Amol University of Special Modern Technologies

Caspian Journal of Veterinary Sciences

doi: 10.22034/cjvs.2026.582570.1069

Journal homepage: https://cjvs.ausmt.ac.ir/

Betaine improves histopathologic recovery after sciatic nerve crush injury in rats: a dose–response experimental study

Kosar Javareshkian[1], Ahmad Asghari[1]*, Pejman Mortazavi[2]

[1]Department of Veterinary Clinical Sciences, SR.C., Islamic Azad University, Tehran, Iran.

[2]Department of Pathobiology, SR.C., Islamic Azad University, Tehran, Iran.

(*) Corresponding Author: dr.ahmad.asghari@iau.ac.ir

Article Info

Article history:

Submit Date: 20 May 2026

Accept Date: 30 May 2026

Online Date: 8 November 2026

Keywords:

Betaine

Histopathology

Peripheral nerve regeneration

Rat

Sciatic nerve

Abstract

Peripheral nerve crush injuries can lead to incomplete structural recovery due to inflammation, edema, and cellular stress. Betaine, a natural osmolyte and methyl donor, has been investigated for potential cytoprotective and immunometabolic effects relevant to neural injury models. To evaluate the dose-range effects of betaine on histopathologic indices of sciatic nerve regeneration in a rat crush injury model. Forty male rats were allocated to five groups (n=8 each): non-injured control, untreated crush injury, and three crush-injury groups treated with betaine (100, 200, or 400 mg/kg/day). At postoperative day 21, harvested sciatic nerves underwent standardized histopathologic assessment using a semi-quantitative composite regeneration score (0–16) derived from perineurium/epineurium formation, inflammatory cell presence, axonal swelling, and density of healthy axons. Composite regeneration scores differed significantly among groups (one-way ANOVA, $p < 0.001$). The injury-only group demonstrated markedly lower scores than controls. Higher composite scores were observed in the 200 and 400 mg/kg/day groups compared to untreated injury, whereas the 100 mg/kg/day group did not differ significantly from injury-only animals. Healthy axon density showed significant overall group differences ($p < 0.05$), with descriptive trends toward higher mean values in betaine-treated groups; however, post-hoc comparisons did not demonstrate statistically significant differences between treated and untreated injured groups. In this rat sciatic nerve crush model, betaine administration was associated with higher composite histopathologic regeneration scores at higher tested doses (200–400 mg/kg/day). These findings support further experimental investigation incorporating functional and mechanistic outcomes to clarify the potential role of betaine in peripheral nerve recovery.

©2026 Published by Amol University of Special Modern Technologies Press.

This is an open-access article under the CC-BY4.0 license (https://creativecommons.org/licenses/by/4.0/).

Introduction

Peripheral nerve injury causes lasting sensory loss, muscle weakness, and chronic pain that often continues even after the nerve fibers grow back (Chen *et al*., 2007; Scheib and Hoke, 2013). Full recovery is difficult to achieve because the biological process requires the successful management of axonal elongation alongside the reconstruction of connective tissue tubes before target muscles undergo permanent atrophy (Chen *et al*., 2007; Gordon, 2020). In mixed nerves like the sciatic nerve, which carries both motor and sensory signals, any failure in this regeneration process leads to a permanent loss of limb function (Gordon, 2020; O'Brien, 2022).

When a nerve is crushed, the segment distal to the injury begins to break down through Wallerian degeneration. This triggers a response from immune cells and glial cells that facilitates repair only if the inflammatory phase remains controlled (Chen *et al*., 2007; Jessen and Mirsky, 2016). Schwann cells manage this repair by changing into a "repair" phenotype where they clear dead tissue with macrophages and build guidance tubes, known as bands of Büngner, to lead new axons back to their targets (Jessen and Mirsky, 2016; Gordon, 2020). However, local swelling and cellular stress can damage these tubes and result in poor-quality nerve fibers (Chen *et al*., 2007; Scheib and Hoke, 2013; Gordon, 2020; O'Brien, 2022).

The sciatic nerve crush model is a standard tool for this research because it mimics human bruise injury, keeps the nerve's outer structure intact, and allows for the testing of drugs intended to improve the quality of repair (Bridge *et al*., 1994; Gordon, 2020). In this model, researchers check specific markers like connective tissue organization, the amount of inflammation, and the number of healthy axons (Bridge *et al*., 1994; Chen *et al*., 2007). While walking-track analysis shows if the nerve is working, grading the tissue on a slide provides a more accurate way to see the first signs of physical healing. (de Medinaceli *et al*., 1982; Hare *et al*., 1993; Gordon, 2020; O'Brien, 2022).

Betaine (trimethylglycine) is a nutrient that helps cells stay hydrated as an osmolyte and assists in chemical reactions as a methyl donor. (Zhao *et al*., 2018; Arumugam *et al*., 2023;) Several studies show that betaine changes how the body handles inflammation by stopping NF-κB signals and reducing the chemicals that cause swelling after an injury (Zhao *et al*., 2018; Zhang, 2022). Several experimental studies also found that betaine protects nerve cells from damage caused by toxins or metabolic stress in different parts of the nervous system (Park *et al*., 1994; Alipourfard *et al*., 2023). Even though betaine looks promising, data describing how oral intake affects the physical structure of a damaged peripheral nerve in a living animal remains limited (Gordon, 2020; O'Brien, 2022).

Testing different doses of betaine is necessary to decide if this compound justifies further investigation using walking-track analysis and molecular markers (de Medinaceli *et al*., 1982; Scheib and Hoke, 2013). This study therefore tested if betaine doses of 100, 200, or 400 mg/kg/day helped crushed sciatic nerves in rats by using a standard scoring system to grade the tissue recovery.

Materials and Methods

Study design and sample size calculation

This experimental, controlled, dose–response animal study evaluated histopathologic recovery following standardized sciatic nerve crush injury and subsequent betaine administration at three dose levels. The selected dose range was chosen to represent low, intermediate, and high levels of systemic exposure, while remaining within doses previously reported to be well tolerated in rodent models. The study was conducted under general animal welfare principles consistent with the Guide for the Care and Use of Laboratory Animals (Alipourfard *et al*., 2023).

The experimental protocol and all animal procedures were formally approved by the Institutional Animal Care and Use Committee under the ethics code IR.IAU.SRB.REC.1404.350.

A total of 40 male rats were allocated into five groups (n=8 per group) using a simple randomization method. Sample size was determined based on previous experimental studies investigating histopathologic recovery following sciatic nerve injury in rat models, in which group sizes of 6–10 animals were commonly used to detect biologically meaningful differences. Histopathologic scoring was

performed in a blinded manner with respect to treatment group.

Study groups

Group 1 (Control; no injury): Animals in the control group did not undergo sciatic nerve crush injury and did not receive betaine gavage, serving as the reference for normal histologic appearance under the study conditions. This group was used to contextualize expected tissue architecture and to anchor interpretation of injury-related pathology and treatment-associated changes.

***Group 2 (Injury; no treatment*)**: Animals in the injury-only group underwent standardized sciatic nerve crush injury and received no betaine treatment, serving as the primary comparator for estimating injury-associated histopathologic disruption at the endpoint. This group provided the baseline against which any apparent betaine-associated improvements in histologic domains could be interpreted.

Group 3 (Injury + betaine 100 mg/kg/day): Animals in this group underwent sciatic nerve crush injury and then received betaine by gavage at 100 mg/kg once every 24 hours for the intended follow-up period. This dose was conceptualized as a lower-dose exposure to evaluate whether modest systemic betaine delivery was associated with measurable histopathologic improvement.

Group 4 (Injury + betaine 200 mg/kg/day): Animals in this group underwent sciatic nerve crush injury and then received betaine by gavage at 200 mg/kg once every 24 hours for the intended follow-up period. This intermediate dose enabled evaluation of dose–response trends relative to both the lower (100 mg/kg) and higher (400 mg/kg) dose levels.

Group 5 (Injury + betaine 400 mg/kg/day): Animals in this group underwent sciatic nerve crush injury and then received betaine by gavage at 400 mg/kg once every 24 hours for the intended follow-up period (Zhao *et al*., 2018; Arumugam *et al*., 2021). This higher dose was included to explore whether greater systemic exposure was associated with stronger histopathologic recovery signals in composite and domain-level scoring.

Surgical procedure: General anesthesia was induced using intraperitoneal ketamine hydrochloride (60 mg/kg) combined with xylazine (30 mg/kg). After confirmation of adequate anesthesia, the left hindlimb was shaved, disinfected, and draped under sterile conditions. A skin incision was made in the posterolateral thigh region, and the sciatic nerve was exposed by blunt separation of the muscle and fascial layers.

A standardized sciatic nerve crush injury was produced using a fine hemostatic clamp fixed at the first ratchet position, with constant pressure applied for 60 seconds. The injury site was marked with a non-absorbable 5-0 silk suture to facilitate later identification. The surgical wound was then closed in layers using 4-0 vicryl for the subcutaneous tissue with simple continuous and 3-0 nylon for the skin with simple interrupted sutures.

Measurements

Endpoint timing and tissue sampling

At the planned endpoint, animals were euthanized, and the lesion site was identified using the previously placed non-absorbable silk marker. A sciatic nerve segment from the injured region was harvested and transferred for histopathologic evaluation. All animals were euthanized at a single predefined endpoint on postoperative day 21. The euthanasia agent and route were reported as intracardiac thiopental.

Tissue processing and staining

Harvested sciatic nerve specimens were fixed in 10% neutral buffered formalin and processed using standard histological procedures, including graded alcohol dehydration, xylene clearing, and paraffin infiltration, followed by paraffin embedding at approximately 60°C. Paraffin sections were cut at a thickness of 5 µm using a rotary microtome. Sections were stained with hematoxylin and eosin (H&E) following routine protocols, including deparaffinization in xylene, rehydration through graded ethanol, hematoxylin staining, differentiation, bluing, eosin counterstaining, dehydration, and clearing. Histopathologic evaluation was performed under light microscopy at 400 magnification, and at least five non-overlapping high-power fields were examined per section. In addition, methylene blue staining was performed to facilitate visualization

of neural tissue architecture.

Histopathologic scoring

Histopathologic recovery was evaluated using a previously described semi-quantitative scoring system, adapted from published experimental studies of peripheral nerve injury and regeneration (Caner *et al*., 2012). The scoring system assessed four histopathologic domains, each graded on a scale from 0 to 4, with higher scores, indicating more favorable regenerative features. The evaluated domains included: (1) perineurium and epineurium formation, (2) inflammatory cell infiltration, (3) axonal swelling, and (4) density of morphologically normal axons per high-power field. A composite regeneration score ranging from 0 to 16 was calculated as the sum of the individual domain scores.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY, USA). Normality of data distribution was assessed using the Shapiro–Wilk test. Homogeneity of variances was evaluated using Levene's test. One-way ANOVA followed by Tukey's post-hoc test was applied for group comparisons. The threshold for statistical significance was set at $p < 0.05$.

Results

Study flow and general observations

All animals were included in the final analysis.

Composite histopathologic regeneration score (0–16)

There was a statistically significant difference in composite regeneration score among groups (one-way ANOVA, $p < 0.001$). Control animals demonstrated the highest composite score, while the injury-only group demonstrated a marked reduction. Betaine-treated groups showed higher composite scores than the injury-only group, with the 200 and 400 mg/kg/day groups, exhibiting the greatest mean scores among treated groups. Post-hoc comparisons using Tukey HSD indicated that the control group differed significantly from all other groups ($p < 0.001$ for all comparisons). The injury-only group differed significantly from the 200 and 400 mg/kg/day betaine groups ($p < 0.001$), while the difference between injury-only and the 100 mg/kg/day group was not statistically significant ($p = 0.066$). In addition, the 100 mg/kg/day group differed significantly from the 200 and 400 mg/kg/day groups ($p < 0.001$), whereas the 200 and 400 mg/kg/day groups did not differ significantly from each other ($p = 0.396$). Domain-level analyses were presented below to provide additional context for the composite findings (Table 1).

Perineurium/epineurium formation (0–4)

Perineurium/epineurium formation did not differ significantly among groups (one-way ANOVA, $p = 0.753$). Scores in this domain were high across all groups, indicating that connective tissue sheath formation showed limited between-group separation at the assessed endpoint within this scoring framework.

Inflammatory cell presence (0–4)

Inflammatory cell presence differed significantly among groups (one-way ANOVA, $p < 0.001$). Tukey HSD post-hoc testing showed that the control group differed significantly from the injury-only group ($p = 0.001$) and from the 100 and 200 mg/kg/day betaine groups ($p < 0.005$ for each). The control group did not differ significantly from the 400 mg/kg/day betaine group ($p = 0.959$). No statistically significant differences were detected among the injury-only group and the three betaine-treated groups in this domain ($p > 0.05$ for all pairwise comparisons among groups 2–5).

Axonal swelling (0–4)

Axonal swelling scores differed significantly among groups (one-way ANOVA, $p < 0.001$). Tukey HSD comparisons indicated that the control group differed significantly from the injury-only group and from the 100 and 200 mg/kg/day betaine groups ($p < 0.005$ for each), whereas the control group did not differ significantly from the 400 mg/kg/day group ($p = 0.369$). No statistically significant differences were observed among the injury-only group and the betaine-treated groups for this domain ($p > 0.05$ for all comparisons among groups 2–5) (Table 1).

Density of healthy axons (0–4)

Healthy axon density differed significantly among groups ($p < 0.05$). In the plotted outcomes, the injury-only group demonstrated a marked reduction in healthy axon density relative to control. Betaine-treated groups demonstrated higher mean values than injury-only, with a graded pattern favoring 200 and 400 mg/kg/day. In post-hoc comparisons described for this outcome, the control group differed significantly from the injury-only group and from the 100 and 200 mg/kg/day groups ($p < 0.05$), while the control group did not differ significantly from the 400 mg/kg/day group ($p > 0.05$). Differences among the injured groups (injury-only vs betaine-treated groups) were not statistically significant by the described comparisons ($p > 0.05$) (Table 2 and Fig. 1).

Table 1. Scoring system for sciatic nerve injury.

Experimental group	Score	Parameter
0	No formation	Perineurium & Epineurium formation
1	< 25%	Perineurium & Epineurium formation
2	25–50%	Perineurium & Epineurium formation
3	50–75%	Perineurium & Epineurium formation
4	Complete	Perineurium & Epineurium formation
0	Severe (> 75%)	Inflammatory cells
1	Moderate (50–75%)	Inflammatory cells
2	Mild (25–50%)	Inflammatory cells
3	Mild (< 25%)	Inflammatory cells
4	Absent	Inflammatory cells
0	Severe (> 75% of normal axon diameter)	Axonal swelling
1	Moderate (50–75% of normal diameter)	Axonal swelling
2	Mild (25–50% of normal diameter)	Axonal swelling
3	Mild (< 25% of normal diameter)	Axonal swelling
4	No swelling	Axonal swelling
0	< 25% of normal nerve	Axon count per field
1	25% of normal nerve	Axon count per field
2	50% of normal nerve	Axon count per field
3	75% of normal nerve	Axon count per field
4	Similar to normal nerve	Axon count per field

Table 2. Digitized mean values from thesis figures for composite score and healthy axon density.

Study groups	Composite regeneration score (0–16)	Perineurium/epineurium formation (0–4)	Inflammatory cell presence (0–4)	Axonal swelling (0–4)	Density of healthy axons (0–4)
Control	16.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00
Injury (no treatment)	8.33 ± 0.58	4.00 ± 0.00	1.33 ± 0.58	1.67 ± 0.58	1.33 ± 0.58
Injury + betaine 100 mg/kg/day	9.67 ± 0.58	4.00 ± 0.00	1.67 ± 0.58	1.67 ± 0.58	1.67 ± 0.58
Injury + betaine 200 mg/kg/day	11.33 ± 1.16	4.00 ± 0.00	2.33 ± 0.58	2.33 ± 0.58	2.33 ± 0.58
Injury + betaine 400 mg/kg/day	12.00 ± 1.00	4.00 ± 0.00	2.67 ± 0.58	2.67 ± 0.58	2.67 ± 0.58

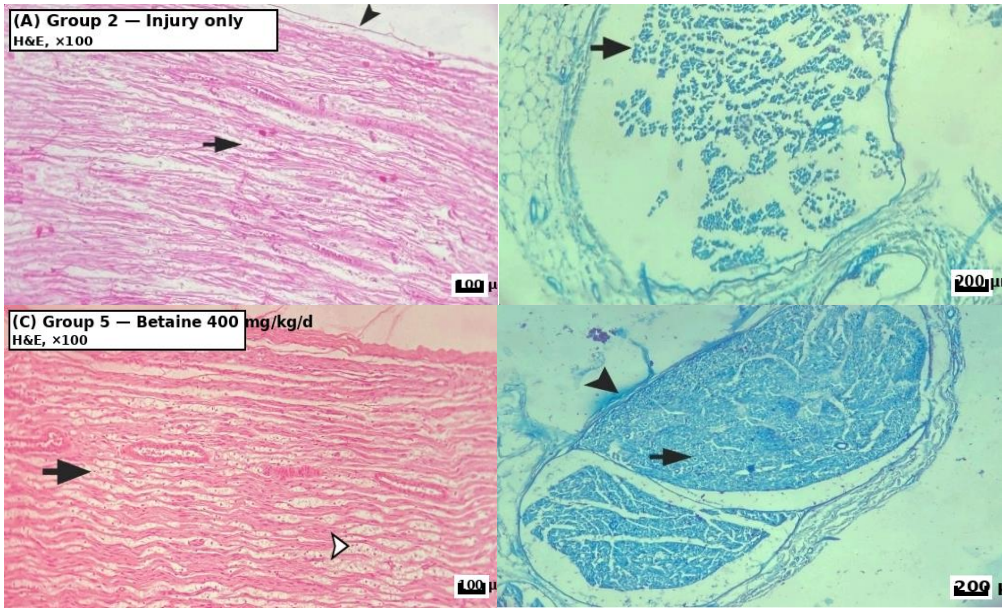


Fig. 1. Representative histologic images of sciatic nerve sections comparing untreated injury (Group 2) and betaine 400 mg/kg/day treatment (Group 5). (A) Group 2, longitudinal section, H&E ×100: axonal swelling (filled arrow) and perineurium (arrowhead). (B) Group 2, cross-section, Methylen blue ×100: intact perineurium (arrowhead) and low axonal density (arrow). (C) Group 5, longitudinal section, H&E ×100: improved axonal architecture with reduced swelling (arrow) and intact perineurium (open arrowhead). (D) Group 5, cross-section, Methylen blue ×100: complete perineurium (arrowhead) and high axonal density (arrow). Scale bars embedded in each panel.

Discussion

This study found that betaine administration after sciatic nerve crush injury was associated with improved overall histopathologic recovery, with higher composite regeneration scores in treated groups compared to untreated injury and with a trend toward higher composite scores at 200–400 mg/kg/day. In parallel, healthy axon density scores showed a similar descriptive trend toward higher values in betaine-treated groups compared to injury-only animals; however, between-group differences among injured groups were not statistically significant, and therefore this finding should be interpreted as a supportive trend rather than a statistically confirmed effect across indices (Chen *et al*., 2007; Gordon, 2020). These findings are relevant because histologic recovery quality after axonotmesis-like injury can shape the trajectory of remyelination and functional restitution even when axonal regrowth is biologically possible (Scheib and Hoke, 2013; Jessen and Mirsky, 2016).

A key strength of the sciatic nerve crush model is that it preserves the gross continuity of endoneurial pathways while still inducing marked axonal disruption and secondary inflammatory stress, making it suitable for identifying therapies that improve the quality of regeneration rather than simply enabling reconnection (Bridge *et al*., 1994; Gordon, 2020). Within that context, the improvement in a composite score that integrates multiple histologic domains suggests that betaine may influence several components of the post-injury tissue environment rather than a single isolated feature. (Chen *et al*., 2007; O'Brien, 2022) The relatively high perineurium/epineurium formation scores across groups in the thesis figures may indicate limited sensitivity of this domain at the selected endpoint or a tendency for connective tissue organization to recover comparably in this specific crush paradigm ((Bridge *et al*., 1994; Gordon, 2020).

The direction of benefit observed here is concordant with a broader mechanistic literature describing betaine as a cellular stress modulator with immunometabolic relevance (Zhao *et al*., 2018; Arumugam *et al*., 2023). Several studies have emphasized that betaine may modulate inflammatory signaling cascades including NF-κB–

linked pathways and inflammasome-associated cytokine biology processes that are implicated in secondary injury amplification and delayed resolution after neural tissue insults (Zhao *et al*., 2018; Zhang, 2022). Because post-crush inflammation and oxidative/metabolic stress can contribute to ongoing axonal pathology and impede optimal remyelination, attenuation of these processes is biologically plausible as a contributor to improved histologic profiles and higher composite recovery scores (Chen *et al*., 2007; Gordon, 2020) Because no mechanistic assays were performed, the proposed pathways should be interpreted as biologically plausible hypotheses rather than causal effects demonstrated by this study.

Concordant evidence supporting betaine's neurobiologic plausibility also comes from experimental studies conducted in non-peripheral-nerve contexts, where betaine exposure has been investigated under diverse neural stressors (Park *et al*., 1994; Im *et al*., 2013). For example, studies examining toxin- or excitotoxicity-related neural injury paradigms have been used to explore whether betaine can mitigate cellular stress and preserve neural structure under adverse conditions (Park *et al*., 1994; Im *et al*., 2013; Arumugam *et al*., 2021). Additional experimental work has considered betaine in systemic or metabolic stress settings with neural implications, reinforcing the concept that betaine can influence stress biology beyond a single pathway (Kanbak *et al*., 2008; Arumugam *et al*., 2021). Taken together, these lines of evidence provide a coherent biologic rationale for why systemic betaine might improve histopathologic recovery indices after peripheral nerve trauma, even though direct mechanistic testing in peripheral nerve injury remains necessary (Gordon, 2020; O'Brien, 2022).

At the same time, discordant or uncertain aspects remain important to acknowledge when interpreting a histology-only endpoint and a composite scoring approach (Scheib and Hoke, 2013; Gordon, 2020). First, improvement in semi-quantitative histopathology does not guarantee proportional functional recovery, particularly if reinnervation is incomplete or if remyelination quality is insufficient for optimal conduction (Gordon, 2020; O'Brien, 2022). Second, individual domains may fail to show strong separation across treatment doses even when a composite score improves, because composite indices can reflect modest improvements across multiple domains that cumulatively produce a clearer signal (Bridge *et al*., 1994; Chen *et al*., 2007). Third, the dose–response pattern observed in the composite score could reflect timing and biology that differ across early inflammatory phases and later maturation phases, which cannot be mapped confidently from a single terminal timepoint (Chen *et al*., 2007; Jessen and Mirsky, 2016).

From a translational standpoint, these findings support the hypothesis that optimizing the systemic and local microenvironment after peripheral nerve crush can improve structural recovery, which is a prerequisite for high-quality reinnervation (Scheib and Hoke, 2013; Gordon, 2020). If betaine's benefit is mediated through reduced inflammatory burden or improved cellular stress tolerance, future studies should incorporate targeted biomarkers (oxidative stress indices, cytokine panels, and inflammasome-related markers) to connect histologic improvement with mechanism (Zhao *et al*., 2018; Zhang, 2022). Additional experimental reports have continued to explore betaine-related modulation of neural injury and inflammatory responses *in vivo*, underscoring the feasibility of mechanistic extensions even when the specific injury model differs (Hassanpour *et al*., 2020; Li *et al*., 2022; Alipourfard *et al*., 2023). More broadly, interest in accessible neuroprotective or recovery-supportive strategies remains high, but rigorous model-specific validation is required before strong translational claims can be made (O'Brien, 2022; Knight and Baskin, 2023)

This study has several limitations that should guide interpretation and manuscript refinement (Gordon, 2020; Alipourfard *et al*., 2023). Most importantly, functional recovery was not assessed using validated measures such as walking-track analysis, sciatic functional index derivations, or detailed lesion-specific functional scoring frameworks, which are central for linking histology to clinically meaningful recovery (de Medinaceli *et al*., 1982; Hare *et al*., 1993). Finally, the absence of mechanistic biomarker profiling limits inference regarding how betaine exerts any observed benefit, and the discussion should therefore remain cautious and hypothesis-driven rather than definitive *(Zhao et al*., 2018; Arumugam *et al*., 2021).

Future studies should build on these results by integrating multi-timepoint sampling to separate

early inflammatory resolution from later maturation/remyelination phases and by adding electrophysiology to quantify conduction recovery alongside histology (Gordon, 2020; O'Brien, 2022). Functional testing should be incorporated as a core outcome to establish whether the observed structural improvements translate into meaningful recovery of gait and nerve function (de Medinaceli *et al*., 1982; Hare *et al*., 1993). If the 200 mg/kg/day dose continues to show a favorable balance of benefit across endpoints, it may represent a pragmatic candidate dose for longer follow-up studies, but dose optimization should be grounded in integrated histologic, functional, and mechanistic outcomes.

Betaine administration after sciatic nerve crush injury was associated with higher composite histopathologic regeneration scores compared to untreated injury in this rat model. Healthy axon density showed a similar descriptive trend toward improvement; however, differences among injured groups were not statistically significant. Composite score patterns favored the 200–400 mg/kg/day doses, although no significant difference was observed between these doses, and therefore a definitive dose–response relationship cannot be concluded. Future work should incorporate validated functional endpoints (walking track/SFI), electrophysiology, and mechanistic biomarker profiling, with explicit reporting of randomization/blinding and a consistent endpoint timeline.

Acknowledgment

I would like to thank Engineer Abedi and Mr. Nosrati for their assistance with the practical work of my thesis

Conflict of Interest

The authors declare no conflicts of interest.

References

Alipourfard, F; Alirezaei, M; Shajiee, H and Hojati, V (2023). Betaine attenuates oxidative stress and cognitive dysfunction in an amyloid beta-induced rat model of Alzheimer's disease. Res. Pharm. Sci., 18: 372–382.

Arumugam, MK; Paal, MC; Donohue, TM; Ganesan, M; Osna, NA and Kharbanda, KK (2021). Beneficial effects of betaine: A comprehensive review. Biol., 10: 456.

Bridge, PM; Bal,l DJ; Mackinnon, SE and Dellon, AL (1994), Nerve crush injuries--a model for axonotmesis. Exp. Neurol., 127: 284–290.

Caner, B; Kafa, MI; Bekar, A; Kurt, MA; Karli, N and Cansev, M (2012) Intraperitoneal administration of CDP-choline or a combination of cytidine plus choline improves nerve regeneration and functional recovery in a rat model of sciatic nerve injury. Neurol Res., 34: 238–245.

Chen, ZL; Yu, WM and Strickland, S (2007), Peripheral regeneration. Ann. Rev. Neurosci., 30: 209–233.

de Medinaceli, L; Freed, WJ and Wyatt, RJ (1982), An index of the functional condition of rat sciatic nerve based on measurements made from walking tracks. Exp. Neurol., 77: 634–643.

Gordon, T (2020), Peripheral nerve regeneration and muscle reinnervation. Int. J. Mol. Sci., 21: 8652.

Hare, GMT; Evans, PJ and Mackinnon, SE (1993), Walking track analysis: utilization of individual footprint parameters. Ann. Plastic Surgery, 30: 147–153.

Hassanpour, S; Rezaei, H and Razavi, SM (2020), Anti-nociceptive and antioxidant activity of betaine on formalin- and writhing tests induced pain in mice. Behavioural Brain Res., 390: 112699.

Im, AR; Kim, YH; Uddin, MR; Kim, YS and Chae, S (2013), Neuroprotective effects of betaine on rotenone-induced cytotoxicity via the inhibition of reactive oxygen species generation in SH-SY5Y cells. Cell. Mol. Neurobiol., 33: 977–986.

Jessen, KR and Mirsky, R (2016). The repair Schwann cell and its function in regenerating nerves. J. Physiol., 594: 3521–3531.

Kanbak, G; Arslan, OC; Dokumacioglu, A; Kartkaya, K and Inal, ME (2008), Effects of chronic ethanol consumption on brain synaptosomes: Protective role of betaine. Neurochem. Res., 33: 539–544.

Knight, LS and Baskin, DS (2023). Betaine and its role in neuroprotection and peripheral nerve recovery: a review of current evidence. Front. Neurosci., 17: 1214976.

Li, Q; Li, X; Wang, L; Zhang, Y and Chen, L (2022). Betaine protects rats against ischemia/reperfusion injury-induced brain damage. J. Neurophysiol., 127: 252–261.

O'Brien, EJ (2022), Promoting nerve regeneration: Electrical stimulation, extracellular matrix molecules, and the promise of CRISPR technology. Physiol., 37: 223–235.

Park, MJ; Kim, SR; Huh, H; Jung, JH and Kim, YC (1994). Betaine attenuates glutamate-induced neurotoxicity in primary cultured brain cells. Arch. Pharm. Res., 17: 343–347.

Scheib, JL and Hoke, A (2013), Advances in peripheral nerve regeneration. Nature Rev. Neurol., 9: 668–676.

Zhang, M (2022). Betaine inhibits NLRP3 inflammasome activation and induces autophagy via the AMPK/SIRT1 pathway. Oxidative Med. Cell. Longevity, 2022: 9313436.

Zhao, G; He, F and Wu, C (2018), Betaine in inflammation: mechanistic aspects and applications. Front. Immunol., 9: 1070.