control group. Neurological outcomes followed the same pattern. Mean modified Tarlov scores were 5.00 in the control group, 0.86 in the ischemia group, and 2.14 in the felbamate-treated group, with all pairwise comparisons reaching statistical significance (p<0.001).

CONCLUSION: Felbamate was associated with reduced apoptosis-related signaling, less severe histopathological damage, and improved early neurological function after experimental spinal cord ischemia-reperfusion injury.

KEYWORDS: Felbamate, Spinal cord ischemia-reperfusion injury, Caspase-3, Histopathology, Neuroprotection, Rat model

ABBREVIATIONS: ANOVA: Analysis of variance, ELISA: Enzyme-linked immunosorbent assay, GABA: Gamma-aminobutyric acid, H&E: Hematoxylin and eosin, SCIRI: Spinal cord ischemia-reperfusion injury, HRP: Horseradish peroxidase, I/R: Ischemia-reperfusion, IQR: Interquartile range, NMDA: N-methyl-D-aspartate, SD: Standard deviation

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■ INTRODUCTION

The spinal cord, extending from the foramen magnum to the filum terminale within the vertebral canal, plays a critical role in transmitting neural signals between the brain and the body while also serving as the anatomical origin and conduit of spinal nerve roots (2). Spinal cord injury secondary to ischemia may occur in a variety of clinical settings, including trauma, tumors, hemorrhage, and thoracoabdominal surgical procedures. Depending on the severity of injury, sensory, motor, and autonomic dysfunction may develop.

Spinal cord injury may result not only from the initial ischemic insult, but also from the subsequent reperfusion period, during which restoration of blood flow leads to reoxygenation and triggers a cascade of secondary injury mechanisms. Excessive production of reactive oxygen species, excitotoxicity, inflammation, and apoptosis all contribute to further tissue damage during this phase, which is commonly referred to as ischemia-reperfusion (I/R) injury (5).

Globally, the incidence of spinal cord injury has been reported to range from 10.4 to 83 cases per million population, depending on the underlying etiology and regional epidemiology (18). Despite extensive investigation, there is still no universally accepted treatment strategy for spinal cord injury caused by trauma, tumors, or related conditions (7). Neuroprotection thus remains a major focus of experimental and translational research, particularly in the setting of spinal cord I/R injury (3,8,16).

Felbamate (2-phenyl-1,3-propanediol dicarbamate; Felbatol®, 600-mg tablet; Meda Pharma S.P.A.) is an antiepileptic drug used as adjunctive therapy for partial seizures in adults and children older than 12 years (13). Its pharmacological effects involve multiple mechanisms within the central nervous system, most notably the inhibition of excitatory neurotransmission through the blockade of pathways mediated by the N-methyl-D-aspartate (NMDA) receptor, as well as additional effects on gamma-aminobutyric acid (GABA)-mediated and voltage-dependent signaling (13,14). Previous experimental studies have suggested that felbamate may exert neuroprotective effects under hypoxic and traumatic conditions, raising the possibility that it may also attenuate I/R-related spinal cord injury (23-25).

Apoptosis is one of the principal mechanisms contributing to delayed neuronal injury after ischemia, and caspase-3 activation is widely regarded as a reliable marker of apoptotic cell death in experimental spinal cord injury models (6,17). In addition to biochemical markers, histopathological alterations and the assessment of neurological function provide important complementary evidence regarding the severity of tissue injury and the extent of recovery after spinal cord ischemia.

The present study aims to evaluate the potential protective effects of felbamate in a rat model of spinal cord I/R injury. These effects were assessed biochemically through measuring tissue caspase-3 levels, functionally through neurological examination, and histopathologically through light microscopic evaluation of spinal cord tissue.

■ MATERIAL and METHODS

Ethical Approval

All experimental procedures were approved by Nesa Experimental Animal Ethics Committee (Approval No. 026, dated January 5, 2024) and were conducted in accordance with the European Communities Council Directive (2010/63/EU) on the protection of animals used for scientific purposes.

Animals and Study Design

A total of 21 male Wistar albino rats weighing 280–300 g were included in this experimental study. The animals were randomly allocated to three groups, with seven rats in each group.

Group I (control/sham group, n=7): Sham laparotomy was performed without aortic occlusion or drug administration. After euthanasia, an L2–L4 laminectomy was performed, and normal spinal cord tissue samples were obtained.

Group II (ischemia group, n=7): Transient spinal cord ischemia was induced through clamping the abdominal aorta for 20 minutes, after which the clip was removed to allow reperfusion.

Group III (felbamate-treated group, n=7): After 20 minutes of aortic occlusion and subsequent reperfusion, felbamate was administered via a nasogastric tube as a single dose of 20 mg/kg. The dose was selected according to clinically relevant antiepileptic dosing regimens.

Anesthesia, Surgical Procedure, and Postoperative Care

All surgical procedures were performed in accordance with previously described experimental standards (29). The animals were housed under controlled environmental conditions at 18–21°C with a 12-hour light–dark cycle, and they had free access to standard chow and water.

Anesthesia was induced with intramuscular ketamine (70 mg/kg; Ketalar, Parke Davis Eczacıbaşı, Türkiye) and xylazine (5 mg/kg; Rompun, Bayer, Türkiye). An adequate depth of anesthesia and spontaneous respiration were maintained throughout the procedure. Core body temperature was monitored using a digital rectal thermometer and maintained at 37°C with heating pads.

Each rat was placed in the supine position and prepared under aseptic conditions. Following skin antisepsis, a midline abdominal incision of approximately 2 cm was made, and the abdominal aorta was exposed through a transperitoneal approach. Heparin (150 U/kg; Nevparin, Mustafa Nevzat, Türkiye) was administered intravenously 5 minutes before aortic clamping for anticoagulation.

Under an operating microscope, the abdominal aorta was occluded for 20 minutes approximately 1 cm distal to the origin of the renal arteries using an aneurysm clip with a closing pressure of 70 g (Yaşargil FE721; Aesculap, Germany). At the end of the occlusion period, the clip was removed and reperfusion was confirmed visually by restoration of blood flow. Direct spinal cord perfusion monitoring was not performed. The abdominal wall was closed in layers using 2-0 silk sutures. In

the felbamate-treated group, the drug was administered immediately after clip removal via a nasogastric tube at a dose of 20 mg/kg.

Two hours after surgery, once anesthesia had worn off and spontaneous movements had resumed, neurological examinations were performed. Thereafter, the animals were allowed free access to food and water. In rats that developed neurogenic bladder dysfunction, Credé's maneuver was performed at least twice daily to ensure bladder emptying. Twenty-four hours after surgery, all rats underwent repeat neurological assessments and were subsequently euthanized with an intraperitoneal overdose of pentobarbital (200 mg/kg; Nembutal, Oak Pharmaceuticals, Lake Forest, IL, USA). The exact elapsed time between euthanasia and tissue harvesting was not prospectively recorded in minutes; however, the L2–L4 spinal cord segments were harvested immediately after confirmation of euthanasia for biochemical and histopathological analyses.

Measurement of Tissue Caspase-3 Levels

Tissue caspase-3 levels were measured using an enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (Cusabio, Hubei, China; 6, 17). This assay is based on a quantitative sandwich enzyme immunoassay technique. Briefly, standards and tissue samples were added to microplate wells precoated with caspase-3-specific antibodies, allowing the caspase-3 present in the samples to bind to the immobilized antibodies. After removal of unbound material, a biotin-conjugated caspase-3-specific detection antibody was added, followed by the addition of avidin-conjugated horseradish peroxidase. After repeated washes, the substrate solution was added, and color development proceeded in proportion to the amount of bound caspase-3. Optical density was measured at 450 nm, and tissue caspase-3 concentrations were calculated using a calibration curve generated from standards of known concentration. Results were expressed in ng/mL.

Histopathological Evaluation

For histopathological analysis, spinal cord specimens were immersed in 10% neutral buffered formalin immediately upon extraction, without any intervening storage or intentional delay. Routine histological processing was initiated within 24 hours. The tissue specimens were then embedded in paraffin, cut into 5-µm-thick sections, and stained with hematoxylin and eosin. Histopathological evaluation was performed by a neuropathologist blinded to group allocation and the study design. Five distinct fields within the gray matter were examined using a 40× objective lens. A semiquantitative histopathological scoring system with scores ranging from 0 to 3 was used to grade tissue injury in all samples. The following six parameters were assessed: hemorrhage, congestion, edema, necrosis, neuronal degeneration, and inflammatory cell infiltration. Each parameter was scored as follows: 0—absent; 1—mild; 2—moderate; and 3—severe. For each animal, the overall histopathological injury score was calculated as the mean of the six parameter scores (9).

Neurological Assessment

Hindlimb motor function was evaluated 24 hours after the procedure using the modified Tarlov scoring system (12,20,26; Table I). All neurological examinations were performed by a physician blinded to group allocation.

Statistical Analysis

Outcome assessments and statistical analyses were performed by investigators blinded to group allocation. Statistical analyses were performed using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA). Tissue caspase-3 levels were expressed as the mean ± standard deviation (SD) and compared across the groups using one-way analysis of variance (ANOVA), followed by Tukey's honestly significant difference test for post-hoc pairwise comparisons. Overall histopathological injury scores were presented as median (interquartile range [IQR]) and analyzed using the Kruskal–Wallis test, followed by Conover's nonparametric multiple comparison test when an overall significant difference was identified. Modified Tarlov scores were summarized descriptively as mean ± SD for consistency of presentation, whereas between-group comparisons were performed using the Kruskal–Wallis test, followed by Conover's nonparametric multiple comparison test. A p-value<0.05 was considered statistically significant.

■ RESULTS

Tissue Caspase-3 Levels

Tissue caspase-3 levels differed significantly across the study groups. The ischemia group showed a marked increase in caspase-3 levels compared with the control group, indicating enhanced apoptotic activity after SCIRI. In the felbamate-treated group, caspase-3 levels were significantly lower than in the ischemia group, but did not return to control levels. One-way ANOVA demonstrated a significant overall difference across the groups ($F=205.19$, $p<0.001$), and Tukey's post-hoc test confirmed significant differences between the control and ischemia groups and between the ischemia and felbamate-treated groups ($p<0.001$ for both comparisons; Figure 1 and Table II).

Table I: Modified Tarlov Scoring System

Score	Definition
0	Complete paraplegia; no hind-limb movement
1	Minor joint movements
2	Major joint movements
3	Able to stand
4	Able to walk
5	Able to climb a 20° inclined plane

Histopathological findings

Light microscopic examination of spinal cord sections from the control group showed preserved, normal histological architecture (Figure 2A). In the ischemia group, diffuse hemorrhage and marked congestion were observed in the gray matter, together with extensive edema and necrosis involving both gray and white matter. Inflammatory cell infiltration, including polymorphonuclear leukocytes, lymphocytes, and plasma cells, was also present in the injured areas. Neuronal pyknosis accompanied by cytoplasmic eosinophilia and loss of normal cellular architecture was also evident in this group (Figure 2B). In the felbamate-treated group, spinal cord tissue was relatively preserved compared with the ischemia group, with less pronounced hemorrhage, congestion, edema, necrosis, and inflammatory cell infiltration (Figure 2C).

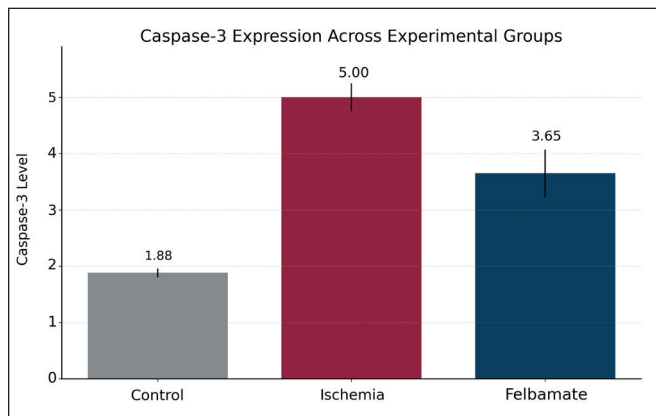


Figure 1: Tissue caspase-3 levels in the control, ischemia, and felbamate-treated groups. Bars represent mean values, and error bars indicate standard deviation (SD). Tissue caspase-3 concentrations were measured by enzyme-linked immunosorbent assay and are expressed in ng/mL. Overall group differences were significant (one-way analysis of variance [ANOVA], $F=205.19$, $p<0.001$). Tukey's post-hoc test showed significantly higher caspase-3 levels in the ischemia group than in the control group and significantly lower levels in the felbamate-treated group than in the ischemia group ($p<0.001$ for both comparisons).

Overall histopathological injury scores differed significantly across the three groups (Kruskal–Wallis test, $p<0.001$). They were significantly higher in the ischemia group than in the control group ($p<0.001$), while the felbamate-treated group showed significantly lower scores than the ischemia group ($p<0.001$). However, histopathological injury scores in the felbamate-treated group remained significantly higher than those in the control group ($p=0.007$; Figure 3 and Table II).

Neurological assessment

Neurological function was assessed 24 hours after the procedure using the modified Tarlov scoring system. The mean modified Tarlov scores were 5.00 (SD, 0.00), 0.86 (SD, 0.69), and 2.14 (SD, 0.69) in the control, ischemia, and felbamate-treated groups, respectively. Tarlov scores were significantly lower in the ischemia group than in the control group ($p<0.001$). Scores in the felbamate-treated group were significantly higher than in the ischemia group ($p<0.001$), but remained significantly lower than those of the control group ($p<0.001$; Figure 4 and Table II).

DISCUSSION

Spinal cord I/R injury (SCIIR) remains one of the most challenging forms of secondary neural injury because tissue damage is driven not only by the initial interruption of blood flow, but also by the complex cascade that follows reperfusion. In clinical practice, this mechanism is particularly relevant during thoracoabdominal aortic procedures, in which spinal cord ischemia may result in severe and often irreversible neurological deficits (4,19). Despite ongoing experimental work, no safe and consistently effective therapy for SCIIR has yet been established. Recent studies have further emphasized that SCIIR is biologically complex and involves overlapping oxidative, inflammatory, mitochondrial, and regulated cell death pathways, including apoptosis, PANoptosis-related signaling, and recently described cuproptotic mechanisms (10,27,28).

In the present study, the rats treated with felbamate after reperfusion showed lower tissue caspase-3 levels, less severe histopathological damage, and better early neurological function than the untreated ischemic animals. Taken together, these findings suggest that felbamate may attenuate early tis-

Table II: Summary of Biochemical, Histopathological, and Neurological Outcomes

Outcome	Control	Ischemia	Felbamate	Pairwise comparisons
Caspase-3 (ng/mL)	1.88±0.08	5.00±0.25	3.65±0.42	Control/Ischemia: $p<0.001$ Ischemia/Felbamate: $p<0.001$ Control/ Felbamate: $p<0.001$
Overall histopathological injury score	0.00 (0.00–0.30)	2.80 (2.65–2.90)	1.00 (0.80–1.30)	Control/Ischemia: $p<0.001$ Ischemia/Felbamate: $p<0.001$ Control/Felbamate: $p=0.007$
Modified Tarlov Score	5.00±0.00	0.86±0.69	2.14±0.69	Control/Ischemia: $p<0.001$ Ischemia/Felbamate: $p<0.001$ Control/Felbamate: $p<0.001$

ANOVA: Analysis of variance, **IQR:** Interquartile range, **SD:** Standard deviation.

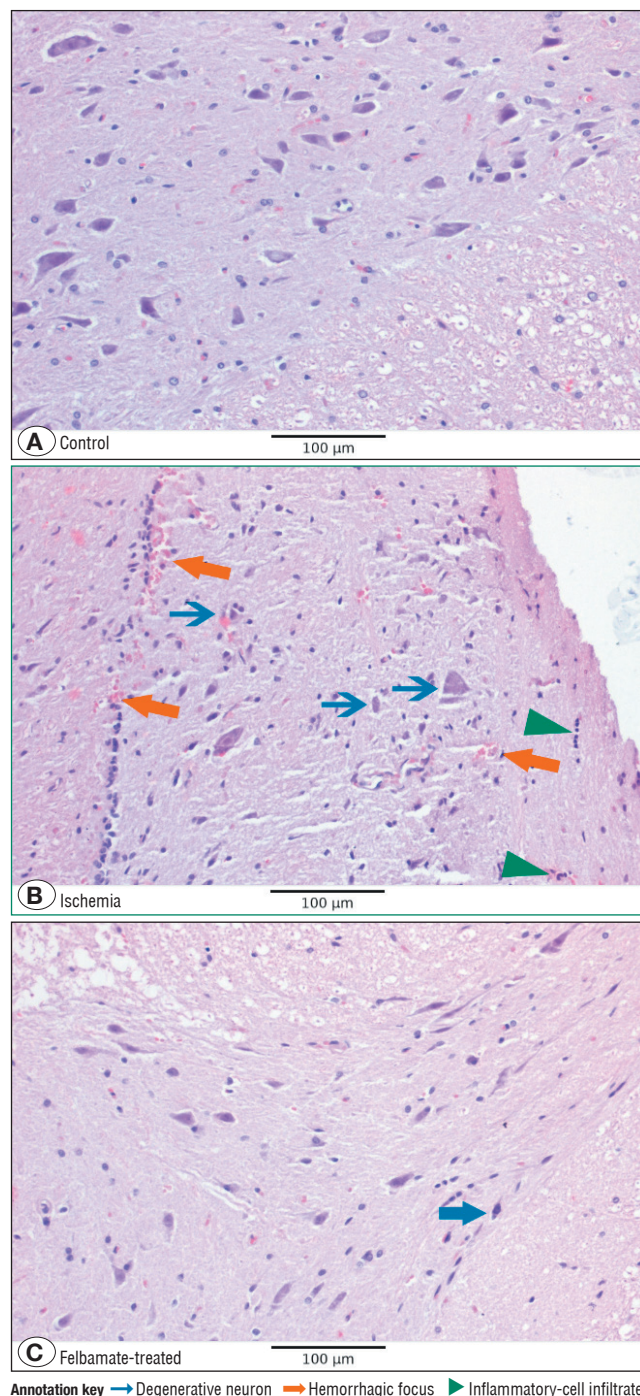


Figure 2: Representative hematoxylin and eosin (H&E)-stained photomicrographs of spinal cord sections from the experimental groups. All images were acquired using a 40× objective lens and are presented at identical dimensions and scale. **A)** Control group: preserved spinal cord architecture and normal-appearing neurons. **B)** Ischemia group: marked histopathological injury on an edematous background, including degenerative neurons (blue arrows), hemorrhagic foci (orange arrows), and inflammatory cell infiltration (green arrowheads). **C)** Felbamate-treated group: milder histopathological injury, with a residual degenerative neuron indicated by the blue arrow and fewer injury-related changes than in the ischemia group. Scale bars=100 µm in all panels.

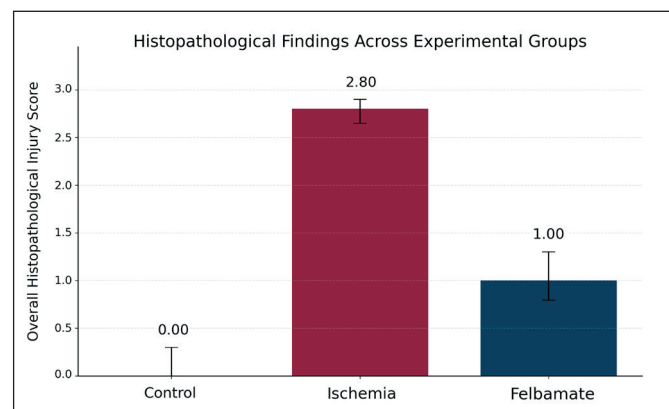


Figure 3: Overall histopathological injury scores in the control, ischemia, and felbamate-treated groups. For each animal, the overall score was calculated as the mean of six semiquantitative histopathological parameters: hemorrhage, congestion, edema, necrosis, neuronal degeneration, and inflammatory cell infiltration. Bars represent median values, and error bars indicate the interquartile range (IQR). Higher scores indicate more severe histopathological injuries.

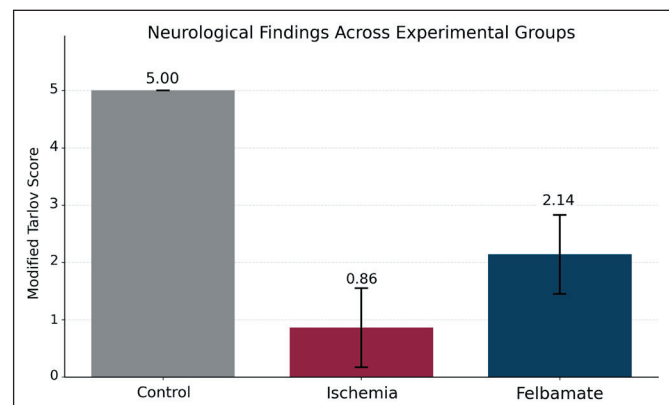


Figure 4: Modified Tarlov scores in the control, ischemia, and felbamate-treated groups. Bars represent mean values, and error bars indicate standard deviation (SD). Mean Modified Tarlov scores were 5.00 (SD, 0.00) in the control group, 0.86 (SD, 0.69) in the ischemia group, and 2.14 (SD, 0.69) in the felbamate-treated group. Higher scores indicate better hindlimb motor function.

sue damage in this rat model of SCI. Importantly, however, the protective effect observed in the felbamate-treated group was partial rather than complete, as neurological scores remained below those of the control group and tissue injury was reduced rather than abolished. This distinction is important, because it places the findings within an appropriately cautious translational framework without implying complete functional recovery.

One of the most consistent findings in SCI is the contribution of apoptosis to delayed neuronal loss. Caspase-3 remains a biologically relevant marker in this setting, and both early and more recent experimental studies support the relevance of apoptosis-related signaling in spinal cord ischemic

injury (6,10,21). In the present study, the marked rise in tissue caspase-3 levels in the ischemia group and their reduction after felbamate treatment are therefore compatible with an anti-apoptotic effect. Although biologically plausible, this interpretation should remain within the limits of the available data: our findings demonstrate an association between felbamate treatment and reduced caspase-3 levels rather than providing a complete mechanistic characterization of the apoptotic pathway.

The pharmacological profile of felbamate provides a plausible basis for this observation. Felbamate modulates excitatory neurotransmission, particularly through NMDA receptor-mediated mechanisms, and may also influence gamma-aminobutyric acid-mediated signaling (11,14). Although recent data on the effects of felbamate in SCIRI are lacking, experimental evidence from a rat model of traumatic brain injury suggests that felbamate may exert broader neuroprotective effects beyond seizure control. In that study, felbamate was associated with lower cytokine levels and less severe histological injury (1). At the same time, translational caution remains warranted, because more recent metabolic work has confirmed reactive metabolite formation in a humanized liver model—a finding relevant to the idiosyncratic toxicity historically associated with felbamate in clinical practice (15). To our best knowledge, however, felbamate has not been specifically investigated in a contemporary SCIRI model. For this reason, direct comparisons with recent SCIRI-focused studies remain limited, and the present findings should be interpreted as preliminary and hypothesis-generating within this specific experimental context.

The histopathological findings were consistent with the biochemical data. Untreated ischemic animals demonstrated the expected pattern of acute tissue injury, including hemorrhage, congestion, edema, necrosis, inflammatory cell infiltration, and neuronal pyknosis. By contrast, these changes were less pronounced in the felbamate-treated group. Although histopathology in this setting cannot establish a single dominant mechanism, the overall pattern suggests that felbamate mitigated the structural consequences of I/R injury. The reduction in the overall histopathological injury score further supports this interpretation.

The neurological findings also deserve careful emphasis. The ischemia group showed profound impairment on the modified Tarlov scale, whereas the felbamate-treated group performed significantly better. Nevertheless, neurological recovery in the treated group remained incomplete relative to that in the sham control group. Clinically, these findings indicate a measurable early functional benefit without normalization of neurological function. This distinction is important because experimental therapies for spinal cord ischemia often demonstrate biological or histological effects without corresponding functional improvement; in the present study, the functional outcomes were consistent with the biochemical and histological findings.

Our findings should also be viewed alongside the broader experimental literature on pharmacological neuroprotection in SCIRI. In rabbit models of SCIRI, several pharmacologi-

cal agents, including low-dose methotrexate, cerebrolysin, and amantadine, have shown protective potential (9,21,22). In a rabbit model of SCIRI, Tonge et al. reported that Cerebrolysin treatment was associated with lower serum and tissue levels of caspase-3, myeloperoxidase, malondialdehyde, and xanthine oxidase; higher catalase levels; and improved histopathological, ultrastructural, and neurological outcomes (21). More recent mechanistic studies have further shown that experimental interventions may attenuate neuronal death, reduce apoptosis-related signaling, and improve neurological outcomes in SCIRI models (27,28). Against that background, felbamate may be considered a candidate adjunct rather than a definitive solution. The present study provides preliminary experimental evidence that felbamate may favorably influence early apoptosis-related, histopathological, and functional outcomes of SCIRI.

Several limitations should be acknowledged. First, the sample size was small, which is common in exploratory animal studies but nonetheless limits precision. Second, only a single dose of felbamate and a single short-term assessment time point were evaluated; the durability of the observed effect therefore remains unknown. Third, direct spinal cord perfusion monitoring was not performed. Because some degree of residual perfusion may have been maintained through collateral vascular pathways despite abdominal aortic cross-clamping, the severity of ischemia may have varied across animals. This limitation should be considered when interpreting both the degree of ischemic injury and the apparent magnitude of felbamate-related protection. Fourth, although caspase-3 provided information as an apoptosis-related marker, the study did not include a broader biochemical panel capable of directly characterizing oxidative stress, inflammatory signaling, or alternative cell death pathways. Fifth, the histopathological assessment supported the overall direction of effect, but the research design does not permit detailed mechanistic resolution. These limitations do not negate the findings, but they do define the boundaries within which the results should be interpreted.

In summary, the present study suggests that felbamate treatment after reperfusion may reduce apoptosis-related signaling, attenuate histopathological damage, and improve early neurological outcomes in experimental SCIRI. The results support a potential neuroprotective effect, but they should be regarded as preliminary and hypothesis-generating. Further studies using larger cohorts, multiple dosing strategies, longer follow-up periods, and broader mechanistic analyses will be needed before stronger conclusions can be drawn.

CONCLUSION

In this experimental model of SCIRI, felbamate treatment after reperfusion was associated with lower tissue caspase-3 levels, less severe histopathological damage, and better early neurological function than in untreated ischemic animals. These findings suggest that felbamate may attenuate early spinal cord injury in this setting and may represent a promising neuroprotective candidate. Nevertheless, the observed benefit was partial rather than complete, and the findings should

therefore be interpreted with appropriate caution. Accordingly, this study should be regarded as preliminary and hypothesis-generating. Further investigations with larger sample sizes, longer follow-up periods, different dosing strategies, and broader mechanistic analyses are warranted to better define the durability, biological basis, and translational relevance of felbamate's potential protective effects in SCIRI.

Declarations

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

Disclosure: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of generative AI use: During the revision of this manuscript, the authors used ChatGPT (OpenAI, GPT-5; accessed July 2026) exclusively for English-language editing and for improving typographical and formatting consistency in the text originally prepared by the authors. The tool was not used to generate or modify scientific content, draft original scientific text, perform or aid data analysis, formulate scientific interpretations or conclusions, or create or modify any figure, image, or other visual material. All scientific content was generated and developed by the authors. The authors critically reviewed and approved all language-editing and formatting suggestions and take full responsibility for the accuracy, integrity, and final content of the manuscript.

AUTHORSHIP CONTRIBUTION

Study conception and design: MEE, ERY, AEH

Data collection: MEE, MYH, EA, AA, EK

Analysis and interpretation of results: MEE, EY, JNN, ERY

Draft manuscript preparation: MEE

Critical revision of the article: ERY, AEH, EY, JNN, MYH, EA, AA, EK

Other (study supervision, fundings, materials, etc...: ERY, AEH, EA, AA

All authors (MEE, ERY, AEH, EY, MYH, JNN, EA, AA, EK) reviewed the results and approved the final version of the manuscript.

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